Nutritional Supplements in Sports and Exercise

Second Edition

Mike Greenwood
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Preface

Over the past two decades, the area of sport nutrition and nutritional supplementation has escalated in monumental proportions. An enormous number of qualified professionals—sport nutritionists, athletic coaches, athletic trainers, sports medicine personal, strength and conditioning coaches, personal trainers, medical representatives, and health practitioners, among others—as well as a variety of athletic and exercise participants have searched for viable dietary ergogenic aids to attain optimal training and performance levels. A multitude of universities have infused relevant sport nutrition courses, academic majors, and critical research agendas into their curriculums to further investigate this popular and dynamic aspect of our society. Professional organizations such as The International Society of Sport Nutrition have evolved to take a scientifically based approach to help further understand the annual billion dollar industry. What an extraordinary challenge this undertaking has been due to the multitude of nutritional supplements that are currently on the market and the plethora of these products that surface on a regular basis.

The editors and the authors noted in this textbook firmly believe that the public has the right to know the truth regarding nutritional supplement ingestion—health, safety, efficacy—and quality-based scientific research is the accepted approach supported by those contributing to this published endeavor. However, it should be noted that even highly acclaimed researchers are not always in agreement regarding specific scientific findings, but such is the nature of research in any realm. Based on this reality, there is a critical need for professionals to bridge the gap between scientific results and common sense approaches related to practical sports and exercise nutritional supplement strategies.

A major purpose of this book is to provide detailed analysis of nutritional supplementation supported by, whenever possible, replicated scientific research regarding sports and exercise performance. Previous chapters have been fully revised and new chapters have been added to cover important cutting edge topics. New chapters include: (1) Carbohydrate Utilization and Disposal in Strength/Power Training & Sports, (2) Exercise for Athletes with Diabetes, and (3) Beyond the Obvious: Future Innovations in Sports Nutrition. Additionally, the book is divided into four parts to accomplish this goal. Part I delves into the industrial component as well as the psychological nature of the consumer-based nutritional supplement game. In Part II, strong emphasis is placed on nutrient-dense food/fluid ingestion basics. Part III provides infor-

mation regarding specialized nutritional supplements and strategies for unique athletic populations, and Part IV addresses the present and future status of nutritional supplements in sports and exercise environments. This book provides the readers with a viable up-to-date reference guide, keeping in mind publication time frames often limit the inclusion of current research outcomes. We have attempted to include relevant nutritional supplement information that is timely and useful in an ever-evolving industry.

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Stow, OH Tim N. Ziegenfuss, PhD, FISSN, CSCS
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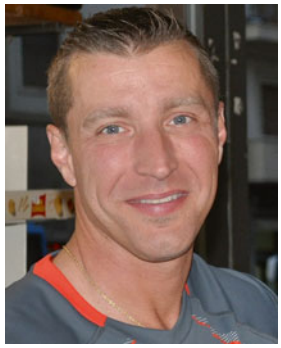
Contents

About the Editors

Mike Greenwood, PhD, FISSN, FNSCA, FACSM, RSCC *D, CSCS *D, is currently a Full Clinical Professor in the Department of Health and Kinesiology at Texas A&M University. In addition to a variety of teaching and research responsibilities, Mike serves as a Research Associate for the Exercise and Sport Nutrition Laboratory located at Research Park in College Station. Over the past 30 years, Mike has served as a Departmental Graduate Director, Graduate Academic Director for Strength and Conditioning, Graduate Research Coordinator, as well as the Ph.D. Director primarily involved with the Institute for Exercise, Nutrition and Preventive Health. Mike is a Fellow of the International Society of Sport Nutrition (ISSN), National Strength and Conditioning Association (NSCA), and American College of Sport Medicine (ACSM). Dr. Greenwood is certified as strength and conditioning specialist recognized with distinction by the NSCA and has previously served as a NCAA collegiate baseball/basketball coach as well as a collegiate strength training/conditioning professional. Mike is the NSCA Texas State Director and currently serves on the Advisory Board of ISSN and on the NSCA Certification and Research Committees. His primary lines of research are in the areas of sport/exercise nutrition and strength and conditioning. Dr. Greenwood serves on the Editorial Boards of the Strength and Conditioning Journal, Journal of the International Society of Sports Nutrition, and has reviewed manuscripts for Medicine and Science in Sports and Exercise as well as The Journal of Strength and Conditioning Research. In 2003, Mike received the Educator of The Year Award from the National Strength and Conditioning Association and in 2005 honored as the Sunshine State Conference Baseball Coach of The Year.

Matthew B. Cooke, BSc (Hons), PhD, received his Bachelor of Science (Biomedical Sciences) with honors and his Ph.D. in Exercise Science from Victoria University in Australia. Dr. Cooke then completed a Post-Doctoral Fellowship and Assistant Professorship at Baylor University from 2006 to 2009. In 2010, Dr. Cooke completed a Post-Doctoral fellowship in Clinical Exercise Physiology in the School of Medicine at the University of Queensland. Dr. Cooke is currently a Senior Lecturer and Deputy leader of the Biomedical and Lifestyle Disease (BioLED) Unit within the College of Health and Biomedicine at Victoria University in Melbourne, Australia. His areas of research interests include: Resistance training and nutritional interventions on the physiological, biochemical, and molecular mechanisms regulating skeletal muscle atrophy (sarcopenia) associated with aging. Nutritional supplementation and/or varied training regimes to manipulate muscle bioenergetics in aged and diseased populations. Exercise training and nutritional interventions on weight loss, weight maintenance, and metabolism in aged and diseased populations.



Tim N. Ziegenfuss, PhD, FISSN, CSCS, is the Chief Executive Officer of The Center for Applied Health Sciences. Dr. Ziegenfuss is a Past President and Fellow of the International Society of Sports Nutrition, a Certified Strength and Conditioning Specialist, and a consultant to several professional sports teams in Europe (soccer) and the United States (American football). In addition to his outreach program with athletes, he is active in clinical/academic research (600 articles in mainstream magazines, 40 scientific papers, 5 book chapters) and new product formulation with select sports nutrition companies.

Douglas S. Kalman, PhD, RD, CCRC, FISSN, FACN, is an Adjunct Professor in the Robert Stempel School of Public Health at Florida International University and a Director in the Nutrition and Endocrinology Research Lab at Miami Research Associates. He has been the Nutrition Program Consultant for IMG Academies in Bradenton, FL, and is currently the Sports Nutritionist for the Blackzilians (UFC) and for the Florida International University in Miami, Florida as well as being the Team Nutritionist for Coral

Springs Aquatic Center. He has been involved in over 300 clinical trials and projects within the pharmaceutical, medical, and nutrition fields. He has published over 75 abstracts and more than 30 peer-reviewed manuscripts. He is a Cofounder of the International Society of Sports Nutrition and Coeditor of the Journal—JISSN (www.jissn.com).

Jose Antonio, PhD, FISSN, FACSM, CSCS, is the CEO and cofounder of the *International Society of Sports Nutrition* (www.theissn.org) and is a Fellow of the National Strength and Conditioning Association. He is an Assistant Professor at Nova Southeastern University in Exercise and Sports Science in Ft Lauderdale FL and an avid outrigger paddler. In his spare time, he writes a lot, gives an occasional seminar, and reads minds. Okay, the last one he can't do. If you love sports nutrition, then you must go to an ISSN event. It's where nerds can have fun and learn at the same time.

About the Contributors

Part I. The Industrial Nature of the Supplement Game
Chapter 1:
Effect of Government Regulation on the Evolution of Sports Nutrition
Rick Collins and Douglas S. Kalman

Rick Collins, ESQ, JD, FISSN, is an internationally recognized legal authority in the field of dietary supplements and performance-enhancing substances. His law firm, Collins, McDonald and Gann, represents numerous companies in the nutritional supplement industry. He is admitted to practice in the State courts of New York, Massachusetts, Pennsylvania, and Texas, in the courts of the District of Columbia, and in various federal courts. He serves as General Counsel to, and is a Fellow of, the International Society of Sports Nutrition and has contributed chapters to two textbooks on sports nutrition. A frequent contributor to various health and fitness publications, he is a monthly columnist for the nationally circulated Muscular Development magazine and has served for years as a member of their Advisory Board. Rick is the official legal advisor to the International Federation of Body Builders (the IFBB, formed in 1946, currently has 173 affiliated National Federations and is recognized by over 90 National Olympic Committees). He has been interviewed as a legal authority in the film "Bigger, Stronger, Faster*" (2008) and on national television talk and news shows, in talk radio interviews, and by countless online and print publications. A former Nassau County Assistant District Attorney, he has been awarded the prestigious Martindale-Hubbell "AV-rating" for his keen legal abilities and ethical standards (AV-rating), and he is listed in the Bar Register of Preeminent Lawyers. He is also a nationally Certified Strength and Conditioning Specialist (NSCA-CSCS).

Douglas S. Kalman, PhD, RD, CCRC, FISSN, FACN, is an Adjunct Professor in the Robert Stempel School of Public Health at Florida International University and a Director in the Nutrition and Endocrinology Research Lab at Miami Research Associates. He has been the Nutrition Program Consultant for IMG Academies in Bradenton, FL, and is currently the Sports Nutritionist for the Blackzilians (UFC) and for the Florida International University in Miami, Florida as well as being the Team Nutritionist for Coral Springs Aquatic Center. He has been involved in over 300 clinical trials and projects within the pharmaceutical, medical, and nutrition fields. He has published over 75 abstracts and more than 30 peer-reviewed manuscripts. He is a Cofounder of the International Society of Sports Nutrition and Coeditor of the Journal—JISSN (www.jissn.com).

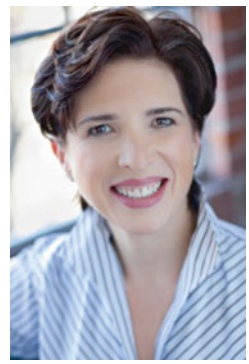
Chapter 2:
The Psychology of Supplementation in Sport and Exercise: Motivational Antecedents and Biobehavioral Outcomes
Shawn M. Arent and Rafer S. Lutz

Shawn M. Arent, PhD, CSCS *D, FACSM, is an Associate Professor in the Department of Exercise Science at Rutgers University, where he is also the Director of the IFNH Center for Health and Human Performance. He is currently the Head Exercise Physiologist for the NJ Devils of the NHL. He completed both his M.S. and Ph.D. in Exercise Science at Arizona State University and received his B.A. from the University of Virginia. He is a Certified Strength and Conditioning Specialist with the NSCA and a Fellow in ACSM. He is on the national staff for the US Soccer Federation and provides performance enhancement advice for a variety of athletes. His research focuses on the relationship between the stress response, health, and performance and has been funded by various sources including NIH, RWJF, and nutritional biotechnology companies.

Rafer S. Lutz, PhD, (Deceased) was an associate professor of sport and exercise psychology in the department of Health, Human Performance, and Recreation at Baylor University. A former winner (2001) of the Dissertation Award by the American Alliance for Health, Physical Education, Recreation, and Dance's Sport Psychology Academy, Dr. Lutz's research focuses primarily on the psychology of exercise participation and related health psychology topics, though he has secondary interests in the study of sport performance enhancement. In his brief career, Dr. Lutz has published 22 papers, 13 as

first or second author, in well-respected, peer-reviewed journals such as Behavioural Brain Research, Journal of Sport and Exercise Psychology, American Journal of Health Behavior, and Psychology of Sport and Exercise. Additionally, Dr. Lutz has been the primary presenter or co-presenter of over 45 presentations to national and international scientific societies such as North American Society for the Psychology of Sport and Physical Activity, American College of Sports Medicine, American Psychological Association, and American Psychological Society. A former Academic All-American golfer, Dr. Lutz has served as a performance enhancement consultant for a variety of business organizations, individual athletes, and athletic teams.

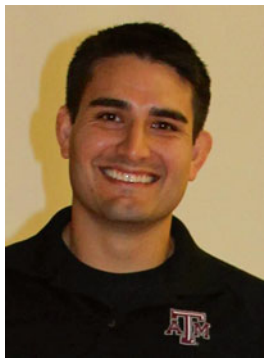
Part II. Nutritional Basics First
Chapter 3:
The Role of Nutritional Supplements Complementing Nutrient-Dense Diets: General Versus Sport/Exercise-Specific Dietary Guidelines Related to Energy Expenditure
Susan M. Kleiner and Mike Greenwood



Susan M. Kleiner, PhD, RD, CNS, FISSN, maintains one foot in the academic world and one foot in the business world. After her doctoral research on the Influence of Dietary Fats and Cholesterol, and Anabolic Steroids, on the Lipoprotein Profiles and Body Composition of Competitive Male Bodybuilders at Case Western Reserve University School of Medicine and The Cleveland Clinic Foundation Department of Sports Medicine, she continued to research and publish her seminal work on male and female bodybuilders. Dr. Kleiner has continued to research and publish in the field of sports nutrition and supplements and has also established herself through research and publications as an expert in hydration and health. Dr. Kleiner has consulted with professional teams, including the Seattle Seahawks, Supersonics, and Storm, the Cleveland Browns and Cavaliers, the Miami Heat, Olympians and elite athletes in countless sports. Dr. Kleiner is the co-CEO of Vynna, LLC, an evidence-based, female-centric sports nutrition company dedicated to the health, well-being and performance of athletic women and girls. She still maintains her 22-year ownership of High Performance Nutrition, LLC, her consulting firm in Mercer Island, Washington. She is a scientific advisor to numerous businesses in the industry and is the author of seven popular books, including POWER EATING®, Fourth Edition, The Oxygen Diet Solution, The Good Mood Diet®, and The POWERFOOD Nutrition Plan.

Mike Greenwood, PhD, FISSN, FNSCA, FACSM, RSCC *D, CSCS *D, is currently a Full Clinical Professor in the Department of Health and Kinesiology at Texas A&M University. In addition to a variety of teaching and research responsibilities, Mike serves as a Research Associate for the Exercise and Sport Nutrition Laboratory located at Research Park in College Station. Over the past 30 years, Mike has served as a Departmental Graduate Director, Graduate Academic Director for Strength and Conditioning, Graduate Research Coordinator, as well as the Ph.D. Director primarily involved with the Institute for Exercise, Nutrition and Preventive Health. Mike is a Fellow of the International Society of Sport Nutrition (ISSN), National Strength and Conditioning Association (NSCA), and American College of Sport Medicine (ACSM). Dr. Greenwood is certified as strength and conditioning specialist recognized with distinction by the NSCA and has previously served as a NCAA collegiate baseball/basketball coach as well as a collegiate strength training/conditioning professional. Mike is the NSCA Texas State Director and currently serves on the Advisory Board of ISSN and on the NSCA Certification and Research Committees. His primary lines of research are in the areas of sport/exercise nutrition and strength and conditioning. Dr. Greenwood serves on the Editorial Boards of the Strength and Conditioning Journal, Journal of the International Society of Sports Nutrition, and has reviewed manuscripts for Medicine and Science in Sports and Exercise as well as The Journal of Strength and Conditioning Research. In 2003, Mike received the Educator of The Year Award from the National Strength and Conditioning Association and in 2005 honored as the Sunshine State Conference Baseball Coach of The Year.

Chapter 4:
Macronutrient Intake for Physical Activity
Elfego Galvan



Elfego Galvan, MS, RD, LD, CSCS, is currently a 4th year doctoral student in the Exercise and Sport Nutrition Lab in the Department of Health and Kinesiology at Texas A&M University. Elfego is a registered dietitian who completed his M.S. at the State University of New York at Buffalo and his undergraduate studies at Baylor University. His research interests lie in the area of nutrition and exercise intervention and the effect they have on mechanisms regulating skeletal muscle physiology, weight loss, and human performance. If all goes as planned, Elfego plans to pursue a post-doctoral fellowship in the field of muscle physiology

Chapter 5:
Essential and Nonessential Micronutrients and Sport
Monica C. Serra and Kristen M. Beavers

Monica C. Serra, PhD, RD, ATC, is an Assistant Professor at the University of Maryland School of Medicine in the Division of Gerontology and Geriatric Medicine and a Supervisory Research Health Scientist at the Baltimore VA Medical Center in the Geriatric Research Education and Clinical Center. She received her BS from Duquesne University in Athletic Training; her MS in Nutrition from Case Western Reserve University; and her PhD from Baylor University in Exercise, Nutrition, and Preventative Health. She is a Registered Dietitian and Certified Athletic Trainer. Her research focuses on the loss of functional independence and cardiovascular disease risk in older chronically disabled adults and the effects of nutritional and exercise rehabilitation in these populations.

Kristen M. Beavers, PhD, RD, is an Assistant Professor in the Department of Health and Exercise Science at Wake Forest University with an adjunct appointment in the Section on Gerontology and Geriatric Medicine at Wake Forest School of Medicine. She received her BS from Cornell University in Human Biology, Health and Society; MPH from The University of North Carolina at Chapel Hill in Nutrition; and PhD from Baylor University in Exercise, Nutrition, and Preventive Health. She is a Registered Dietitian and certified by the American College of Sports Medicine as a personal trainer. Dr. Beavers' academic and professional interests lie in the study of nutrition and exercise as interdisciplinary sciences, specifically as they relate to prevention and etiology of chronic disease and disability. Her current research focuses on the identification of optimal weight loss therapies for overweight and obese, older adults.

Chapter 6:
Fluid Balance and Hydration for Human Performance
Neil M. Johannsen and Conrad P. Earnest

Neil M. Johannsen, PhD, is an Assistant Professor in the School of Kinesiology at Louisiana State University in Baton Rouge, LA. In addition, Dr. Johannsen is an Adjunct Assistant Professor at Pennington Biomedical Research Center in Baton Rouge. In 1998, he graduated from South Dakota State University with a Bachelor of Science in Chemistry. His graduate training was conducted at Iowa State University where he obtained a Ph.D. within the Department of Health and Human Performance in 2007 with a focus on the Biologic Basis of Exercise, in particular, exercise metabolism and physiologic responses to fluid intake during exercise. During his time at Iowa State University, he was awarded the Future Faculty Fellowship Award for demonstrating outstanding scholarship and promise for becoming a faculty member in higher education. His research focus at Pennington is the study of physical activity and exercise training effects on chronic disease and special populations and has played an integral role in more than 10 research studies involving populations ranging from young lean adults to older adults, overweight/obese people, individuals with type 2 diabetes, and women with a history of breast cancer. Recently, Dr. Johannsen was awarded the Robert and Patricia Hines Endowed Professorship at LSU and received the College of Human Sciences and Education Early Career Award and the LSU Alumni Association Rising Faculty Award.

Conrad P. Earnest, PhD, FACSM, in Exercise Physiology, has published over 140 journal articles including notable journals such as JAMA, JAMAArchives, Lancet Oncology, Diabetes Care, and numerous sport/exercise related journals. Dr. Earnest takes an integrative approach to health, nutrition, and athletic performance by looking at various ways to bridge gaps between sport performance and disease states. He is also one of the most frequently published authors examining professional cyclists competing in the Grand tours of Cycling (Tour de France, Giro d'Italia and Vuelta a Espana). Dr. Earnest is the current Director of Research for Nutrabolt International which holds a parttime graduate faculty appointment at Texas A&M University and was formerly a professor at The University of Bath, and associate professor at Pennington Biomedical, and VP of Research at The Cooper Institute.

Part III. Specialized Nutritional Strategies & Supplements
Chapter 7:
Building Muscle Mass: Physiology, Nutrition, and Supplementation
Kyle Levers and Kelley Vargo

Kyle Levers, PhD, CSCS, is currently an Exercise Physiology Doctoral Research Assistant in the Exercise and Sport Nutrition Laboratory as part of the Department of Health and Kinesiology at Texas A&M University. Mr. Levers received his B.A. in both Exercise Science and Chemistry from McDaniel College and his M.S. in Exercise Science with a concentration in Strength and Conditioning from George Washington University. He is a Certified Strength and Conditioning Specialist (CSCS) through the National Strength and Conditioning Association (NSCA) and continues to consult as a sports performance coach. His current research focuses on the effects of recovery modalities and supplementation interventions on the physiological adaptations and biochemical mechanisms regulating skeletal muscle protein degradation and hypertrophy, blood flow, inflammation, soreness, and performance in subsequent bouts of exercise. His other research interests include effects of proper performance and recovery supplementation on hydration and electrolyte status in addition to skeletal muscle hypertrophy in power, sprint, endurance, and concurrent training athletes. Additionally, Mr. Levers is focused on analyzing the physiological, biomechanical, and biochemical effects of active and under-loaded recovery, in addition to water temperature and subfreezing temperatures on markers of muscle damage, muscle hypertrophy, blood flow, and performance in subsequent bouts of exercise.

Kelley Vargo, MS, MPH, CSCS, CISSN, earned her B.S. Health and Exercise Science from Wake Forest University. She earned her graduate degrees from The Milken Institute School of Public Health at The George Washington University, an MS in Exercise Science with a concentration in Strength and Conditioning, and an MPH in Communication and Marketing. Ms. Vargo is a certified Health Coach through the American Council on Exercise and member of the Delta Omega Public Health Honors Society. She has contributed content to Discovery Health as well as the ACE Fitness Journal. She contributes content for the American Council on Exercise and serves as an adjunct instructor at The George Washington University Exercise and Nutrition Sciences Department. Ms. Vargo independently consults for both personal and group training, health coaching, and speaking engagements.

Chapter 8:
Weight Loss Nutritional Supplements
Joan M. Eckerson

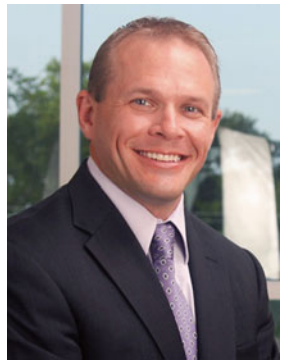
Joan M. Eckerson, PhD, CSCS, FNSCA, FACSM, is Professor in the Department of Exercise Science and Pre-Health Professions at Creighton University. She has over 50 publications in the area of body composition and dietary supplementation and currently serves on the editorial board for the Journal of Strength and Conditioning Research and the Journal of the International Society of Sports Nutrition.

Chapter 9:
Effective Nutritional Supplement Combinations
Matthew B. Cooke and Paul J. Cribb

Matthew B. Cooke, BSc (Hons), PhD, received his Bachelor of Science (Biomedical Sciences) with honors and his Ph.D. in Exercise Science from Victoria University in Australia. Dr. Cooke then completed a Post-Doctoral Fellowship and Assistant Professorship at Baylor University from 2006 to 2009. In 2010, Dr. Cooke completed a Post-Doctoral fellowship in Clinical Exercise Physiology in the School of Medicine at the University of Queensland. Dr. Cooke is currently a Senior Lecturer and Deputy leader of the Biomedical and Lifestyle Disease (BioLED) Unit within the College of Health and Biomedicine at Victoria University in Melbourne, Australia. His areas of research interests include: Resistance training and nutritional interventions on the physiological, biochemical, and molecular mechanisms regulating skeletal muscle atrophy (sarcopenia) associated with aging. Nutritional supplementation and/or varied training regimes to manipulate muscle bioenergetics in aged and diseased populations. Exercise training and nutritional interventions on weight loss, weight maintenance, and metabolism in aged and diseased populations.

Paul J. Cribb, PhD, CSCS, FATES His self-designed Ph.D. program focused on nutrient timing, and the results have been published in top peer-reviewed journals and magazines. For his contributions to the exercise sciences, Dr. Cribb has been recognized as one of Australia's leading researchers. Dr. Cribb serves on the Advisory Board for the ISSN and is the creator of Metabolic Precision, mp-body.com—the first ever science-based, nationally accredited body transformation program.

Chapter 10:
Nutritional Supplements for Strength and Power Athletes
Colin Wilborn



Colin Wilborn, PhD, CSCS, ATC, is currently Dean of the Graduate School and Research, an Associate Professor of Physical Therapy and Director of the Human Performance Lab at the University of Mary Hardin-Baylor. He has a BS in Exercise Science from the University of Mary Hardin-Baylor and a MSEd and PhD in Exercise Physiology and Nutrition from Baylor University. Colin has published numerous peer-reviewed articles, abstracts, and book chapters on the effects of sport supplements and exercise on body composition, metabolism, and performance. Colin's professional and personal interests are the effects resistance training and sport nutrition on health, body composition, and performance. Colin is a Fellow of the International Society of Sports Nutrition.

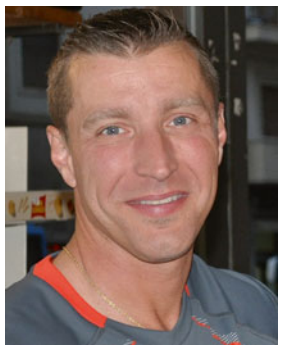
Chapter 11:
Nutritional Supplements for Endurance Athletes
Conrad P. Earnest and Christopher Rasmussen

Conrad P. Earnest, PhD, FACSM, in Exercise Physiology, has published over 140 journal articles including notable journals such as JAMA, JAMAArchives, Lancet Oncology, Diabetes Care, and numerous sport/exercise related journals. Dr. Earnest takes an integrative approach to health, nutrition, and athletic performance by looking at various ways to bridge gaps between sport performance and disease states. He is also one of the most frequently published authors examining professional cyclists competing in the Grand tours of

Cycling (Tour de France, Giro d'Italia and Vuelta a Espana). Dr. Earnest is the current Director of Research for Nutrabolt International which holds a parttime graduate faculty appointment at Texas A&M University and was formerly a professor at The University of Bath, and associate professor at Pennington Biomedical, and VP of Research at The Cooper Institute.

Christopher Rasmussen, MS, CSCS, currently serves as a Research Associate in the Exercise and Sport Nutrition Laboratory (ESNL) within the Department of Health and Kinesiology (HLKN) at Texas A&M University in College Station, TX. He received Bachelor's degree from Kansas University in Lawrence, KS, in 1997 and Master's degree from the University of Memphis in Memphis, TN, in 2000. Chris has over 15 years' experience conducting human clinical trials in the exercise and nutrition arena. I have three beautiful and wonderful women in my life, my wife Heather and daughters Katherine and Kelsie. My hobbies include spending time with family, running, and striving to maintain a healthy lifestyle.

Chapter 12:
Nutritional Supplements to Enhance Recovery
Tim N. Ziegenfuss, Jamie Landis, Darryn Willoughby, and Mike Greenwood



Tim N. Ziegenfuss, PhD, CSCS, FISSN, is the Chief Executive Officer of The Center for Applied Health Sciences. Dr. Ziegenfuss is a Past President and Fellow of the International Society of Sports Nutrition, a Certified Strength and Conditioning Specialist, and a consultant to several professional sports teams in Europe (soccer) and the United States (American football). In addition to his outreach program with athletes, he is active in clinical/academic research (600 articles in mainstream magazines, 40 scientific papers, 5 book chapters) and new product formulation with select sports nutrition companies.

Jamie Landis, MD, PhD, CSCS, received a B.S. in Biology from Ferris State University, followed by an M.S. in Endocrine Physiology, and a Ph.D. in Neuroscience, both from Bowling Green State University. His M.D. was earned at the University of Toledo, followed by an internship in medicine at Michigan State University, and a residency appointment in Physical Medicine and Rehabilitation at the Mayo Clinic. He holds several awards for teaching excellence and has been named a Distinguished Professor of Biology at Lakeland Community College.

Darryn Willoughby, PhD, FACSM, FISSN, FACN, CSCS, CISSN, holds B.S. and M.S. degrees in Exercise Science from Tarleton State University and a Ph.D. in Neuromuscular Physiology and Biochemistry with sub-emphases in Nutritional Biochemistry and Molecular Biology from Texas A&M University. He is a Fellow of the American College of Sports Medicine, International Society of Sport Nutrition, and American College of Nutrition. He is a Certified Strength and Conditioning Specialist through the National Strength and Conditioning Association and a Certified Sports Nutritionist through the ISSN. He is also a Past-President of the ISSN. Dr. Willoughby is presently an Associate Professor of Exercise and Nutritional Biochemistry and Molecular Physiology at Baylor University in Waco, TX.

Mike Greenwood, PhD, FISSN, FNSCA, FACSM, RSCC *D, CSCS *D, is currently a Full Clinical Professor in the Department of Health and Kinesiology at Texas A&M University. In addition to a variety of teaching and research responsibilities, Mike serves as a Research Associate for the Exercise and Sport Nutrition Laboratory located at Research Park in College Station. Over the past 30 years, Mike has served as a Departmental Graduate Director, Graduate Academic Director for Strength and Conditioning, Graduate Research Coordinator, as well as the Ph.D. Director primarily involved with the Institute for Exercise, Nutrition and Preventive Health. Mike is a Fellow of the International Society of Sport Nutrition (ISSN), National Strength and Conditioning Association (NSCA), and American College of Sport Medicine (ACSM). Dr. Greenwood is certified as strength and conditioning specialist recognized with distinction by the NSCA and has previously served as a NCAA collegiate baseball/basketball coach as well as a collegiate strength training/conditioning professional. Mike is the NSCA

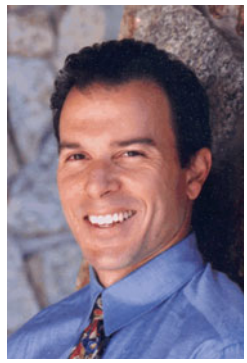
Texas State Director and currently serves on the Advisory Board of ISSN and on the NSCA Certification and Research Committees. His primary lines of research are in the areas of sport/exercise nutrition and strength and conditioning. Dr. Greenwood serves on the Editorial Boards of the Strength and Conditioning Journal, Journal of the International Society of Sports Nutrition, and has reviewed manuscripts for Medicine and Science in Sports and Exercise as well as The Journal of Strength and Conditioning Research. In 2003, Mike received the Educator of The Year Award from the National Strength and Conditioning Association and in 2005 honored as the Sunshine State Conference Baseball Coach of The Year.

Chapter 13:
Nutrient Timing
Chad M. Kerksick and Nathan H. Cole

Chad M. Kerksick, PhD, CSCS *D, ATC, currently works as an Assistant Professor in the Exercise Science Department and also serves as the Graduate Program Director in the School of Sport, Recreation and Exercise Sciences at Lindenwood University in St. Charles, MO. In addition to this appointment, Dr. Kerksick serves on the Executive Council for the Nutrition, Metabolism and Body Composition Special Interest Group and as a member of the Scholarship Review Committee for the National Strength and Conditioning Association Foundation. He received his Ph.D. in Exercise, Nutrition, and Preventive Health from Baylor University and is currently certified with distinction as a strength and conditioning specialist (CSCS*D) and certified personal trainer (NSCA-CPT*D) by the National Strength and Conditioning Association and as an athletic trainer (ATC) by the National Athletic Trainers Association. He is recognized as a Fellow of the American College of Sports Medicine and International Society of Sports Nutrition and received his Master's degree at the University of Memphis and Bachelor's degree at Truman State University. Dr. Kerksick's research continues to focus on studying the impact of exercise and nutrition on numerous aspects of health and performance, and from this work he has published over 60 articles in peer-reviewed scientific journals, given over 100 research presentations, authored multiple chapters, and edited a recent book on nutrient timing.

Nathan H. Cole, BS, has received his Bachelor's degree in Exercise Science from the University of New Mexico and is currently a Master's student studying Exercise Physiology in the Health, Exercise and Sport Sciences department at the University of New Mexico. He has previously presented his research at the Southwest Chapter of the American College of Sports Medicine regional meeting and is currently a member of the National Strength and Conditioning Association. His research interests revolve around human health and performance, particularly the biochemical, nutritional, and endocrinological factors governing skeletal muscle action and adaptation.

Chapter 14:
Carbohydrate Utilization and Disposal in Strength/Power Training and Sports: Examining the Underexamined
Anthony L. Almada and David Barr



Anthony L. Almada, MSc, FISSN, started his career in the natural products industry in 1975, working in retail nutrition stores. He has a B.Sc. in Physiology (Cal State U, Long Beach) and performed his Master's thesis research in Nutritional/Exercise Biochemistry at UC Berkeley. In 1990 he created the "thermogenic" category of dietary supplements. In 1992 he cofounded EAS, which pioneered creatine monohydrate and evidence-based sport nutrition in most of the world, and was the first company to introduce Vitargo® outside of Scandinavia (in 1997). He has collaborated on over 50 university-based clinical trials (nutrition intervention, in health and disease) and is a coauthor on over 30 peer-reviewed scientific journal articles. He is a frequently sought out nutrition business, science, and intellectual property expert, having been quoted in the New York Times, Business Week, and Forbes. He is on the editorial board of several scientific journals and is a member of the editorial advisory board of Nutrition Business Journal. He is a cofounder and Fellow of the International Society of Sports Nutrition (ISSN). He is the Founder and CEO of Vitargo Global Sciences, LLC.

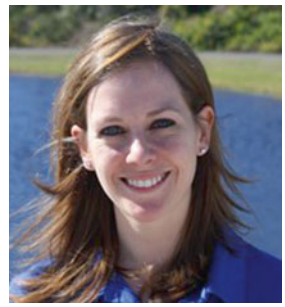
David Barr, BSc, CSCS, CISSN His research experience includes work for NASA at the Johnson Space Center, as well as clinical research on the effect of amino acid intake on muscle growth. He has interviewed more than 100 key influencers throughout strength and conditioning, personal training, and sports nutrition. He is a registered Strength and Conditioning Coach with the NSCA and holds certifications through the ISSN, Precision Nutrition, USA Track and Field, and USA Weightlifting**.**

Chapter 15:
Exercise for Athletes with Diabetes
Anupam Ohri, Stephen H. Schneider, Stephanie Wilson, and Gabe Wilson

Anupam Ohri, MD, is currently working as a Clinical Assistant Professor at Rutgers Robert Wood Johnson University Hospital. Anupam trained for her fellowship in Endocrinology from State University of New York at Buffalo. She completed her residency in Internal medicine at Jersey Shore University Medical Center in New Jersey. She also received residency training in Pathology in India. She is a member of American Association of Clinical endocrinologists. She has published peer r-viewed articles in several medical journals. She has keen interest in areas of research in exercise, nutrition, and Diabetes.

Stephen H. Schneider, MD, was a graduate of Boston University Medical School were he served on the faculty for a number of years. He is currently a Professor of Medicine at the Rutgers-Robert Wood Johnson Medical School in New Brunswick New Jersey in the Division of Endocrinology, Metabolism, and Nutrition. He was one of the founders of the council on exercise for the American Diabetes Association and has twice served as Chairman. During that time he contributed to the exercise recommendations of the ADA and edited and contributed to ADA publications for the use of exercise in diabetes. He has served as president of the New York Metropolitan chapter of the American College of Sports Medicine and as a board member of the Diabetes Exercise and Sports Association. In 2011, Dr. Schneider was awarded the lifetime achievement award of the New Jersey Diabetes Foundation in part for his early work on exercise and the metabolic syndrome. Dr. Schneider has published numerous articles and chapters on the

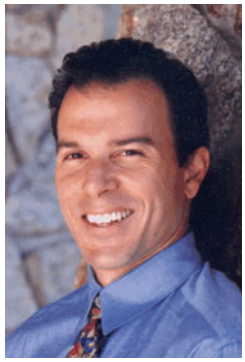
use of exercise in the treatment and prevention of diabetes and continues his interest in the application of exercise and diet for that patient population as a clinician and participant in multicenter studies. He maintains an active teaching and clinical practice for patients with diabetes and other endocrine disorders at the Rutgers Medical School.



Stephanie Wilson, MS, RD, LD, is the Head of Nutrition at IMG Academy in Bradenton, Florida, where she oversees the development and implementation of researched-based sport nutrition programs for over 900 student-athletes and over 200 professional athletes yearly, including dozens of gold medal recipients. Originally from St. Louis, Stephanie graduated summa cum laude from Saint Louis University with her Bachelor of Science degrees in Nutrition/Dietetics and Spanish. Stephanie holds a Master of Science degree in Nutrition with Sports Nutrition emphasis and a minor in Applied Physiology and Kinesiology from the University of Florida. Currently, Stephanie is a Ph.D. Candidate at Grand Canyon University, where she is pursuing a degree in psychology: cognition and instruction for athletes. Stephanie has published in multiple high-impact, peer-reviewed journals and coauthored book chapters. Stephanie's excellence has been recognized on multiple occasions, having been a recipient of the American Dietetic Association (ADA) Undergraduate of the Year Award (2007), St. Louis University Doisy College Undergraduate of the Year award (2007), Missouri Dietetic Student of the Year (2007), ADA Intern of the Year Award (2009), the Florida Dietetic Association Intern of the Year Award (2009), and the William and Agnes Brown Research Scholar Award (2009).

Gabriel Wilson, PhD, is the Head of Science and Innovation at Maximum Human Performance (MHP) in West Caldwell, New Jersey, where he has a lead role in research and product development, innovation, and ideation. Gabriel is originally from Richmond, California, where he pursued a bachelors and master's degree in Kinesiology from Cal State University East Bay. Gabriel has a Ph.D. in nutritional sciences from the University of Illinois and has extensive research experience in the area of protein and amino acid metabolism and nutritional supplementation, and their impact on health and athletic performance. Dr. Wilson has published over 50 peer-reviewed papers, manuscripts, and book chapters, and spoken at several scientific conferences including the ISSN and Experimental Biology. Gabriel also has extensive experience in the sports nutrition field, having served as a Nutrition Coach at IMG Academy in Bradenton Florida, and having consulted numerous institutes and nutritional companies including Saint Mary's College Nutrition program, Post Foods, and Champion Nutrition.

Part IV. Present and Future Directions of Nutritional Supplements
Chapter 16:
Beyond the Obvious: Future Innovations in Sports Nutrition
Anthony L. Almada



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Part I

The Industrial Nature of the Supplement Game

Effect of Government Regulation on the Evolution of Sports Nutrition

1

Rick Collins and Douglas S. Kalman

Abstract

The sports nutrition segment of the dietary supplement industry enjoyed over a decade of unfettered growth under federal legislation passed in 1994. A series of breakthroughs in the dietary supplement field led to the development and marketing of innovative products designed to enhance performance, build muscle, or lose excess fat. As the popularity of these products soared and evolved into a multibillion dollar industry, the sports nutrition supplement market drew the attention of federal and state regulatory bodies and sports anti-doping authorities. Growing concerns over potential consumer health risks, banned substance contamination, and unfair athletic advantages have spurred government regulators and legislators to heighten the scrutiny of this market in recent years, leading to legislative amendments and increased government enforcement action.

Keywords

Dietary Supplement Health and Education Act of 1994 • Food and Drug Administration • Dietary supplements • FTC • Nutrition

1.1 Dietary Supplement Health and Education Act of 1994

The Dietary Supplement Health and Education Act of 1994 (DSHEA) was passed with the unanimous consent of Congress. This statute was enacted amid claims that the Food and Drug Administration (FDA) was distorting the then-existing provisions of the Food, Drug, and Cosmetic Act (FDCA) [1] to try improperly to deprive the public of safe and popular dietary

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supplement products. The FDA was perceived as engaging in anti-supplement policy and enforcement tactics, provoking a groundswell of legislative criticism. In its official report about the need for DSHEA to curtail excessive regulation of dietary supplements by the FDA, the Senate Committee on Labor and Human Resources charged that the "FDA has been distorting the law in its actions to try to prevent the marketing of safe dietary supplement substances" [2]. The Senate Committee also concluded that the "FDA has attempted to twist the statute (i.e., the provisions of the FDCA, as it then existed) in what the Committee sees as a result-oriented effort to impede the manufacture and sale of dietary supplements" [3].

DSHEA represented a sharp rebuke to the FDA's regulatory tactics of the time. However, although DSHEA defined "dietary supplements" and "dietary ingredients," set certain criteria for "new dietary ingredients," and prevented FDA from overreaching, it did not, as some critics have charged, leave the industry unregulated. The dietary supplement industry is in fact regulated by the FDA as a result of DSHEA. The Center for Food Safety and Applied Nutrition (CFSAN), a branch of the FDA, along with the Office of Dietary Supplements (ODS) assists the FDA in the regulation of dietary supplements. This power ensures the FDA's authority to provide legitimate protections for the public health. The Federal Trade Commission (FTC) also continues to have jurisdiction over the claims (marketing, from implied to direct claims) that manufacturers make about their products. The FDA and FTC work together to regulate the dietary supplement industry. There is increased sharing of information and overlapping of jurisdiction with regard to marketing and advertising of dietary supplements.

DSHEA regulates dietary supplements more like conventional foods than like drugs. Why? The reasoning is that the ingredients in supplements are inherently safe because they are contained in the foods that humans eat. Unlike drugs, dietary supplements do not require pre-approval from the FDA. Dietary supplements, unlike drugs, cannot be marketed to treat or cure diseases. Accordingly, dietary supplements with claims on the labeling that promote treatment, prevention, or cure for a specific disease or condition would be considered an unapproved—and thus illegal—drug.

1.2 Government Protections from Dietary Supplement Hazards and Risks

How is the FDA authorized to protect the public in the realm of dietary supplements? What if evidence showed that a particular supplement product was causing an acute epidemic of illnesses and fatalities? What could the FDA do about it? The FDA is an Operating Division of the US Department of Health and Human Services (HHS), which is headed by the Secretary of HHS. The Secretary has the power to declare a dangerous supplement to be an "imminent hazard" to public health or safety and immediately suspend sales of the product [4].

The FDA also has the authority to protect consumers from dietary supplements that *do not* present an imminent hazard to the public but *do* present certain *risks* of illness or injury to consumers. The FDCA prohibits introducing *adulterated* products into interstate commerce [5]. Two important provisions exist by which unsafe dietary supplements can be deemed to be adulterated [6].

The first provision, which applies to all dietary supplements, states that a supplement shall be deemed adulterated if it presents "a significant or unreasonable risk of illness or injury under … conditions of use recommended or suggested in labeling, or … if no conditions of use are suggested or recommended in the labeling, under ordinary conditions of use" [7]. The standard does not require proof that consumers have *actually* been harmed or even that a product will harm anyone. It was under this provision that the FDA concluded that dietary supplements containing ephedra presented an unreasonable risk. The criminal penalties for a first conviction of introducing adulterated supplement products into interstate commerce can include a fine of up to

$1,000, imprisonment for up to 1 year, or both [8]. Subsequent convictions, or convictions for offenses committed with the intent to defraud or mislead, can include fines of up to $10,000, imprisonment of up to 3 years, or both [9].

The second provision by which supplements may be deemed adulterated addresses only dietary supplements containing "new dietary ingredients" for which the FDA believes there may be inadequate information to provide a reasonable assurance that the ingredient does not present a significant risk of illness or injury.

1.3 New Dietary Ingredients

Recognizing that new and untested dietary supplement products may pose unknown health issues, DSHEA distinguishes between products containing dietary ingredients that were already on the market and products containing new dietary ingredients that were not marketed prior to the enactment of the law [10]. A "new dietary ingredient" (NDI) is defined as a dietary ingredient that was not marketed in the United States before October 15, 1994 [11]. DSHEA grants the FDA greater control over supplements containing new dietary ingredients. A new dietary ingredient is deemed adulterated and subject to FDA enforcement sanctions unless it meets one of the two exemption criteria: either (1) the supplement in question contains "only dietary ingredients which have been present in the food supply as an article used for food in a form in which the food has not been chemically altered," or (2) there is a "history of use or other evidence of safety" provided by the manufacturer or distributor to the FDA at least 75 days before introducing the product into interstate commerce [12]. The first criterion is silent as to how and by whom presence in the food supply as food articles without chemical alteration is to be established. The second criterion—applicable only to new dietary ingredients that have not been present in the food supply—requires manufacturers and distributors of the product to take certain actions. Those actions include submitting, at least 75 days before the product is introduced into interstate commerce, information that is the basis on which a product containing the new dietary ingredient is "reasonably be expected to be safe" [13]. That information would include (1) the name of the new dietary ingredient and, if it is an herb or botanical, the Latin binomial name and (2) a description of the dietary supplement that contains the new dietary ingredient, including (a) the level of the new dietary ingredient in the product; (b) conditions of use of the product stated in the labeling or, if no conditions of use are stated, the ordinary conditions of use; and (c) a history of use or other evidence of safety establishing that the dietary ingredient, when used under the conditions recommended or suggested in the labeling of the dietary supplement, is reasonably expected to be safe. For most of DSHEA's existence, there was no guidance as to what evidence might be required to establish a reasonable expectation of safety. In fact, the FDA specifically stated that the person submitting the application is responsible for determining what information provides the basis for the conclusion that the product is reasonably expected to be safe. The only hint given was that the FDA expects the applicant to "consider the evidence of safety found in the scientific literature, including an examination of adverse effects associated with the use of the substance" [14].

In July 2011, the FDA released a Draft Guidance for Industry, entitled "Dietary Supplements: New Dietary Ingredient Notifications and Related Issues" [15]. While a guidance does not carry the authority or the enforceability of a law or regulation, the FDA's NDI draft guidance represented the agency's current thinking on the topic:

> The purpose of this guidance is to give manufacturers and distributors of these products information and recommendations to help them decide when a NDI notification is necessary and to improve the quality and quantity of NDI notifications. There are an estimated 55,600 dietary supplement products on the market, and FDA has received approximately 700 NDI notifications since we began reviewing NDI notifications approximately 16 years ago. Additionally, the Institute of Medicine has estimated that 1,000 new dietary supplements are introduced to the market each year These figures, coupled with recent concern by both the agency and industry regarding the

> presence of undeclared active ingredients in products marketed as dietary supplements, highlight the necessity for marketers of dietary supplements to submit NDI notifications as an important preventive control to ensure that the consumer is not exposed to potential unnecessary public health risks in the form of new ingredients with unknown safety profiles. [16]

The controversial draft guidance was met by staunch criticism from the supplement industry. Senators Orrin Hatch (R-UT) and Tom Harkin (D-Iowa), who were the principal authors of DSHEA, asked the FDA Commissioner to withdraw the guidance and replace it with a new draft that "will provide needed clarification on what constitutes an NDI, but does not undermine the balance Congress struck in DSHEA to provide consumers with access to safe, affordable dietary supplement products" [17]. Other members of Congress and various industry trade groups have asked the FDA to clarify its positions, including the subject of identity information for NDI notifications. Other questions surround whether NDI notifications should be submitted when a firm changes its manufacturing process or the ratio of ingredients and what would cause an ingredient to be "chemically altered." Given the many uncertainties surrounding the draft guidance, the FDA eventually agreed (after initially refusing) to withdraw the document. As of this writing, the FDA has not issued further NDI guidance documents.

1.4 New Dietary Ingredient Review: Application Process

If a supplement manufacturer seeks to market an ingredient to the public that was not previously sold on the US market (prior to October 15, 1994), a dossier of animal and human safety data and/or proof of historical use as a food must be compiled. Unless the ingredient has been present in the food supply as an article used for food in a form in which the food has not been chemically altered, the history of use or other evidence of safety must be presented to the FDA/CFSAN at least 75 days before introducing the product into interstate commerce. What sort of information should be presented? By what process would the FDA evaluate the data to determine if the ingredient should be allowed on the market? Let us take an example.

Excluding discussions of whether animal safety studies have utility as related to efficacy outcome-oriented research in humans, let us assume that the product of interest was found to be of acceptable safety margins when used in human doses. This means that the animal studies found the ingredient to be noncarcinogenic, to have a high LD_{50} (median lethal dose), and not to be organotoxic. In addition, let us assume that the human studies also found the product not to have an effect on blood pressure or heart rate or on markers of safety as denoted by specific blood tests (e.g., liver, kidney). Based on the compilation of animal and brief human studies, we can believe that the product is nontoxic, although further and more invasive safety data are warranted.

For example, the dietary supplement popularly known as 7-Keto®, also known as 3-acetyl-7-oxo dehydroepiandrosterone, was "approved" by the FDA via the NDI premarket notification process. Prior to marketing 7-Keto as a dietary supplement, it was submitted for a review of safety to the FDA in the form of an NDI premarket notification. This document, which can be viewed at the FDA website, received no comments or concerns expressed from the FDA. Subsequent to this initial filing, another NDI premarket notification has been filed specific to the use of 7-Keto for weight loss in adults at the prescribed dosage. This notification also has received no comments or concerns expressed from the FDA.

The FDA has a searchable database of submitted NDIs that the public can view, located online [18]. In addition to 7-Keto, other popular dietary supplements (e.g., creatine ethyl ester, vinpocetine, Diosmin 95) have successfully undergone the NDI process. Some applications to the FDA fail to meet the bar of demonstrating relative safety, usefulness, and other criteria requested by the FDA in the application, and thus the rejection or failure rate for NDI applications is thought to be about 65–70 % of the applications submitted.

1.5 FDA Regulatory Action: Ephedra Supplements and DMAA

In February 2004, the FDA issued a final rule prohibiting the sale of dietary supplements containing ephedrine alkaloids, reasoning that this category of supplements presented an unreasonable risk of illness or injury (based on a risk-to-benefit evaluation) [19]. The rule took effect on April 12, 2004, 60 days from the date of publication, at which time companies that continued to sell supplements containing ephedra alkaloids found themselves subject to a variety of enforcement possibilities, including seizure of the product, injunction against the manufacturers and distributors of such products, and criminal prosecution of violators. Three months after the rule was announced, Utah-based Nutraceutical Corp. filed suit challenging the ban, specifically the FDA's risk-to-benefit analysis, arguing that the FDA had not shown ephedra supplements to present an undue risk at low doses.

In April 2005, a federal court in Salt Lake City (US District Court for the District of Utah, Central Division) issued its decision on a legal challenge to the FDA's 2004 Final Rule banning all ephedrine-alkaloid dietary supplements. Judge Tena Campbell's decision made two key points:

- It held that the analysis used by the FDA was incorrect and improper. The FDA's analysis weighed risks against benefits. DSHEA, however, requires a straightforward *risk* assessment. The court held that requiring supplement companies to demonstrate a benefit as a precondition to marketing violated DSHEA by shifting the burden from the FDA to industry.
- It held that the FDA did not have adequate scientific evidence to find that a daily dose of 10 mg or less of ephedrine alkaloids presented a "significant or unreasonable risk of illness or injury" [under 21 U.S.C. § 342(f)(1)(A)]. The court effectively held that it is improper to ban all ephedra supplements because the FDA lacks data to determine what dosage might be safe.

The FDA filed a notice of appeal in the 10th Circuit Court of Appeals.

On August 17, 2006, the US Circuit Court of Appeals in Denver reversed and remanded the Utah ruling that challenged the FDA ban on products containing ephedra. The federal appeals court overturned Judge Campbell's decision, ruling that the FDA was correct in its 2004 analysis of ephedrine products, concluding that the FDA had properly examined the facts when it ruled, in 2004, that dietary supplements containing ephedrine alkaloids present an "unreasonable risk of illness or injury" and that there is no acceptable dose of the ingredient. Pursuant to this, the government has since seized numerous products containing the herbal ingredient.

Further appeals/petitions were filed by Nutraceutical, followed by a petition for a writ of certiorari to the US Supreme Court. The US Supreme Court denied Nutraceutical's petition for certiorari on May 14, 2007, refusing to consider their appeal, establishing a precedent for the applicable legal standards, and confirming the FDA's regulatory authority over the issues.

In 2012, the FDA again targeted a fat-loss ingredient. This time, it was a stimulant called DMAA, also known as 1,3-dimethylamylamine, methylhexanamine, or geranium extract. Citing evidence that DMAA, especially in combination with other ingredients such as caffeine, can pose health risks to consumers, FDA issued warning letters to companies notifying them that DMAA products were adulterated and needed to be taken off the market [20]. One company resisted, defending its marketing of the substance as legal, until FDA took administrative detention actions. In July 2013, the remaining stock of the products, estimated to have been worth more than $8 million at the retail level, was voluntarily destroyed by the firm [21].

1.6 FDA Regulatory Actions: Androstenedione, Piracetam, and ATD

The ban on androstenedione is another example of the authority of the FDA to prohibit the marketing of ingredients the agency believes are adulterated. On March 11, 2004, the FDA pronounced that dietary supplement products

containing androstenedione were adulterated new dietary ingredients under DSHEA. For the second time in as many months, the FDA took regulatory action against the sports nutrition industry. There was no evidence of an imminent health hazard posed by androstenedione. However, instead of the formal administrative procedure of issuing a proposed rule and inviting public comment, the FDA took unilateral action, issued a press release, held a news conference, and sent warning letters to 23 companies that had manufactured, marketed, or distributed the products containing androstenedione. In its warning letters, the FDA threatened possible enforcement actions for noncompliance. The effect was to cause retailers, manufacturers, and distributors alike to cease selling products containing androstenedione. No meaningful dialogue between the FDA and industry occurred prior to the FDA taking this action.

Supplements containing androstenedione were introduced during the mid-1990s and were promoted as a natural way to help increase strength and muscle mass as well as to combat the effects of the aging process in older men, much of which is attributed to declining testosterone levels. Like dehydroepiandrosterone (DHEA), androstenedione is a naturally derived precursor to testosterone. Androstenedione converts directly to testosterone in the metabolic pathway. The fact that it is naturally derived and, as described below, present in the food supply is important in relation to the action taken by the FDA. In its press release [22] and warning letters, the FDA declared androstenedione to be an adulterated new dietary ingredient based on its position that no evidence demonstrates "that androstenedione was lawfully marketed as a dietary ingredient in the United States before October 15, 1994" [23]. It seems to be correct that androstenedione was not marketed before 1994, given that the first commercial marketing of products containing androstenedione appears to have been in 1996. Furthermore, a review of the FDA's electronic database indicates no submission of an application for a new dietary ingredient involving androstenedione [24]. Interestingly, however, the FDA went beyond the explicit words of the statute and used the term "lawfully marketed" in their letters instead of simply "marketed." The implication was that to receive "grandfathered" status into DSHEA as a pre-1994 supplement ingredient, the product must not only have been marketed but must have met the additional requirement of having been *lawfully* marketed. At least one commentator has interpreted this language to impose a burden on industry to prove the product was generally recognized as safe (GRAS) pre-1994—an impossible standard for any product that was not explicitly affirmed as such by the FDA prior to the enactment of DSHEA [25]. Assuming that androstenedione is indeed a new dietary ingredient, the FDA could determine that products containing androstenedione are adulterated under DSHEA unless they meet either of the two exemption criteria stated above.

Accordingly, it appears that the question of exemption turns on (1) whether androstenedione is present in the food supply as an article used for food without chemical alteration and (2), if not, whether the product could satisfy the requirement of reasonable expectation of safety. With respect to the first exemption, according to scientific journals, androstenedione is indeed present in the food supply without chemical alteration [26]. Had there been open communication between the FDA and industry, the scientific evidence that androstenedione is present in the foods we eat could have been presented and discussed. Moreover, until 1998, which is the date for the most recent information, there were no reports of adverse events reported on the FDA's database [27]. Adverse events comprise one of the few specific pieces of information that the FDA sets forth in their "information" about what safety data they require [28]. The FDA's requirements to show safety have never been fully articulated; arguably, the FDA's policy creates a nearly impossible procedure to demonstrate safety. Unlike the situation regarding ephedra supplements, industry did not formally challenge the FDA's regulatory action regarding androstenedione, and sales of androstenedione ceased.

The FDA's action on androstenedione marked the start of a heightened enforcement policy against what the agency deems to be adulterated new dietary ingredients. In August 2010, the FDA took actions with respect to *piracetam* and *1,4,6-etioallocholan-dione* (also known as *3,17-keto-etiochol-triene* and more commonly referred to as *ATD*). The FDA sent a letter to a dietary supplement firm indicating that the agency did not believe that piracetam and ATD are dietary ingredients, and when combined with claims that the products affect the structure or function of the body, these substances are "new drugs," not supplements [29]. Significantly, in a footnote to the letter, the FDA referenced a 2003 NDI notification filed by the firm for piracetam and a 2004 reply by CFSAN, stating FDA's position that piracetam is "not a dietary ingredient." Although the company apparently complied with the 75-day premarket NDI notification requirement, the FDA failed to respond to the company's notification within the 75-day waiting period (the response was more than 90 days after the notification had been filed). The warning letter was not issued until 6 years after the notification was filed and after the products had been discontinued.

Due to the long-after-the-fact timing of these particular enforcement actions, little substantive debate or review of the NDI regulations was generated. The FDA actions do, however, reinforce the need for clarification and guidance with respect to NDI notifications. These actions should also serve as notice to the dietary supplement industry as a whole that FDA is shifting its focus toward NDIs and that we can likely expect more enforcement actions in the near future.

If a new dietary ingredient is exempted from adulterated status because it is present in the food supply as an article used for food in a form in which the food has not been chemically altered, it is prudent for supplement companies to document that information prior to marketing the product or even to communicate that information to the FDA. If a new dietary ingredient is not exempted from adulterated status based on the food-supply exemption, premarket notification of history of use or other evidence of safety establishing that the dietary ingredient, when used under the conditions recommended or suggested in the labeling of the dietary supplement, is reasonably expected to be safe must be provided to the FDA at least 75 days before the product is introduced into interstate commerce.

1.7 Contaminated Supplements and Banned Ingredients

Research conducted by the United States Olympic Committee in 2004 found that 90 % of athletes use some form of dietary supplements. To ensure a "level playing field" and protect the health of athletes, sports bodies are free to create their own lists of banned ingredients. Athletes are generally held under a standard of "strict liability" by their respective sport bodies and are therefore held responsible for everything they put into their bodies.

Highly publicized cases, however, have shown that when athletes fail drug tests, tainted dietary supplements may be blamed, and expensive litigation may follow. Such lawsuits may seek not only compensation for the athlete's lost potential income during the ever-lengthening suspensions from athletic bodies and the tarnishing of the athlete's name in the publicity that follows a positive test but also punitive damages in the tens of millions. One of the most well-known lawsuits against a dietary supplement company involved world-class swimmer Kicker Vencill, who tested positive for the anabolic steroid nandrolone. He blamed it on contaminated dietary supplements—vitamin capsules. When he received a 2-year suspension from competition, he sued the sports nutrition company Ultimate Nutrition and received a nearly $600,000 verdict, which was later appealed. The case was later settled for an undisclosed amount with no direct admission of guilt by the manufacturer.

The National Football League (NFL) running back Mike Cloud, a Boston College graduate playing for the Patriots, tested positive for norandrostenedione and androstenediol (two nandrolone metabolites). He claimed that a tainted whey protein powder (Nitro-Tech™) caused his positive test and consequent four-game suspension,

while the supplement's Canadian manufacturer, MuscleTech, countersued, maintaining that the allegations were false and amounted to trade libel. Pavle Jovanovic, a US bobsledder, tested positive for 19-norandrosterone (also a nandrolone metabolite) in 2001. He was suspended for 2 years and disqualified from the Salt Lake City Olympics in 2002. He blamed his troubles on MuscleTech's whey protein, saying it was cross-contaminated by one of its prohormone products. Jovanovic also filed suit, and MuscleTech countersued. Both Cloud and Jovanovic submitted tests showing containers of the product contained nandrolone metabolites not listed on the label (these results were also televised nationally on Bryant Gumbel's HBO Inside Sports show).

Graydon Oliver, a tennis player, tested positive in 2003 for the prohibited substance hydrochlorothiazide, a diuretic used as a masking agent for other banned substances (used medically typically for hypertension). He blamed a purportedly homeopathic Chinese herbal sleeping aid called Relax-Aid. He filed suit on October 1, 2004, against Keimke Inc. (a.k.a. Barry's Vitamin and Herbs), a Boca Raton purveyor of food and health supplements. The Association of Tennis Professionals panel found that Oliver was aware of the ATP warnings regarding using supplements and that he failed to investigate the product as thoroughly as possible. ATP suspended Oliver for 2 months and directed him to forfeit $5,000 in prize money and championship points. Oliver had retained a sample of Relax-Aid for testing (*note*: his sample of Relax-Aid also tested positive for chlordiazepoxide, the active ingredient in Librium). Allegedly, the store owner, even after being informed that the user was a professional athlete subject to mandatory testing, told Oliver's mother who purchased the product that the dietary supplement was safe for all sports organizations as it contained no banned ingredients. Graydon brought suit alleging $15 million in damages (economic and noneconomic losses).

In 2013, Australian middleweight boxing champion Sam Soliman beat German champion Felix Sturm by unanimous decision in Dusseldorf, Germany, in a voluntary eliminator for the #1 position. Subsequently, it was revealed that Soliman's A sample from a urine test was positive for oxilofrine which is a banned stimulant on the WADA list. He was suspended for 9 months by the German authorities, although the positive finding likely resulted from a contaminated supplement product. Soliman was ultimately exonerated when his B sample was tested and retained his position as the IBF's #1 contender for the World Middleweight title. There have been cases tracking from at least 2009 of other athletes who have for some reason tested position for this stimulant [30]. Some of the athletes who have tested positive for this banned medication have also maintained that they were only taking dietary supplements and that the supplement was contaminated. These positive drug tests from potentially tainted supplements have led to greater awareness and messaging by the testing organizations to athletes and the public. As oxilofrine falls under as a regulated class of medication, it ought not to be part of any legal dietary supplement.

A 2002 International Olympic Committee (IOC) study titled "Analysis of Non-Hormonal Nutritional Supplements for Anabolic-Androgenic Steroids" done by an IOC-accredited drug testing laboratory found that 94 of the 634 (14.8 %) dietary supplement samples it studied contained substances not listed on the label that would trigger positive drug tests. The dietary supplements were from 12 countries. The dietary supplements from the United States tested positive in 45 of the 240 products tested, at a fail rate of 18.8 %. During the 2002 Salt Lake City Winter Games, athletes from the Netherlands submitted 55 supplements to be confidentially analyzed for banned substances. In total, 25 % of the supplements tested positive for prohibited substances.

When DSHEA was passed in 1994, it contained a provision requiring that FDA establish and enforce current Good Manufacturing Practices (cGMPs) for dietary supplements. However, it was not until 2007 that the cGMPs were finally approved, and not until 2010 that the cGMPs applied across the industry, to large and small companies alike. The adherence to cGMPs has helped protect against the contamination issues discussed and should serve to improve consumer

confidence in dietary supplements. We should expect an improving market, as these regulations impose new, stringent requirements such as vendor certification, document control procedures, and identity testing. These compliance criteria address the problems that have damaged the reputation of the industry with a focus on quality control, record keeping, and documentation.

However, it does appear that some within the industry continue to struggle with compliance. In 2010, it was reported that about one-third of FDA's 90 dietary supplement cGMP inspections that year revealed severe compliance problems. The most common problem was reportedly "inadequate identity testing." Undoubtedly, relying on certificates of analysis from the raw materials, supplier without further testing, or failing to conduct identity testing of a finished product, can result in the creation of a product that contains something it should not—such as synthetic chemicals or even pharmaceutical drugs. All members of the industry need to ensure compliance with cGMPs.

1.8 Anabolic Steroid Control Act

During the past decade, the use of performance-enhancing substances in sports has been in the media spotlight like never before, with publicized positive doping tests in major and minor league professional baseball, professional football, track and field, cycling, weightlifting, tennis, inline skating, boxing, soccer, swimming, softball, Paralympics, and even horse racing. Chemically induced advantages can undermine the traditional principle of a level playing field, and the abuse of these substances can lead to health risks. The war against the use of performance-enhancing substances in sports has been waged mostly on two fronts: (1) prohibition of the substances by athletic bodies that have implemented drug testing of players and (2) federal and state legislation of the substances as dangerous drugs with criminal penalties imposed on violators. Federal legislators responded to the reports of extensive use of anabolic steroids and steroid precursors among sports competitors by subjecting possessors of a plethora of steroid precursor products—openly sold in US health food stores until January 2005—to arrest and prosecution. The law, passed by Congress in 2004, was an expansion of anti-steroid legislation passed in 1990 and demonstrates the evolution of government regulation in this area.

1.8.1 Anabolic Steroid Control Act of 1990

During the mid-1980s, reports of the increasing use of anabolic steroids in organized sports, including a purported "silent epidemic" of high school steroid use, came to the attention of Congress. When Canadian sprinter Ben Johnson tested positive for the steroid stanozolol (popularly known as Winstrol) at the 1988 Seoul Olympics and was stripped of his gold medal, the ensuing media frenzy galvanized the US Congress into action. Between 1988 and 1990, Congressional hearings were held to determine whether the Controlled Substances Act should be amended to include anabolic steroids [31]. Significantly, medical professionals and representatives of regulatory agencies (including the FDA, DEA, and National Institute on Drug Abuse) testified *against* the proposed amendment to the law. Even the American Medical Association opposed it, maintaining that steroid abuse does *not* lead to the physical or psychological dependence required for scheduling under the Controlled Substances Act [32]. However, any "psychologically addictive" properties of steroids or public health dangers seemed to be secondary considerations to Congress. Most of the witnesses at the hearings were representatives from competitive athletics whose testimony, and apparently Congress's main concern, focused on the purported need for legislative action to solve an athletic "cheating" problem [33].

Congress passed the Anabolic Steroid Control Act of 1990 [34], criminalizing the possession of anabolic steroids without a valid prescription. This was accomplished by amending Title 21 of the United States Code (U.S.C.) § 812(c), which contains the initial schedules of

controlled substances [35]. Anabolic steroids were listed under subsection (e) of Schedule III. The law placed steroids in the same legal class as barbiturates, ketamine, LSD precursors, and narcotic painkillers such as Vicodin. To this day, anabolic steroids remain the only hormones in the schedules.

Once the law became effective, in 1991, mere unlawful possession of any amount of anabolic steroids, even without any intent to sell or distribute, became a federal crime [36]. A conviction is punishable by a term of imprisonment of up to 1 year and/or a minimum fine of $1,000; and prior state or federal drug convictions increase the possible sentence. Unlawful steroid distribution or possession with intent to distribute became punishable by up to 5 years in prison for a first offender or 10 years for a prior drug offender [37].

The 1990 law listed only 27 compounds, along with their salts, esters, and isomers [38]. In theory, however, there are hundreds or even thousands of anabolic steroidal compounds—many of which might enhance athletic performance—that could be created in laboratories and offered for human use. By the early part of the past decade, some of these substances were being openly marketed as performance-enhancing dietary supplements. Called "prohormones" or in some cases "prosteroids," these products were frequently metabolic precursors to testosterone or other listed anabolic steroids. Prosecution of those responsible for selling these compounds—including androstenedione, norandrostenedione, norandrostenediol, 1-testosterone, and 4-hydroxytestosterone—was hampered by the absence of these compounds from the list [39].

1.8.2 Anabolic Steroid Control Act and DASCA

Although dietary supplements have never been embraced by anti-doping agencies, prohormone supplements were of particular concern, presenting at least four problems beyond any perceived health issues. First, by their very nature and design, they defied traditional sports values: They were pills that might give the player who swallowed them a chemically induced advantage over the player who did not. Second, some of the steroid precursor products shared metabolites with banned anabolic steroids, raising the specter of false-positive tests [40]. Third, traditional drug screening might fail to detect some of the newer "designer" steroid configurations. Lastly, poor quality control at the manufacturing level presented the possibility that some dietary supplement products might inadvertently contain steroid precursors by "cross-contamination," resulting in false-positive tests for anabolic steroids [41]. Amid the searing media attention to the issue, legislators publicly cried out for broader and stiffer steroid laws. Congress drafted bills and held hearings [42]. On October 22, 2004, President Bush signed into law the Anabolic Steroid Control Act of 2004, and it took effect in January 2005 [43]. The new law expanded the original steroid law that had been passed in 1990, also providing $15 million for educational programs for children regarding the dangers of anabolic steroids and directing the US Sentencing Commission to consider revising federal guidelines to increase the penalties for steroid possession and distribution.

The law added 26 new steroid compounds to the previous list of substances that are legally defined as "anabolic steroids" and classified them as Schedule III controlled substances [44]. An exhaustive analysis of all the new compounds is beyond the scope of this chapter, but a few observations are in order. Some of these compounds were being marketed as dietary supplements, whereas others, such as bolasterone, calusterone, furazabol, and stenbolone, are actually early pharmaceutical steroids that were missed in the original federal law (note, however, that some states, among them California, did include some of these compounds in their own steroid laws). These dusty old compounds were likely added to the list after the highly publicized reemergence of norbolethone (also added to the list) in an Olympic urine sample. Listed also is tetrahydrogestrinone, or THG, the so-called designer steroid that precipitated the BALCO scandal. Mere possession of any of these products is now a basis for a person's arrest and prosecution as a federal drug criminal.

The new law also changed the general requisite elements of an anabolic steroid. Ironically, no longer is there any requirement for evidence that an anabolic steroid is "anabolic" (i.e., that it promotes muscle growth). It simply needs to be chemically and pharmacologically related to testosterone and either on the new list of substances or be any salt, ester, or ether of a substance on the list. The omission of the criterion of promoting muscle growth profoundly affects the process by which a newly created "designer" steroidal compound may be added to the list. Even under the 1990 law, the US Attorney General had the authority [45] to schedule additional or newly discovered steroidal compounds without going back to Congress for approval. However, under the old law, for a compound to qualify as an anabolic steroid, the Attorney General was required to prove that the compound had anabolic properties. Now, for administrative scheduling, the Attorney General must only establish that the compound is chemically and pharmacologically related to testosterone [46].

After a protracted battle on the issue among members of Congress, the law permits the continued sale of DHEA [47] as a dietary supplement by adding it to the other hormonal substances explicitly excluded from scheduling (estrogens, progestins, and corticosteroids). The law also fixes some of the mistakes and poor draftsmanship of the 1990 law [48].

The new law retains the "catch-all" provision of the 1990 law concerning certain variations of the listed compounds and includes specific isomers of a compound under that compound's heading [49]. However, not all prohormone products fall under the new law, nor do all conceivable anabolic steroids.

The DEA tried to remedy the problem administratively, issuing a final rule [50], effective January 2010, classifying three more compounds as anabolic steroids (boldione, desoxymethyltestosterone, and 19-nor-4,9(10)-androstadienedione, along with their salts, esters, and ethers). Then, the DEA last year published a notice of proposed rulemaking to add yet two more steroidal compounds, prostanozol and methasterone (marketed as Superdrol), along with their salts, esters, and ethers, to the list. The final rule on these two was issued on July 30, 2012 [51], effective August 29, 2012.

Recognizing the difficulties in attempting to administratively schedule new prohormones one by one, Congress has attempted to fix this problem through yet another version of the law. The "Designer Anabolic Steroid Control Act of 2014" (DASCA) was signed into law on December 18, 2014 [52]. DASCA lists 25 steroidal compounds as newly criminalized anabolic steroids. DASCA criminalizes very close relatives of explicitly listed steroids. It says that "a drug or hormonal substance (other than estrogens, progestins, corticosteroids, and dehydroepiandrosterone) that is not listed ... and is derived from, or has a chemical structure substantially similar to, 1 or more [listed] anabolic steroids [is considered an anabolic steroid] if ... [it] has been created or manufactured with the intent of [promoting muscle growth or having pharmacological effects like testosterone or] has been, or is intended to be, marketed or otherwise promoted [to suggest it will promote muscle growth or have pharmacological effects like testosterone]." In other words, derivatives and slight variations on compounds which are on the list can violate the law if they are made or if they are marketed, or intended to be marketed, to build muscle or have effects like testosterone. DASCA prohibits a compound from being a drug or hormonal substance under the law if it is "an herb or other botanical" or "a concentrate, metabolite, or extract of, or a constituent isolated directly from, an herb or other botanical" or if it is a dietary ingredient (under DSHEA) and "is not anabolic or androgenic." DASCA places the burden of proof upon anyone seeking to claim an exemption. The law also introduces a new theory by which to prosecute steroid cases by making it a crime to import, export, manufacture, distribute, dispense, sell, offer to sell, or possess with intent to manufacture or sell any anabolic steroid, or any product containing an anabolic steroid, unless it bears a label clearly identifying the anabolic steroid by accepted (IUPAC) nomenclature. This provision would apply to manufacturers who use deceptive or

"creative" ingredient labeling to conceal that the product is an anabolic steroid. It would also apply to distributors and retailers who know, intend, or have reasonable cause to believe that the product contains an anabolic steroid. The Attorney General will be able to add new "designer" compounds to the list of anabolic steroids with greater ease and speed (with only 30 days' notice for temporary scheduling).

It is important to recognize, however, that regardless of whether a steroidal substance is scheduled under the Controlled Substances Act, the marketing of these compounds as dietary ingredients is an "adulteration" or "misbranding" violation of the FDCA unless they comply with DSHEA. Numerous prosecutions have been instituted against prohormone marketers over the last 5 years, resulting in criminal convictions of both companies and, in a few cases, their principals [53].

1.9 Adverse Event Regulation and Legislation

In response to growing criticism of the dietary supplement industry, which is often inaccurately characterized by mass media and sometimes the US government as "unregulated," the 109th Congress passed the first mandatory Adverse Event Reporting (AER) legislation for the dietary supplement industry. On December 22, 2006, President Bush signed into law the Dietary Supplement and Nonprescription Drug Consumer Protection Act. This Act, which took effect on December 22, 2007, was sponsored by Senator Orrin Hatch (Utah) and cosponsored by Senators John Cornyn (Texas), Michael Enzi (Wyoming), Edward Kennedy (Massachusetts), Richard Durbin (Illinois), and Tom Harkin (Iowa). After much debate in Congress and input from the FDA, the American Medical Association (AMA), many of the major supplement trade associations, and a host of others, the group finally agreed that the legislation was necessary and the final version was approved by all. In short, the Act requires that all "serious adverse events" regarding dietary supplements be reported to the Secretary of Health and Human Services.

An adverse event, as defined in section (a)(1) of this new law, is any health-related event associated with the use of a dietary supplement that is adverse. A *serious* adverse event, as defined in section (a)(2)(A), is an adverse event that results in (i) death, (ii) a life-threatening experience, (iii) inpatient hospitalization, (iv) a persistent or significant disability or incapacity, (v) or a congenital anomaly or birth defect or (B) requires, based on reasonable medical judgment, a medical or surgical intervention to prevent an outcome described under subparagraph (A).

Once it is determined that a serious adverse event has occurred, the manufacturer, packer, or distributor of a dietary supplement whose name appears on the label of the supplement shall submit to the Secretary of Health and Human Services any report received of the serious adverse event accompanied by a copy of the label on or within the retail packaging of the dietary supplement.

This law strengthens the regulatory structure for dietary supplements and builds greater consumer confidence in this category of FDA-regulated products, thus ensuring and protecting Americans' continued access to safe, beneficial dietary supplements. Consumers have a right to expect that if they report a serious adverse event to a dietary supplement manufacturer, the FDA will be advised about it. The Council for Responsible Nutrition, Natural Products Association, American Herbal Products Association, and the Consumer Healthcare Products Association all support the AER legislation and have structured educational presentations for the dietary supplement industry in order to educate and implement programs for all companies to comply with this useful law.

1.10 Contamination or Adulteration: A Need for Better Consumer Confidence

We must ask ourselves: Can the dietary supplement/nutrition industry do anything more to enhance the image and/or quality of the products being sold? Most health professionals would emphatically state that conducting clinical trials that examine the products as they are intended to be used or as they are marketed to ensure that they deliver on their promise is well worthwhile.

The research industry intersects with many other industries in more than one way. Research is used to plan marketing, create a product, and learn more about the product. Research can be used to delineate consumer demographics within the dietary supplement industry, to define safety and efficacy, and for intellectual property means. However, a point to consider is whether there exists a responsibility on the part of a company that markets a product to research and learn the unknowns about their products. To paraphrase former US Secretary of Defense Donald Rumsfeld: Are you responsible for known-unknowns? Before we explore the potential answers, one must also wonder just who in the chain of product retailing is really responsible for the product dossier. Many companies purchase their finished products from other companies and simply relabel the products for their own marketing purposes (private labeling). Yet other companies source raw materials or sometimes branded ingredients from a supplier and then retail it as their own in the finished product. This is all perfectly legal and quite common in many industries.

To utilize a popular ingredient for the purposes of this chapter, the example of blue-green algae is examined. Blue-green algae are often skimmed or collected from surface waters. Among the most popular site in the United States for cultivating blue-green algae is the Upper Klamath Lake in southern Oregon. In 1996, the state of Oregon noted that the Upper Klamath Lake was experiencing an extensive growth of *Microcystis aeruginosa* (a type of blue-green alga) that is known to produce hepatotoxins (microcystins). A local public uproar occurred, and the local health departments decided to test the waters and blue-green algae dietary supplements (61 to be exact) for the presence of microcystins. Among the dietary supplements tested was spirulina (15 samples), which is also considered a blue-green alga and is not from the Upper Klamath Lake. The researchers established a "no-observed adverse effect level" for the presence of microcystins via animal data and guidance from Health Canada along with the World Health Organization. The "tolerable human dose" was determined to be 0.04 μg/kg/day or 2.4 total μg for a 60 kg person. Most people who use these types of supplement ingest 2 g/day; thus, the safe dose of the hepatotoxin from blue-green algae was determined to be 1.0 μg/g of product.

The results of the study were surprising (and perhaps not well distributed among the companies that sell these types of dietary supplement). In general, the average microcystin level of the blue-green algae from this lake was found to be >2.15 μg/g of product (more than double the "safe" limit). Some samples tested were from the same lot (meaning that three bottles of product were purchased from the same lot), and the variation within the same lot from bottle to bottle ranged from <30 to 99 %. This indicates that a wide variation and potential for this particular hepatotoxin exists within this class of dietary supplements harvested from this region. The spirulina dietary supplements did not contain any serious amounts of hepatotoxins.

The exposure to high levels of microcystins is known to disrupt liver function and can result in intrahepatic hemorrhage as well as hypovolemic shock; less is known about the risks of exposure to low levels of this hepatotoxin over time. In animals, chronic exposure to low doses of this hepatotoxin is correlated with tumor progression (liver cancer). The blue-green algae often harvested for dietary supplements are harvested during the bloom when microcystins in the surface water are at their maximum. Because spirulina is grown under controlled conditions, the contamination risk is less likely. Blue-green algae are harvested from the surface waters; therefore, the microcystins contained therein are known also to contain neurotoxins that are produced from cyanotoxins.

Under DSHEA, it is the marketer's responsibility to ensure the safety of the dietary supplement being retailed to the public. It appears that the most common "adverse effect" associated with blue-green algae supplements is gastrointestinal disturbance and that this side effect is sometimes interpreted by the industry to be "detoxification." There are no known cases in the FDA database of serious AERs regarding blue-green algae. Once the appearance of microcystin hepatotoxin in surface water and in blue-green

algae dietary supplements became known, some states have enacted public health measures (Vermont and Oregon).

It may be wholly possible that every company in the product distribution chain, from the original raw material supplier through the wholesalers and distributors (with the possible exception of the retail store outlet selling other companies' brands), should conduct safety studies [54, 55]. These safety studies might run the gamut from animal toxicity surveillance all the way to human safety studies. In addition, the safety dossier may include laboratory analysis for the presence of known carcinogens, adulterated medications, and other standard safety parameters. Perhaps, it is the responsibility of the raw material company and the finished goods retailer to know directly with first-hand evidence that their product is safe from known agents that can negatively affect the heart, kidneys, liver, and so on. This is where it is important for both types of company to employ the services of a firm or in-house individual to create a dossier ("Product Master File") that has direct and/or third-party peer-reviewed published science denoting the safety of the ingredient and to contract with a laboratory—either private or at a university—to do first-hand product safety studies. Companies that do all of this can feel comfortable that they have directly satisfied the safety aspects of DSHEA for their products; consumers should feel more confident as well. It is true that unknown safety issues may still be lurking; however, a company that is responsible in doing its due diligence by having a complementary file on safety compiled from third-party science and direct "owned" science is taking the steps that the public should expect members of the sports nutrition supplement industry to take.

1.11 Substantiation from the Perspective of Research

If you were set up on a blind date or better yet get involved in online dating and were told that the person who you will be meeting for drinks was six foot two and in decent physical shape and had brown hair and hazel eyes, but when you got to the club you saw no such person, would you wonder what was going on? You find the club just fine; it is located where he said it would be; the music is just as cool as you thought it would be; and then a man taps you on the shoulder, says your name ("Hi Staci, nice to meet you!"). You stare at him wondering, "Who are you?" Finally he says his name and thanks you for meeting him. He compliments your attire and perfume and notes that your drink of choice is one of his favorites as well. Still, you remember the online picture you saw of him, the details of his height, build, even the type of work that he said he did. So why does he not appear as well as he should? Why is not the real thing (the guy) *substantiating* the claims he made about himself in his online dating profile? Do you think he was fudging to hedge his bet? To perhaps increase the likelihood he could *make the sale*?

The scenario occurs not only socially but in business as well. For example, years ago you could go to a used car lot and test-drive any car there. The car would start, roar even; however, after you plunked down your money for the vehicle of your temporary dreams, the car would start to stutter and often not even start. After an almost epidemic of bad cars being sold, many states enacted laws to protect the car buyers—known as "lemon laws." The typical scenario encompasses a car being test-driven and enjoyed for its supposedly superior strength and looks that just does not pan out to have the "muscle" you expected. Simply put, the advertising was not *substantiated*. Can you think of other industries that may also need a "lemon law"?

1.12 Advertising

Imagine you read an advertisement for a dietary supplement that stated "other natural supplements appear to treat only 15 %, or one type of pain." Would you then believe that the supplement ad is implying that the particular product being promoted treats or is useful for *all* types of pain? Because a product is being directed or sold to consumers, should it not have direct research demonstrating support for its marketing claims? In the case of comparing one product versus

others for a specific effect, once a specific effect is mentioned there is a further implication that substantiation must exist. A lawyer or even a regulatory agency might say that the advertisement is playing fast and loose with the scientific record.

Another example of a common advertisement that we all see in the major periodicals and trade journals is for a product purported to "reduce stress, improve sleep quality, diminish PMS, enhance mental sharpness, and reduce negative side effects of caffeine." This product is popular; in fact, it is a branded ingredient in many products. The studies on the branded ingredient have been carried out mostly in Japan, with few having been conducted in the United States. One may wonder if studies carried out in a foreign land, on people who may have genotypes and phenotypes different from those in the typical US population, would yield the same results here. In other words, does the research *substantiate* the advertising claims that are made in the US market? The current Guidance for Substantiation released by the FDA in December 2008 addresses this very issue. In fact, the FDA indicates that foreign studies may not have equivalence for US substantiation but will be considered as part of the portfolio. This is surely something that must be a consideration for any dietary supplement company, and thus some motivation to organize a clinical trial platform is there. It is also a factor that consumers should consider when reading supplement marketing materials [56–59].

1.13 Is There Legal Precedence?

In January 2002, the FDA issued guidance regarding claims and compliance guidelines for dietary supplements. According to the Guidance for Industry Regarding Structure/Function Claims, claims can be made on or for dietary supplements if you have substantiation that the claims are truthful and not misleading. The substantiation must be in place prior to the claim being made; and, in fact, the FDA is to be notified within 30 days of first marketing the product. So although there is clear guidance regarding what constitutes a structure/function claim (for more information, see the set of 10 criteria in section 101.93(g) of Title 21 Code of Federal Regulations), it appears from the above two product advertisement examples that these laws are not being followed. Section 101.93(g) of Title 21 contains guidance regarding claims, and this section keys in on disease or symptom claims, implied claims, and much more. This is of utmost importance because the document contains clear guidance regarding what a company could say or how a company could structure the label, advertisements, and other product-supportive literature when marketing the product.

However, the lack of clarity as to what constitutes substantiation for a claim is a concern. For example, if you had one small-scale pilot open-label study on what you considered the key ingredient (the "active") in your product and the small study found efficacy of that ingredient, is this enough substantiation on which to base advertising claims? Or think about a situation in which you have a single-ingredient product, and studies on that ingredient have already been published in decent scientific journals and in the United States. Would this be considered substantiation? In this case, the answer appears to be that the substantiation of prior "third party" (borrowed science, if you will) is valid if the product that you sell has the same exact dosage and quality of the studies on which you are basing your claims. In other words, if there are five studies on "product X" and in those studies the ingredient is dosed at 250 mg three times per day but you decide to sell it at 100 mg for twice per day usage, the published science does not support your claims.

The FTC has announced its intention to be more active in policing the advertising of weight loss products. In fact, the FTC's publication *Gut Check: A Reference Guide for Media on Spotting False Weight Loss Claims* detailed the types of claims that the agency believes to be almost impossible to substantiate. The FTC was granted this power in the Federal Trade Commission Act by the simple words within the Act that note the prohibition of "unfair or deceptive acts or practices." It is clear that deceptive claims are those that are misleading or false in some way because facts are misstated or omitted or important information was not disclosed [60–62]. Even if "puffery" is used in an advertisement, it can be

considered deceptive if substantiation for the basis of the claim is not real or valid. There are many other areas that the FTC and FDA consider when evaluating if an advertisement (of any form) is valid, and these parameters should not be discarded. However, one should be cognizant of the FTC advertising and substantiation policy (known as the "substantiation doctrine") that was first enacted in 1972 and then further articulated in 1984. Within the FTC's actions, the use of the "Pfizer factors" in noting if a claim is substantiated is typically used [63]. The factors evaluating substantiation include (1) type of product, (2) type of claim, (3) the benefits of a truthful claim, (4) the cost/feasibility of developing substantiation, (5) consequences of a false claim, and (6) the amount of substantiation that experts in the field believe is reasonable. Did you know that the FTC's experts have stated that weight loss beyond 1 pound per week without dieting or exercise should be considered scientifically not feasible?

In new FTC cases, the agency appears to be attempting to redefine "competent and reliable scientific evidence" through consent decrees. In an action involving POM Wonderful in 2013, the standard suggested by FTC is two randomized, well-controlled, human clinical trials [64]. At present, this is not the law and only applies to these companies, but we may see a move toward a broader application of this standard. The FTC requires that companies identify all express and implied claims that the advertisement conveys to consumers. Once these claims are identified, the scientific evidence is assessed to determine whether there is adequate support for those claims. Companies are barred from conveying other claims beyond those expressly stated. As a result, an advertiser is equally responsible for the claims stated as well as those implied in the ad. Additionally, an advertisement is considered deceptive if it fails to disclose certain information. Advertisers are required to disclose information if it is material in light of representations made or suggested by the ad. This also applies in situations where material would alter the way in which consumers would ordinarily use the product [65].

1.14 The Cost of Nontruth

Although the FTC has not clearly defined what constitutes substantiation, it has provided a global overview of how the agency analyzes marketing claims. In addition, the FDA along with the FTC points to a 1994 ruling as related to weight loss claims that states that at least two well-designed randomized clinical trials are needed to support weight loss and appetite suppressant claims. Because both the FDA and FTC point to this 1994 ruling, we now have some specific guidance as to what constitutes substantiation from the perspective of the amount of clinical trials needed for claims support [66].

Companies that have run afoul of either the FTC or FDA guidelines for advertising and marketing have been pursued in courts for their private actions and have paid financially. Fines appear to have ranged from the cost of consumer redress to outright fines payable to the respective agency. In a recent case, the manufacturer and subsequent retailer of one popular weight loss supplement paid $100,000 to the FTC and consented to not advertise any weight loss supplements that did not have substantiation (not all parties in this suit have settled with the FTC). In another FTC action, one company touting an oral growth hormone product paid the FTC $485,000 for consumer redress with a balloon clause of $5.9 million if the individual violates the consent order. Two other companies who also marketed oral growth hormone products have consented to pay the FTC up to $20 million dollars for their unsubstantiated marketing claims. In addition to the $20 million dollar notation, the companies and officers named in the FTC action may have to pay up to an additional $80 million dollars if the FTC finds that they misrepresented their personal and corporate finances. The consent order notes that substantiation is needed for claims and that the defendants have agreed to acquire the proper substantiation for future products they wish to retail. Do you think that with the possibility of losing $100 million dollars, this company will spend the money on studies to support their marketing? The FTC has been very active over the past few years, and it appears that they are more active than ever in

enforcing the laws regarding misleading advertising and substantiation [67–71]. This should be motivation enough for any dietary supplement company to learn and to conduct themselves in the right manner. In the big picture, because research and development is tax-credible (IRS Codes 41 and 174), why not spend the money now rather than paying fines and facing possible disbarment from the industry and, heaven forbid, jail time later for being guilty of unsubstantiated marketing claims?

1.15 Conclusion

As we have seen, after a decade of quietude, recent Congressional legislation and FDA regulatory actions have targeted sports and fitness supplements, banning some products and criminalizing others. The future may yet see additional regulatory efforts, or even legislative initiatives, as the market continues to evolve. Although the rules and regulations set forth by the Federal Trade Commission and the Food and Drug Administration were designed with the best intentions, the role that political pressure and potential lobbying by other industries plays in the enforcement of these rules and regulations cannot be ignored. Part of the problem lies with the industry itself, which could assist in uplifting the perception of sports supplements by creating a structured "self-policing" policy to ensure product purity and quality. Meanwhile, despite certain governmentally imposed limitations, sports nutrition supplements will likely continue to grow in popularity. The Internet has provided consumers with access to a wealth of information to research dietary supplements from a multitude of perspectives conveniently, helping individuals to make more informed decisions. Millions of members of the consuming public continue to enjoy the right to decide for themselves whether to take a wide variety of dietary supplements.

References

1. Pub. L. No. 75–717, 52 Stat. 1040 (1938) [codified as amended 21 U.S.C. 301 et seq. (1994)].
2. *Id.*, citing Senate Report No. 103–410, 103d Congress, 2d Session, Committee on Labor and Human Resources (October 8, 1994), at page 16.
3. *Id.*, citing Senate Report No. 103–410, at page 22.
4. Provided that the Secretary then initiates on-the-record rulemaking to affirm or withdraw the declaration. See 21 U.S.C. § 342(f)(1).
5. 21 U.S.C. § 331(a) and (v).
6. 21 U.S.C. §§ 342(f)(1), 350b(a).
7. 21 U.S.C. § 342(f)(1)(A).
8. 21 U.S.C. § 333(a)(1).
9. 21 U.S.C. § 333(a)(2).
10. A "dietary ingredient" may be a vitamin, a mineral, an herb or other botanical, an amino acid, a dietary substance for use by man to supplement the diet by increasing the total dietary intake, or a concentrate, metabolite, constituent, extract, or combination of any of these. See 21 U.S.C. 321 (ff)(1).
11. 21 U.S.C. § 350b(d).
12. 21 U.S.C. § 350b(a).
13. See FDA, Center for Food Safety & Applied Nutrition (CFSAN), New dietary ingredients in dietary supplements. Available at http://www.fda.gov/food/dietarysupplements/ucm109764.htm; see also, 21 CFR § 190.6.
14. "To date, we have not published guidance defining the specific information that the submission must contain. Thus, you are responsible for determining what information provides the basis for your conclusion." FDA, CFSAN, New Dietary Ingredients in Dietary Supplements, archived at http://archive.today/XyhTR.
15. FDA, CFSAN, Draft guidance for industry: dietary supplements: New dietary ingredient notifications and related issues. Available at http://www.fda.gov/food/guidanceregulation/guidancedocumentsregulatoryinformation/dietarysupplements/ucm257563.htm
16. Id.
17. Natural Products Insider, Senators Hatch, Harkin Call for NDI Guidance Redo. Available at http://www.naturalproductsinsider.com/news/2012/01/senators-hatch-harkin-call-for-ndi-guidance-redo.aspx
18. FDA, CFSAN, 95S-0316: 75-Day premarket notifications for new dietary ingredients. Available at http://www.fda.gov/ohrms/dockets/dockets/95s0316/95s0316.htm
19. FDA, CFSAN, FDA issues regulation prohibiting sale of dietary supplements containing ephedrine alkaloids and reiterates its advice that consumers stop using these products. Available at http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2004/ucm108242.htm
20. FDA, CFSAN, DMAA in dietary supplements. Available at http://www.fda.gov/food/dietarysupplements/qadietarysupplements/ucm346576.htm
21. *Id*.
22. FDA, CFSAN, HHS launches crackdown on products containing andro. Available at http://www.fda.gov/newsevents/newsroom/pressannouncements/2004/ucm108262.htm
23. See, e.g., FDA, CFSAN, Scientific fitness androstenedione warning letter. Available at http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm170182.htm

24. FDA, CFSAN, 95S-0316: 75-day premarket notifications for new dietary ingredients. Available at http://www.fda.gov/ohrms/dockets/dockets/95s0316/95s0316.htm
25. Siegner W. FDA's actions on ephedra and androstenedione: understanding how they erode the protections of DSHEA. Paper presented at FDLI's 47th Annual Conference, April 2004.
26. Johnson SK, Lewis PE, Inskeep EK. Steroids and cAMP in follicles of postpartum beef cows treated with norgestomet. J Anim Sci 1991;69:3747–3753. Braden TD, King ME, Odde KG, Niswender GD. Development of preovulatory follicles expected to form short-lived corpora lutea in beef cows. J Reprod Fertil 1989;85:97–104. Wise TH, Caton D, Thatcher WW, Lehrer AR, Fields MJ. Androstenedione, dehydroepiandrosterone and testosterone in ovarian vein plasma and androstenedione in peripheral arterial plasma during the bovine oestrous cycle. J Reprod Fertil 1982;66:513–518.
27. Margolis M. Dietary supplements: caveat athlete. Available at http://www.law.uh.edu/healthlaw/perspectives/Food/980910Dietary.html
28. FDA, CFSAN, New dietary ingredients in dietary supplements. Archived at http://archive.today/XyhTR
29. See FDA, CFSAN, Unlimited nutrition warning letter. Available at http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm225605.htm
30. See, e.g., Oliveira v. United States Anti-Doping Agency, Court of Arbitration for Sport, CAS 2010/A/2107, available at http://www.usada.org/uploads/oliveiraCAS.pdf; United States Anti-Doping Agency (USADA), Supplement Red Flags, available at http://www.usada.org/uploads/redflag-spdf.pdf; USADA, Supplement 411: The Anti-Doping Authority's Dilemma, available at http://www.usada.org/supplement411/supplement-dilemma/anti-doping-authoritys-dilemma; Christopher Chavez, Asafa Powell Suspended, availableathttp://www.flotrack.org/coverage/251077-News-from-the-Track-and-Field-World/article/26098-Asafa-Powell-suspended#.U1lmg2dOUpF
31. See generally, Legislation to Amend the Controlled Substances Act (Anabolic Steroids): Hearings on H.R. 3216 Before the Subcomm. on Crime of the House of Representatives Comm. on the Judiciary, 100th Cong., 2d Sess. 99, July 27, 1988; Steroids in Amateur and Professional Sports—The Medical and Social Costs of Steroid Abuse: Hearings Before the Senate Comm. on the Judiciary, 101st Cong. 1st Sess 736, April 3 and May 9, 1989; Abuse of Steroids in Amateur and Professional Athletics: Hearings Before the Subcomm. on Crime of the House Comm. on the Judiciary, 101st Cong., 2d Sess. 92, March 22, 1990; Hearings on H.R. 4658 Before the Subcomm. on Crime of the House Comm. on the Judiciary, 101st Cong., 2 nd Sess. 90, May 17, 1990.
32. Pursuant to 21 U.S.C. 812(b), a substance in Schedule III is to be placed there if: (A) the drug or other substance has a potential for abuse less than the drugs or other substances in schedules I and II; (B) the drug or other substance has a currently accepted medical use in treatment in the United States; and (C) abuse of the drug or other substance may lead to moderate or low physical dependence or high psychological dependence.
33. John Burge, Legalize and regulate: a prescription for reforming anabolic steroid legislation, 15 Loy. L.A. Ent. L.J., 33, 45 (1994).
34. Pub. L. No. 101–647, Sec. 1902, 104 Stat. 4851 (1990).
35. Revised schedules are published in the Code of Federal Regulations, Part 1308 of Title 21, Food and Drugs.
36. 21 U.S.C. § 844.
37. 21 U.S.C. § 841(b)(1)(D).
38. For a comprehensive examination of the 1990 steroid legislation, *see* this co-author's treatise, Legal Muscle: Anabolics in America (2002).
39. Androstenedione or "andro," a precursor to the sex hormone testosterone, achieved national notoriety in 1998 when a bottle of the pills was spotted in the locker of St. Louis Cardinals slugger Mark McGwire.
40. Norsteroid prohormones, for example, can result in a positive test for nandrolone because both nandrolone and the norsteroid prohormones give rise to the urinary excretion of the metabolites norandrostenedione and norandrostenediol.
41. The problem of positive doping results from cross-contamination made national headlines when U.S. bobsledder Pavle Jovanovic was disqualified from the Salt Lake City Olympics for a test result he blamed on a cross-contaminated protein powder supplement and when research conducted at an IOC-accredited drug testing laboratory in 2002 found that 94 of the 634 samples contained substances not listed on the label that would trigger positive drug tests.
42. Examples: Anabolic Steroid Penalties: Hearings on H.R. 3866 Before the Subcomm. on Crime of the House of Representatives Comm. on the Judiciary, 108th Cong., 2 nd Sess., March 16, 2004; Consolidating Terrorist Watchlists: Hearings on H.R. 3866 Before the Subcomm. on Crime, Terrorism, and Homeland Security, House of Representatives Comm. On the Judiciary, 108th Cong., 2 nd Sess., March 25, 2004; Anabolic Steroid Control Act of 2004: Hearings on S. 2195 Before the Senate Comm. on the Judiciary, 108th Cong., 2 nd Sess., October 6th, 2004.
43. Public L. No. 108–358; 118 Stat. 1661 (2004).
44. The new compounds are androstanediol; androstanedione; androstenediol; androstenedione; bolasterone; calusterone; *1-dihydrotestosterone (a.k.a. "1-testosterone"); furazabol; 13β-ethyl-17α-hydroxygon-4-en-3-one; 4-hydroxytestosterone; 4-hydroxy-19-nortestosterone; mestanolone; 17α-methyl-3β,17β-dihydroxy-5α-androstane; 17α-methyl-3α,17β-dihydroxy-5α-androstane; 17α-methyl-3β,17β-dihydroxyandrost-4-ene;17α-methyl-4-hydroxynandrolone; methyldienolone; methyltrienolone;17α-methyl-*1-dihydrotestosterone(a.k.a."17α-methyl-1-testosterone"); norandrostenediol; norandrostenedione; norbolethone; norclostebol; normethandrolone; stenbolone; and tetrahydrogestrinone.
45. 21 U.S.C. § 811.

46. Note that litigation may be required to explore what "pharmacologically related" means with respect to steroidal compounds, including whether a steroid's anabolic capacity is inherent to its pharmacologic effect.
47. DHEA, or dehydroepiandrosterone, is a steroid hormone that serves as a metabolic precursor to the sex hormones estrogen and testosterone. It has become a popular dietary supplement among middle-aged and elderly consumers seeking improved vigor.
48. The errors in the 1990 law were exposed by coauthor Collins in *Legal Muscle* (see endnote 38). However, at least one typographic error appears in the new law: 13α-ethyl-17α-hydroxygon-4-en-3-one (a demethylated version of norbolethone) should read as 13β-ethyl-17β-hydroxygon-4-en-3-one. A new bill [S. 893] was introduced on April 25, 2005 to fix the problem (it also amends the chemical nomenclature for stanozolol).
49. The definition of an anabolic steroid under the old law included, under subparagraph (xxviii), is "any salt, ester, or isomer of a drug or substance described or listed in this paragraph, if that salt ester, or isomer promotes muscle growth." The new law says, "any salt, ester, or ether of a drug or substance described in this paragraph." Note that the reference to muscle growth in the old law has been omitted [from what is now, in the longer list, subparagraph (xlx) of the new law] and that the word "isomer" has been replaced by "ether."
50. Classification of three steroids as schedule III anabolic steroids under the controlled substances act, 74 Fed. Reg. 63,603 (Dec. 4, 2009) (codified at 21 C.F.R. pt. 1300). Available at http://www.gpo.gov/fdsys/pkg/FR-2009-12-04/pdf/E9-28572.pdf
51. Classification of two steroids, prostanozol and methasterone, as schedule III anabolic steroids under the controlled substances act, 77 Fed. Reg. 44,456 (July 30, 2012) (codified at 21 C.F.R. pt. 1300), available at (http://www.gpo.gov/fdsys/pkg/FR-2012-07-30/pdf/2012-18495.pdf).
52. Public L. No. 113-260 128 STAT. 2929 (2014).
53. See, e.g., FDA, Office of Criminal Investigations, May 22, 2012: Bodybuilding.com, LLC and Jeremy DeLuca Plead Guilty in Federal Court to Violating FDCA. Available at http://www.fda.gov/ICECI/CriminalInvestigations/ucm305494.htm.
54. Gilroy DJ, et al. Assessing potential health risks from microcystin toxins in blue-green algae dietary supplements. Environ Health Perspect. 2000;108:435–9.
55. Department of Health & Human Services, Centers for Disease Control & Prevention, Facts about cyanobacteria & cyanobacterial harmful algal blooms. Available at www.cdc.gov/hab/cyanobacteria/pdfs/facts.pdf
56. FDA, CFSAN, Guidance for industry: substantiation for dietary supplement claims made under Section 403(r) (6) of the Federal Food, Drug, and Cosmetic Act. Available at http://www.fda.gov/food/guidanceregulation/guidancedocumentsregulatoryinformation/dietarysupplements/ucm073200.htm
57. FDA, CFSAN, Guidance for industry: structure/function claims, small entity compliance guide. Available at http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/DietarySupplements/ucm103340.htm
58. Correia EW. The federal trade commission's regulation of weight loss advertising claims. Food Drug Law J. 2004;59(4).
59. Federal Trade Commission (FTC), Bureau of Consumer Protection Business Center, Dietary Supplements: an advertising guide for industry. Available at http://www.business.ftc.gov/documents/bus09-dietary-supplements-advertising-guide-industry
60. FTC, gut check: a reference guide for media on spotting false weight loss claims. Available at http://www.business.ftc.gov/documents/0492-gut-check-reference-guide-media-spotting-false-weight-loss-claims
61. 15 USC 45(a)(1)(2000).
62. FTC, FTC Policy Statement Regarding Advertising Substantiation, available at http://www.ftc.gov/ftc-policy-statement-regarding-advertising-substantiation; see *In re* Thompson Medical Co., 104 F.T.C. 648 (1984), aff'd, 791 F.2d 189 (D.C. Cir. 1986).
63. *In re* Pfizer, Inc., 81 F.T.C. 23 (1972).
64. *POM Wonderful LLC v. F.T.C.*, 894 F. Supp. 2d 40 (2012).
65. FTC, Bureau of Consumer Protection Business Center, Dietary supplements: an advertising guide for industry. Available at http://www.business.ftc.gov/documents/bus09-dietary-supplements-advertising-guide-industry
66. *In re* Schering Corp., 118 FTC 1030, 1123, 1127 (1994).
67. FTC, FTC concludes case against marketers of xenadrine efx; court ruling requires final defendant to accept settlement terms. Available at http://www.ftc.gov/news-events/press-releases/2009/04/ftc-concludes-case-against-marketers-xenadrine-efx-court-ruling
68. FTC, Florida man settles FTC charges of sending illegal spam and making false "human growth hormone" product claims. Available at http://www.ftc.gov/news-events/press-releases/2005/06/florida-man-settles-ftc-charges-sending-illegal-spam-and-making
69. FTC, FTC targets bogus anti-aging claims for pills and sprays promising human growth hormone benefits. Available at http://www.ftc.gov/news-events/press-releases/2005/06/ftc-targets-bogus-anti-aging-claims-pills-and-sprays-promising
70. FTC, FTC settles claims with marketers of FiberThin and Propolene. Available at http://www.ftc.gov/news-events/press-releases/2005/06/ftc-settles-claims-marketers-fiberthin-and-propolene
71. FTC, defendants who deceptively marketed the himalayan diet breakthrough settle FTC charges. Available at http://www.ftc.gov/news-events/press-releases/2005/06/defendants-who-deceptively-marketed-himalayan-diet-breakthrough

2 The Psychology of Supplementation in Sport and Exercise: Motivational Antecedents and Biobehavioral Outcomes

Shawn M. Arent and Rafer S. Lutz

Dr. Rafer Lutz Dedication On May 23, 2012, we lost an incredible colleague and friend, Dr. Rafer S. Lutz, to mucosal melanoma at the age of 42. Rafer was one of the kindest and most thoughtful people we've had the good fortune to know. Not only was Rafer an excellent researcher, but his dedication to the education of his students was second-to-none. He was one of those people about which no one ever had a bad word to say. Rafer and I became close friends in graduate school at Arizona State University. The many long hours in the lab were always made more entertaining when he was present, and I was proud to see the impact he eventually had on his colleagues at Baylor University, where he ultimately served as department chair in Health, Human Performance, and Recreation. Any time I run into his former colleagues, students, or friends, the fondness they each had for him is evident. Above all else, though, Rafer was a loving husband and father. He is survived by his wife, Lori, and his two sons, William and Carson. The memory of Rafer lives on in all of us who were fortunate to cross paths with him, and he will always remain close in our minds and hearts. In keeping with this idea, the chapter in this text on the Psychology of

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Supplementation was the last major project I worked on with Rafer before his untimely passing. The updated version of this chapter is dedicated to Rafer and his family. While we all miss him tremendously, the lasting impact he has had on us cannot be overstated.

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Abstract

Research concerning the physiological and biobehavioral effects of supplements commonly used in sport or exercise settings has multiplied rapidly over the last decade. However, less attention has been directed to understanding the motivational pathways leading to sport and exercise supplement use. This chapter summarizes known usage rates for sport/fitness supplements and describes motivational theories and constructs which may be of use for understanding individuals' use of these substances. In this respect, we contend that researchers should consider behavioral approaches, the theory of planned behavior, balance theory, achievement goal theory, social physique anxiety, and muscle dysmorphia as useful for developing an understanding of the psychological influences on supplement use. For some of the latter theories/constructs, research has already shown support for their explanatory abilities, whereas research is scant and the utility for understanding sport/exercise supplement use is yet to be determined for many of the theories. In addition to describing the motivation behind supplement use, this chapter summarizes the biobehavioral effects of a select group of supplements commonly used to improve performance, fitness, or health. Specifically, we consider psychobiological effects of caffeine, creatine, *Ginkgo biloba*, St. John's wort, and omega-3 fatty acids related to enhanced arousal, improved memory and cognition, enhanced brain function and protection, and reduced depression. There is promising initial evidence for the efficacy of these compounds in producing favorable psychological outcomes, though certain shortcomings of many studies on these compounds must be taken into account before reaching definitive conclusions.

Keywords

Attitudes • Norms • Persuasion • Goal orientations • Motivational climate • Body image • Creatine • Caffeine • Ginkgo • St. John's wort • Fish oil

2.1 Introduction

Over the last decade, there have been numerous high-profile cases of athletes testing positive for performance-enhancing drugs (PEDs) and claiming it was due to a tainted supplement or examples of individuals having psychotic episodes and ultimately attributing them to drug-supplement interactions (e.g., Terrell Owens). While there is considerable drama and attention surrounding such high-profile cases, it does show some of the reason for concern in a largely unregulated and sometimes poorly researched industry. As supplement use has grown in sport and exercise settings, it becomes increasingly important to understand the reasons for supplements use. Additionally,

while many supplements target physiological systems, it is important to understand that these systems impact behavior (and vice versa). Such interactions of biological processes and behavior are termed biobehavioral effects and represent the intersection of the fields of physiology and psychology.

The growth of the overall supplement industry over the past decade is startling. According to the 1994 congressional Dietary Supplement Health and Education Act, it was reported that there were an estimated 600 dietary supplement manufacturers in the United States producing in the neighborhood of 4,000 products [1]. The total annual sales of these products were estimated to be at least $4 billion [1]. In 1998, this figure had grown to $13.9 billion and by 2012 equaled to $23.5 billion with an estimated annual increase of 5–7 % [2]. Anecdotally, it seems there are several motivations for this explosion in the use of supplements in sport and exercise—the increase in overweight and obesity and the pursuit of an ideal body shape have likely spurred the growth of supplements purporting to aid weight loss, media portrayal of "ideal" body images for males may be causing adolescent and adult males to increase supplement use to increase their muscle size, and the ever-increasing stakes in the sporting world seem to be causing athletes to continue to strive for new ways to gain an edge on the competition.

As an initial foray into the psychology of supplementation, this chapter proposes to look at three questions: (1) what do we know about the prevalence of supplement use, particularly considering supplementation among athletic populations or among those trying to gain muscle mass or lose weight, (2) what accounts for the motivations causing the explosive growth in the sport and exercise/weight loss supplement industry, and (3) what do we know about psychobiological outcomes related to sport performance, fitness, and health for a select group of supplements with purported biobehavioral effects? Reviewing the literature considering each of the latter three questions reveals some interesting research findings as well as significant gaps in the body of knowledge. It is our hope that an initial review concerning supplement use in sport and exercise from a psychological perspective will serve as an impetus to further research allowing a better understanding of the reasons for sport and exercise supplement use, their effects, and areas of potential concern.

2.2 Review of Literature

2.2.1 Definition of a Dietary Supplement

In the United States, a summary definition of dietary supplements as defined by the DSHEA of 1994 [1] can be stated as "a product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients: (a) a vitamin, (b) a mineral, (c) an herb or other botanical, (d) an amino acid, (e) a dietary substance for use by man to supplement the diet by increasing the total dietary intake, or (f) a concentrate, metabolite, constituent, extract, or combination of any ingredient described in clauses a, b, c, d, or e." It should be noted, additionally, that any claims a manufacturer or individual makes about a supplement might change its classification. Dietary supplements claimed to cure, mitigate, or treat disease would be considered to be an unauthorized new drug rather than a supplement. Researchers have also differentiated "nonvitamin, nonmineral supplements" (NVNM) as those primarily consisting of herbal, botanical, protein/amino acid, brewer's yeast, and shark cartilage and a variety of other plant-based and nonplant dietary supplements such as enzymes and fish oil [3, 4]. Finally, in the arena of competitive sport specifically, it should be noted that there are both "accepted" and "illegal/banned" substances, including some supplements. Making this distinction somewhat difficult, various sport governing bodies do not necessarily agree about which supplements should constitute banned substances, with inconsistencies appearing between the IOC, WADA, USOC, and the NCAA [5].

In an interesting quandary for the field of performance enhancement, many supplements

marketed to athletes may contain banned substances—either overtly or because of impurities in these supplements. Geyer and colleagues' [6] IOC-commissioned study examined nonhormonal supplements to determine the prevalence of anabolic–androgenic steroids (AAS) in these products not listed on the label. Researchers bought supplements from 215 suppliers in 13 different countries testing 634 nonhormonal supplements. A meaningful percentage of the supplements (14.8 %) contained substances that would lead to a positive drug test. These results indicate that a proportion of supplements would be considered drugs; further, they would be considered drugs with potentially deleterious side effects. The difficulty for many athletes and the various sport governing bodies is that it is difficult to determine which supplements may truly be supplements and which contain substances that would be considered drugs.

Despite the possibility for failed doping tests, athletes typically take supplements because they want an advantage over their competition. Supplement use should not be surprising considering that some athletes are willing to take illegal/banned drugs to improve performance. Thus, it would appear that the desire for money, fame, and feelings of achievement associated with athletic success are driving forces for the use of sport supplements. Yet not all athletes use supplements, and some are extremely cautious about the substances they ingest. Perhaps there are more subtle psychological factors at work that should be considered.

Problems also abound for individuals who supplement in order to achieve added weight loss and/or muscle gain (or even improved recovery post-workout) from their exercise programs. Products of dubious efficacy are plentiful, and little is known about drug/supplement or supplement/supplement interactions which may be hazardous to the user's health [7, 8]. Substances such as brindleberry (*Garcinia cambogia/indica*), capsaicin, caffeine, L-carnitine, chromium picolinate, and *Ginkgo biloba* have purported weight loss benefits; however, not all of these substances have research support in the published literature [9]. Considering a worldwide ongoing obesity epidemic [10] and problems in particular in the United States, it is not surprising that many individuals are seeking new ways to lose weight. Supplements promise, though probably seldom deliver, a magic bullet of sorts—easy, hassle-free weight loss with little in the way of dietary sacrifice. Motivation for users of weight loss supplements, however, is likely not simple or straightforward. A range of issues ranging from body image concerns to obsessive tendencies may be important to consider.

2.2.2 Prevalence of Supplement Use

There have been several large-scale surveys of supplement use among US citizens. The Slone Survey [11] used random digit dialing to survey 2,590 US citizens to determine commonly used herbals/supplements (nonvitamin, nonmineral: NVNM) and vitamins and minerals. The ten most commonly used substances in these categories are reported in Tables 2.1 and 2.2, respectively. Additionally, 14.0 % of individuals reported use of a herbal/supplement over the previous 7-day period. Popular reasons given for the use of herbal/supplements included health (16 %), arthritis (7 %), memory improvement (6 %), energy (5 %), and immune booster (5 %). Recent analysis of NHANES data from 2003 to 2006 [12] found that of the 18,758 individuals included in the analysis, 49 % reported supplement use, with multivitamins being the most commonly consumed (33 %) followed by botanical supplements (14 %). Over 70 % of adults over 71 years indicated using at least one dietary supplement [12].

Other large surveys have been conducted to examine supplement use and find, generally, greater usage rates among older individuals, nonobese, Caucasians, females, nonsmokers, physically active individuals, those with higher levels of educational attainment, as well as those with higher fruit and fiber intake [3, 13, 14]. In a study of 1,000 university students, Perkin and colleagues [4] found that 26.3 % indicated use of a NVNM supplement and 16 % had used in the

Table 2.1 Understanding the motives for supplement use in sport and exercise settings

Theory Pertinent construct(s)	Expected relationship to supplement use	Research support
Behaviorism/operant conditioning		
Positive reinforcement	Supplement use that leads to reward/praise should promote future use	No known *direct* support
Punishment	Supplement use leading to punishment/ sanction should reduce future use	Indirect support (success of doping sanctions)
Theory of planned behavior		
Attitude	Attitudes that supplements are good/healthy should promote use	Supported w/ limited research
Subjective norm	Beliefs that others feel you ought (injunctive norm) to use or beliefs that others commonly do use (descriptive norm) should promote use	Supported w/ limited research
Perceived behavioral control	Perceptions that supplements are easy to use, available, or inexpensive should promote use	Supported w/ limited research
Balance theory		
	If subject likes a celebrity spokesperson promoting a supplement and perceives that celebrity approves of the supplement, the subject should be more willing to try the supplement as they should like it more (to achieve psychological balance)	Well supported generally; no known *direct* support
Achievement goal theory		
Goal orientation	Individuals who have a high ego orientation for their sport would be expected to be more willing to use supplements, even if these supplements are potentially harmful	No known *direct* support
Motivational climate	Individuals within ego-promoting climates would be expected to be more willing to use supplements, even if these supplements are potentially harmful	No known *direct* support
Other constructs		
Social physique anxiety	High social physique anxiety may promote supplement use in some circumstances	No known *direct* support
Muscle dysmorphia	Higher levels of muscle dysmorphia may promote supplement use	Supported w/ limited research

Table 2.2 Ten most commonly used herbals/supplements in the United States: 1-week percentage prevalence by sex and age[a]

		Men			Women			
Rank	Herbal/supplement	18–44 years	45–64 years	≥65 years	18–44 years	45–64 years	≥65 y	Total
1	Ginseng	4	4	<1	2	5	2	**3.3**
2	*Gingko biloba* extract	<1	4	1	1	4	5	**2.2**
3	*Allium sativum*	<1	4	4	1	3	3	**1.9**
4	Glucosamine	<1	2	4	<1	5	4	**1.9**
5	St. John's wort	<1	2	0	2	3	<1	**1.3**
6	*Echinacea angustifolia*	1	1	0	1	3	<1	**1.3**
7	Lecithin	<1	<1	1	1	3	1	**1.1**
8	Chondroitin	<1	1	1	0	3	2	**1.0**
9	Creatine	4	0	0	0	0	0	**0.9**
10	*Serenoa repens*	1	1	4	0	<1	0	**0.9**
	Any use	12	17	11	10	23	14	**14.0**

Adapted from [11]

[a]Percentages weighted according to household size

past. ginseng, echinacea, protein powder/amino acids, and *Ginkgo biloba* were the most frequently used supplements. Reasons for use included to improve energy (61.2 %), to promote weight loss (38 %), to burn fat (36.1 %), to supplement inadequate diet (35 %), to build muscle (27.8 %), and to relieve stress/improve mood (24.7 %). It appears the reasons for use in the university population are more performance- and appearance-driven than the reasons for the general US population, which are more health-focused [11].

Sport Specific Use Athletes undoubtedly account for a large portion of those who use dietary supplements, and there are a variety of products that are marketed directly at competitive athletes. Sobal and Marquart's [15] meta-analytic review of vitamin/mineral supplement use among athletes reported an overall use rate of 46 %. They also found that elite athletes tended to more commonly take supplements than did college or high school athletes, and women used supplements more often than men. Another conclusion was that some athletes take high doses that may lead to nutritional problems. Regarding other herbal or other agents (e.g., AAS), use rates widely vary depending on the sport population investigated or the definition of supplement. Froiland and colleagues [16] actually found use rates as high as 89 % in a survey of 115 male and 88 female Division I athletes, with energy drinks being the most commonly consumed supplement (73 %) followed by calorie replacement products (61.4 %), multivitamins (47.3 %), and creatine (37.2 %). In some studies, though, use rates are lower—often when investigating younger or less competitive athletes and when using a definition of supplement that excludes sports drinks and vitamins. Scofield and Unruh [17] found 22.3 % of adolescent athletes reported supplement use in a small sample in Nebraska. In their study, athletes defined supplements on their own terms and most did not consider sport drinks to be a supplement. Considering elite Canadian athletes participating at the Atlanta and Sydney Olympics, respectively, prevalence rates of 69 % and 74 % were reported [18]. Though vitamin use was most common (58–66 %), nutritional supplements were also commonly used (Atlanta, 35 % of men, 43 % of women; Sydney, 43 % of men, 51 % of women) and typically consisted of creatine and/or amino acid supplementation. Nutritional supplement use occurred most often in cycling (100 %) and swimming (56 %). Based on overall results, it appears that supplementation increases with competitive level of sport and is somewhat higher for female athletes.

2.2.3 Motivational Theories Applied to Supplement Use

Examining the literature as a whole, it is well-established that supplement use is high among athletic populations and those who want to either build muscle or lose weight. What existing theoretical paradigms, however, might inform our future study of this area concerning reasons for use and potential abuse? To answer this question, it is perhaps best to consider three specific categories—supplement use to produce athletic performance benefits, supplement use to build muscle for aesthetic purposes or body image concerns, and supplement use to lose weight for aesthetic purposes, body image concerns, or health. Each of the three reasons for use likely has different motivational underpinnings. Therefore, in our description of theoretical paradigms that may be applied to understand supplement use, we have tried to identify the areas where each theory may be particularly effective for understanding supplementation. Overall, it should be considered that there are likely to be multifaceted, overlapping motivations for supplement use. Table 2.3 gives an overview of psychological/motivational theories and constructs that may be related to supplement use. As is obvious upon examination of this table, little direct inquiry has been conducted to explain motivation to use supplements in sport and exercise settings.

Certainly, there is a behavioristic explanation possible for the use of supplements in that athletes' use may lead to reward contingencies (e.g., more prize money) thus driving future behavior.

Table 2.3 Ten most commonly used vitamins/minerals in the United States: 1-week percentage prevalence by sex and age[a]

Rank	Herbal/supplement	Men			Women			Total
		18–44 years	45–64 years	≥65 years	18–44 years	45–64 years	≥65 years	
1	Multivitamin	19	29	31	25	29	33	**26.0**
2	Vitamin E	3	18	14	4	19	19	**10.0**
3	Vitamin C	4	13	12	5	16	14	**9.1**
4	Calcium	3	4	7	6	19	23	**8.7**
5	Magnesium	1	2	5	2	6	5	**3.0**
6	Zinc	2	2	3	1	5	3	**2.2**
7	Folic acid	<1	3	4	2	3	4	**2.2**
8	Vitamin B_{12}	<1	2	2	2	3	3	**2.1**
9	Vitamin D	<1	<1	2	<1	5	7	**1.9**
10	Vitamin A	<1	3	2	<1	4	3	**1.8**
	Any use	24	46	47	35	51	59	**40.0**

Adapted from [11]

[a]Percentages weighted according to household size. Numbers (excluding multivitamins) indicate prevalence of use in nonmultivitamin products

Similarly, supplements that build muscle or promote weight loss could produce rewarding results. Also, there are undoubtedly social influences at work considering that coaches, parents, athletic trainers, and peers have been reported as influential to the decision to take supplements [17, 19, 20]. Finally, other extant motivational theories may be useful to predict supplement use and abuse. Most of these potential explanations have received limited research, if any, in the context of supplement use, so our primary purpose is to describe how theory or previous research would predict the stated constructs' explanatory ability and direct future inquiry to understand motivation for supplementation.

Operant Conditioning If supplements work quickly and effectively to produce performance changes or body shape changes resulting in reward or praise, it is possible to use operant conditioning as a means of explaining the choice to take supplements. Operant conditioning focuses on the manner in which our behavior and action are influenced by the outcomes that follow them [21]. Derived from the behavioristic research tradition [22], the sum of findings in this area would dictate that some outcomes/stimuli strengthen the behavior that preceded them, while others weaken the likelihood of the behavior that preceded them. Outcomes or consequences that increase the likelihood of behavior are known as reinforcers, and those that decrease the likelihood of behavior are known as punishment. In the present context, prize money, praise from others, or rewards due to improved performance are reinforcers of the behavior to take supplements. However, it should be apparent that this theory demands that the reward is contingent upon taking the supplement—in other words, the supplement must work effectively and ostensibly. Additionally, it must likely work quickly in order to provide effective reinforcement of use. If it takes months to see the results, the behavior/reward timeline may be too protracted to encourage future use, particularly in an age of instant gratification. Otherwise, we must use other motivational explanations to understand supplement use. Because most legal supplements likely would not produce dramatic sport performance gains, muscle mass gains, or weight loss results, perhaps the best explanation for use is found in other theories. Behavioristic explanations, however, might be very applicable considering the use of illegal substances such as steroid use.

Persuasion and Conformity A set of ideas/principles that might best explain supplement use across areas (performance enhancement, weight

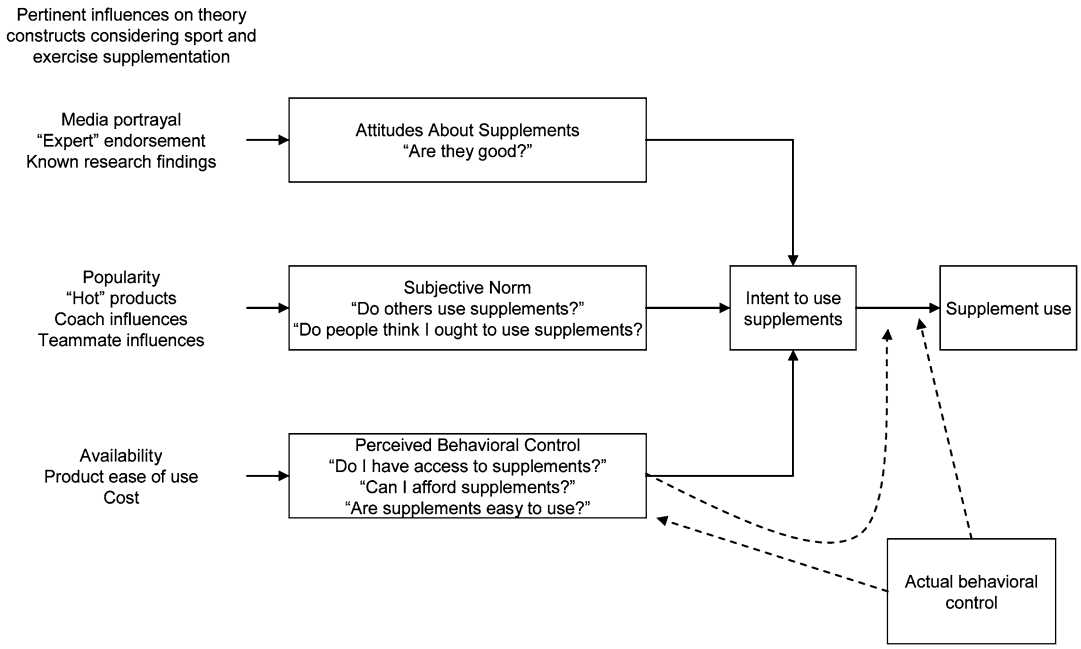

Fig. 2.1 The theory of planned behavior applied to sport/exercise supplement use. Adapted from [27]

loss, and muscle building) can be found examining research on persuasion and conformity to norms. Edwin Moses, one of the greatest hurdlers of all time, once estimated that use rate of illegal drugs in track and field to be about 50 % at the elite level [23]. Such a statement is reflective of a descriptive norm indicating what you believe others actually do. In an exercise setting, this would manifest in one's belief that others commonly take weight loss supplements or muscle-building supplements. The power of such norms to influence behavior is well documented [24–26], and if supplement use is perceived as the norm, there will be social pressure to conform—even in the face of negative outcomes that might be due to use.

Among theories adopting the concept of normative influence on behavior, the **theory of planned behavior** (TPB) may be useful for understanding motivation to use supplements. This theory proposes the existence of three psychological constructs which are believed to influence behavior through the mediator of intent: normative influences, attitude, and perceived behavioral control (see Fig. 2.1) [27]. Within normative influences, it is important to consider what one believes concerning what others feel you *ought* to do, known as the *injunctive norm*, in addition to the actual, *descriptive norm* relating to what others do themselves [27, 28]. Attitudes pertain to the degree that a behavior is positively or negatively valued. Specifically, in this context, would taking supplements be considered "good"? Perceived behavioral control pertains to one's beliefs about factors that might facilitate/impede performance of a behavior. Factors such as cost and availability of supplements would be expected to influence perceptions of behavioral control. No known study has focused on supplement use among athletes/exercisers using this theory, though it has shown very good predictive ability examining supplement use in other populations. In a study of 400 randomly selected women from the UK Women's Cohort Study including 15,000 participants who completed variables pertinent to TPB constructs and supplement use, Conner and colleagues [28] found that intent very accurately predicted supplement use (82.9 % accuracy) and that attitude was the strongest predictor of intent, though subjective norm and

perceived behavioral control were also significant predictors of intent. The latter three variables predicted an astonishing 70 % of variance in intent to use supplements. Certainly, these findings suggest that attitudes, normative beliefs, and perceptions of control are important correlates of supplement use among women. What is not known, however, are the ultimate reasons for use in this sample (e.g., weight loss, health benefits, etc.). Future research examining the TPB's predictive ability given different reasons for supplement use may be informative as these reasons may moderate the relative association of these predictors with intent to use and actual supplement use.

When trying to change attitudes about whether supplements are good or bad, it is likely that some individuals will be more persuasive than others. For example, individuals will be more persuasive if they are seen as trustworthy or having pertinent expertise [29]. The supplement industry often uses exactly such a strategy to help market their products. University research and "expert" sport and exercise nutritionists are increasingly being used to support the efficacy of performance-enhancing, muscle-building, or weight loss supplements. While this is a wise strategy on the part of the supplement industry from an economic standpoint, consumers should also consider that a company may contract with multiple universities to test their product and only report the results of the positive outcomes in their advertisements. Such a practice should be viewed as unethical, yet this is certainly a possibility. In recent years, certain research labs have even garnered a reputation for somehow always producing positive results for certain supplements. In some cases, these findings run contrary to a majority of previous research. Even in the published literature, there is likely to be a bias to the benefits of supplements as opposed to studies documenting no effects due to the file drawer problem in current scientific practice where significant results are published more frequently than nonsignificant results [30, 31]. Scientists conducting investigations in the area of supplements should attempt to publish nonsignificant and significant findings alike because of these issues.

Another theory that might inform persuasive efforts to effect attitude change is Heider's [32] balance theory. According to this theory, people want to view the world in a consistent manner. In other words, if your favorite athlete has admitted using a controversial supplement but you do not generally approve of the use of performance-enhancing substances, you are likely to change either your opinion of the athlete or acceptability of substance use in order to achieve harmony of thought and action. In this manner, we might expect that overt or covert messages from well-liked or well-respected athletes that indicate their use of supplements will cause others to view use as acceptable even if they initially resist. This would also support supplement companies' use of well-liked spokespersons to tout the use of their products. Similarly, using well-liked spokespersons to advertise supplements with purported weight loss benefits should have similar effects.

Achievement Goal Theory While the latter theoretical explanations allow some insight into the use of supplements among athletic populations, perhaps no theory addresses supplement use in this population as precisely as achievement goal theory [33, 34]. Within this theoretical paradigm, it is assumed that there are differences in the manners by which athletes judge their competencies, successes, or failures. Such differences of goal involvement may be influenced by environmental/situational influences, termed the climate [33], and individual differences, termed goal orientations [35]. Individuals who are task-oriented tend to judge their success on the basis of personal improvement (e.g., I am successful if I learn or improve), whereas those who are ego-oriented tend to judge their success on the basis of social comparison with others (e.g., I am successful if I win). Task-oriented individuals typically view personal ability as changeable and will exhibit strong motivation regardless of their perceptions of competence [36]. Those who are ego-oriented, in contrast, tend to view ability as more static and are thus more likely to engage in questionable strategies to ensure winning [37] and would be expected to engage in more

frequent doping activities and perhaps a greater willingness to use supplementation strategies. Interestingly, there is little direct evidence to link ego-goal orientations or ego climates with supplement use. However, this would be an important topic of inquiry in future studies. Certainly, this is an important topic of study in youth sport. If young athletes who are ego-involved begin using supplements, we must consider that they may not be as likely to comprehend (or care about) the potential for drug/supplement interactions.

Body Image and Eating Disorders The desire to win in athletics couched within the achievement goal framework appears to be a good model to understand sport supplement use. In exercise and fitness settings, however, theories directed to body image may be more useful. While obesity rates have dramatically increased in the United States over the past few decades [38], a similar increase in the ideal body size has not occurred in the female population. In fact, the "ideal" waist size for females may have become unhealthily small [39]. Because of these two contradictory trends, it is no surprise that the use of supplements targeted at weight loss has increased dramatically during this same time period. The nation is getting heavier and feeling worse about it, specifically in the female population. While we know that a large portion of supplement use is driven by a desire to lose weight [4], less is known about more severe body image disturbances in females as it may impact unhealthy supplement practices. Risky supplementation involving taking high doses or mixing supplements may occur among individuals who have more severe body image disturbances. More research is needed to investigate the relations between social physique anxiety, the degree to which people are anxious or nervous when others are observing or evaluating their physique [40], and supplementation practices. Social physique anxiety has been shown to be positively related to percent body fat and body dissatisfaction [40, 41], and it is logical that such dissatisfaction would be an impetus for the use of weight loss supplements that may be used in exercise settings. The feelings associated with social physique anxiety are often so distressful that they have even been found to be related to cortisol secretion in exercise-related settings [42]. Given the intensity of these emotions, it is reasonable to assume that practices that may make one feel better about their physique (i.e., weight loss with supplements) would be likely behaviors.

In a similar vein, it may be informative to look at disordered eating practices and supplement use. Examining the diagnostic criteria for bulimia [43], one of the notable symptoms is "recurrent inappropriate compensatory behavior in order to prevent weight gain, such as self-induced vomiting; misuse of laxatives, diuretics, enemas, or other medications; fasting; or excessive exercise" (p. 549). It might be expected that individuals suffering from bulimia, and perhaps anorexia nervosa, would have excessive or unhealthy supplementation practices. Research has shown that among women at risk for eating disorders, approximately 65 % engage in frequent use of "diet pills" [44], of which it is reasonable to assume a large portion would be considered supplements. Again, as the supplement industry has surged ahead promoting an ever-increasing range of products, researchers must try to determine how this may pose yet another risk for those who have eating disorders. It may also be that high levels of supplementation could be a warning sign of an eating disorder. More research simply needs to be done in this area. We do know that a warning sign of eating disorders is excessive exercise [43], and those working in exercise settings should be alert to this.

The Adonis Complex Typically, when one considers issues related to body image concerns in the United States, one focuses upon female populations. However, Pope and colleagues [45] have identified a similar, but opposing set of preoccupations afflicting males termed the Adonis Complex, which seems to be afflicting boys and men more specifically in the last few decades. Those afflicted with the Adonis Complex may compulsively lift weights or exercise, engage in steroid abuse, elect to undergo plastic surgery, or suffer from eating disorders or body dysmorphic disorders, all in attempts to gain muscle mass,

change fat distribution, or otherwise alter their appearance to some ideal.

In one of the seminal works in this area, Pope and colleagues [46] interviewed 108 bodybuilders (55 steroid users and 53 nonuser controls) and found a higher than normal incidence of anorexia nervosa (2.8 % incidence) and a surprising incidence of "reverse anorexia" (8.3 % incidence) in which respondents believed they appeared small and weak despite a very large, muscular appearance. The latter finding indicated that some of these bodybuilders exhibited unusual preoccupations with their appearance. Such pathological preoccupations with muscularity have been termed *muscle dysmorphia*, and research concerning this issue has found it to be relatively common among adolescents and young males [45]. As an important link to potential supplement use or abuse, in Pope and colleagues' [46] research, all of the bodybuilders indicating muscle dysmorphia (then termed "reverse anorexia") were in the sample of steroid users, and many reported that the symptoms of muscle dysmorphia were a factor that led to steroid use. If these individuals are driven to use illegal substances, one might expect higher than normal use of any substance (i.e., muscle-building supplements) purported to promote strength or muscle mass gains. As an indication of the degree of this obsession, individuals with this affliction have reported lifting weights for hours a day while sacrificing other areas of their lives. For example, some of these individuals reported earning degrees in business, law, or medicine but did not pursue a career or gave up a career in these areas because they needed more time to lift weights [47].

Recent research indicates that bodybuilders suffering from higher levels of muscle dysmorphia are more likely to experience body dissatisfaction, social physique anxiety, and use muscle-building- or fat-reducing-targeted supplements [48]. While the association between "muscle dissatisfaction" and frequency of exercise has been questioned, indicating that incidence of muscular dissatisfaction is similar among frequent and infrequent exercisers [49], this study used perhaps an overly simplistic measure of muscular dissatisfaction likely not sensitive to indications of muscle dysmorphia. Nonetheless, further research is necessary to determine the incidence of muscular dissatisfaction or muscle dysmorphia and their impact on a variety of important outcomes such as supplement use. At present, there is some evidence that supplement use is greater among individuals with muscle dissatisfaction [49], muscle dysmorphia [48], or a high drive for muscularity [50]. It also appears that illegal supplement use may accompany muscle dysmorphia as data indicate that one million or more US males have used these substances (such as anabolic steroids) primarily to promote muscle growth as opposed to performance enhancement purposes [45]. Finally, it should also be noted that research finds that some men have become preoccupied with fat as opposed to muscle and, in contrast to attempting to gain weight, may develop eating disorders [45]. This suggests that body image concerns among males may drive some to obsessively attempt to build muscle mass, whereas others may obsessively work to lose fat—and in both cases, it is likely that legal or illegal supplementation is a common means to achieve such goals.

2.3 Biobehavioral Effects of Selected Supplements Commonly Employed for Performance, Fitness, and Health

In addition to the psychological reasons underlying supplement use, there are also a number of psychological and biobehavioral effects that are associated with certain supplements or ergogenic aids. In some illegal ergogenic aids (i.e., AAS), many of these effects are considered negative side effects associated with the use of the drug or substance. For example, AAS abuse has been reported to result in mood changes, irritability, aggression, and psychotic or manic behavior [51–55]. There has been mixed support for these effects in experimental studies using supraphysiological doses of testosterone [56–58]. However, it appears that this may be due to considerable individual

variability in the psychological responses to AAS use, with those individuals predisposed to aggression or hostility most likely to respond with increased aggressive behaviors or anger [56, 57]. It is worth noting, though, that due to ethical restrictions in human subjects research, even the "supraphysiological" doses of testosterone used in the above studies (200–600 mg week^{-1}) fall well below what some individuals typically use when on an AAS cycle. The negative psychological responses likely become more apparent as the dosage increases.

In contrast to the negative psychological outcomes associated with AAS administration, there are actually many positive psychobiological responses for some of the legal ergogenic aids and nutritional supplements used in sport or exercise settings such as caffeine, creatine, omega-3 fatty acids, *Ginkgo biloba*, and St. John's wort. Some of these effects include enhanced arousal, improved memory and cognition, enhanced brain function and protection, and reduced depression. Unfortunately, definitive conclusions are difficult for each of these compounds due to the typically small-scale studies conducted on each of them as well as likely publication bias in some cases [59]. In light of this, emphasis will be placed on meta-analytic results and findings of well-controlled, randomized trials where available when reviewing the evidence for each supplement.

Caffeine Caffeine, particularly in the form of coffee, is one of the most commonly used ergogenic aids and CNS stimulants [60]. In fact, according to Sinclair and Geiger [61], caffeine is the worlds' most abused substance. Its effects on physical performance (particularly endurance) are well established, but there are also many studies that have examined the role of caffeine as a psychological ergogenic. Caffeine would be used by athletes as a performance aid in athletic situations, yet it is likely that this is a widely used substance among those populations in exercise settings as well. Research has generally supported a beneficial effect of caffeine intake on sensorimotor performance as well as vigilance and attention. Some of these findings include improvements in simple and choice reaction time [60, 62–64], faster response rate for a tapping task [64], sustained attention and vigilance [64–66], and improved decision-making [67]. Furthermore, these effects appear to be even more pronounced under the situation of sleep deprivation or fatigue [67–69]. While it has been suggested that many of these findings could be due to reversal of withdrawal effects after caffeine abstinence rather than actual performance benefits per se, there is recent evidence that this is not the case [70].

Lieberman et al. [71] examined the impact of three different doses of caffeine (100, 200, or 300 mg) or a placebo on cognitive performance in 68 Navy SEAL trainees under extreme conditions during their Hell Week. At the time of testing, the SEAL trainees had been sleep-deprived for approximately 72 h. Furthermore, due to standard SEAL training policy, they had refrained from caffeine intake for the entire week, thus controlling for possible "reversal of withdrawal" effects. Results indicated significant improvements in visual vigilance, choice reaction time, fatigue, repeated acquisition, and alertness in both the 200 and 300 mg groups, with the greatest effects at 1 h post-ingestion but still persisting at 8 h post. There were no differences between the 200 and 300 mg groups. Additionally, though marksmanship was not improved, caffeine also did not adversely affect it, which had previously been expressed as a concern with a fine-motor steadiness type of task due to muscle tremors associated with caffeine [72, 73]. It could be that even if caffeine disrupts "steadiness," it improves target acquisition and detection [74, 75]. In tasks requiring less fine-motor control (i.e., a tennis serve), accuracy has been found to improve with caffeine administration [76]. Caffeine administration pre- and in-task has also been found to improve both endurance performance as well as decision-making ability [77], which has implications for sports requiring concentration and decision-making late in games. In general, the arousal effects induced by caffeine appeared to benefit most areas of cognitive and psychological performance tested.

Caffeine can be linked to a state of arousal through specific physiological mechanisms. Research has shown caffeine intake leads to more positive frontal P2 and parietal P3 components of event-related potentials (ERP) [78]. This increase

in CNS activity indicates elevated levels of arousal, heightened information processing, and control-oriented mechanisms [78]. The arousal-inducing properties of caffeine appear to be tied primarily to its binding to adenosine A_1 and A_{2A} receptors, though recent research has suggested that the A_{2A} receptor is primarily responsible for mediating these effects [79]. This may help explain the positive effects that caffeine ingestion appears to have on the risk of Parkinson's disease (PD), which is characterized by central dopamine deficiency [80]. Because of an interaction between dopamine D_2 receptors and adenosine A_{2A} receptors [81], caffeine appears to have dopamine agonist-like effects [82]. Though two small-scale clinical trials have failed to find an effect of caffeine on Parkinson's symptoms, the dosage used was extremely high (>1,000 mg), which may have eradicated the motor benefits seen at lower caffeine doses [83]. A more recent study found benefits on certain freezing-gait characteristics (i.e., total akinesia) using a low-dose (100 mg) caffeine treatment in patients with PD, though there appear to be distinct "responder" and "nonresponder" effects [84].

According to Ferrauti, Weber, and Struder [76], caffeine can also produce improvements in psychomotor coordination and neuromuscular function through its effect on contractile status. Other effects include increased heart rate and the release of epinephrine, norepinephrine, and cortisol [78, 85]. Because of caffeine's stimulatory effects on the hypothalamic–pituitary–adrenal (HPA) axis [86], it has the potential to induce an endocrine response similar to that seen under mental or physical stress. Individuals classified as "at risk" for hypertension appear to be especially sensitive to this HPA activation [87, 88], particularly when also exposed to a psychosocial stressor [88]. In light of this, it would appear prudent to caution those at risk for hypertension on the use of caffeine, particularly during periods of high stress.

When evaluating the psychological or biobehavioral effects of caffeine, it is important to keep in mind that plasma concentrations typically reach their peak within 30–60 min after ingestion [89]. Therefore, test administration must be timed appropriately. Additionally, some studies have evaluated the psychological and cognitive effects using absolute doses, while others have standardized dose by bodyweight. Depending upon the heterogeneity of the study sample, these two approaches could provide distinctly different interpretations of a dose–response effect. This can become even more problematic if pretreatment caffeine intake is not accounted for or controlled [90]. This may be particularly important for the study of skills requiring concentration, reaction speed, and accuracy. Finally, Mikalsen et al. [91] found mixed evidence for potential expectancy and placebo effects for caffeine and arousal. Further research in this area appears warranted in order to determine the extent of these effects and the impact on actual psychological performance.

Creatine Creatine use is common among both athletic and exercise populations. Much like the research on caffeine, there is abundant evidence that creatine supplementation improves physical performance, particularly for tasks requiring strength and power. Because of this, and because of the role of creatine in brain function and neuroprotection [92], interest has risen for investigating the role of creatine in the treatment of certain clinical conditions such as traumatic brain injury (TBI) and Huntington's disease (HD), as well as for general cognitive functioning.

Overall, TBI affects approximately between 1.7 and 3.8 million people each year in the US alone [93]. Emergency room visits due to sport-related TBI in children and adolescents have risen 60 % in the last 10 years and account for almost 200,000 TBIs annually [94], which can result in subdural hematomas, deterioration of cognitive function, or even death [95, 96]. These injuries are occurring despite improvements in safety equipment, rule changes, and training methods. Furthermore, there is currently very little in the way of "therapeutic intervention" to help prevent or even treat this type of injury [97]. It has been hypothesized that creatine might exert neuroprotective effects through provision of sufficient ATP immediately after trauma or by inhibiting the mitochondrial permeability transition pore (mPTP) [95, 96]. In an effort to examine the potential neuroprotective effects of creatine on this type of injury as well as underlying mechanisms,

Sullivan et al. [95] employed an animal model of experimentally induced TBI. They found that chronic creatine administration reduced cortical damage due to experimentally induced TBI by as much as 36 % in mice and 50 % in rats. They also found that chronic creatine supplementation resulted in maintenance of cellular ATP levels, reductions of free radical formation, decreased intramitochondrial Ca^{2+}, and maintenance of mitochondrial membrane potential [90]. There also appeared to be inhibition of mPTP, though recent research using ubiquitous mitochondrial creatine kinase (UbMi-CK)-deficient mice suggests that the neuroprotective effects of creatine are most likely due to the maintenance of ATP/ADP and PCr/Cr levels rather than mPTP inhibition [93]. Nonetheless, the overall findings of Sullivan et al. [95] are encouraging and warrant further investigation into the potential use of creatine supplementation in the prevention and treatment of TBI.

The use of a human model in a true-experimental design of TBI and creatine supplementation would likely not be ethically acceptable or logistically feasible at this point. However, there is evidence supporting the cognitive benefits of creatine in humans. Using a double-blind, placebo-controlled, crossover design, Rae et al. [98] found that 6 weeks of creatine supplementation (5 g day^{-1}) in 45 young adult vegetarians resulted in improved brain function as evidenced by significant improvements on speed of processing tasks, including working memory and intelligence. Similarly, Watanabe et al. [99] found that supplementing with 8 g of creatine per day for 5 days reduced mental fatigue resulting from a repeated serial calculation task. Perhaps more importantly, they found that creatine ingestion was associated with increased oxygen utilization in the brain during the task as measured with near-infrared spectroscopy [99]. This is consistent with in vitro results demonstrating that mitochondrial oxygen consumption is greater in the presence of higher creatine concentrations [100]. A recent, intriguing study [101] found that 6 months of creatine administration (0.4 g kg^{-1} day^{-1}) in children (ages 1–18 years) admitted to a hospital in Greece with TBI resulted in trends for improved duration of posttraumatic amnesia, period of intubation, and length of the ICU stay compared to a placebo. It also significantly improved linguistic understanding [101].

Another potential area of clinical utilization for creatine supplementation has been in the treatment of HD, which is a progressive neurodegenerative disease for which there currently is no effective therapy. One of the side effects to HD that might contribute to neuronal death is impaired energy metabolism, particularly in the brain [102]. Given creatine's demonstrated neuroprotective effects as well as its role in bioenergetics, researchers have begun to examine the utility of the supplement in delaying or improving the symptoms associated with HD. Fortunately, a transgenic mouse model of HD was developed [103] that has allowed examination of mechanistic effects of HD and potential treatments. Using this model, Ferrante et al. [102] found that creatine supplementation enhanced brain creatine concentrations, delayed brain atrophy, delayed atrophy of striatal neurons, and significantly improved survival. Body weight and motor performance were also improved with creatine supplementation. Matthews et al. [104] used a slightly different animal model of HD by inducing HD-like striatal lesions with malonate and 3-nitropropionic acid (3-NP). They found that both creatine and cyclocreatine provided protective effects against malonate and 3-NP lesions in a dose–response manner. There was actually a reduction in the neuroprotection afforded by creatine supplementation at its highest dose, suggesting a curvilinear (U-shaped) dose–response curve for treatment efficacy. It is also worth noting that creatine appeared to function as either a free radical scavenger or as an inhibitor of hydroxyl radical formation [104]. The authors suggest that by preventing ATP depletion, creatine and cyclocreatine serve to prevent the cascade of events leading to free radical generation or accumulation and cell death [104]. Unfortunately, these effects have not always translated into symptom improvements in studies utilizing creatine supplementation in human HD patients [105]. However, it is possible that the supplementation method was less than

ideal for attenuating declines associated with this disease in humans or that differential effects will be seen depending upon the stage of the disease. Given the promising results from animal studies, further research is clearly warranted to determine whether the effects seen in an animal model of HD translate to the human model.

Ginkgo Biloba The use of *Ginkgo biloba* as a therapeutic aid can be traced back over 5,000 years to early Chinese medicine [106]. It was not until the 1960s that *Ginkgo biloba* extract (EGb) was introduced into Western medicine [106]. EGb is commonly found in energy drinks that would be commonly used by sport and exercise populations, though the doses in these drinks are usually quite low. Athletes may be persuaded to take EGb because of its professed effects on mental alertness or focus. Purported clinical uses now include treatment for memory impairment, dementia, Alzheimer's disease, and intermittent claudication [59, 107]. There is even evidence that EGb might help prevent symptoms of seasonal affective disorder (SAD) during the winter months [108]. While there have been well over 40 controlled trials examining these effects, much of the early research was relatively small-scale and of questionable methodological quality [107]. Meta-analyses that have included the more rigorous of these trials have generally found positive results for the effects of EGb on memory impairment, Alzheimer's disease, and dementia [107, 109–111]. Despite the generally positive findings, however, Birks and Grimly Evans [111] conclude that the evidence for EGb having significant benefit for treatment of dementia or cognitive impairment is both inconsistent and unconvincing. Part of the reason for this conclusion appears to be based on concern for publication bias in this area [107, 111]. Ernst [59] argues that the evidence for EGb's effects on normal cognitive function is not compelling, but that the average effect associated with EGb and Alzheimer-related dementia is likely to be clinically relevant. There is some evidence that acute EGb ingestion can provide enhanced cognitive effects in even healthy, young adults, though this effect was significantly more pronounced when EGb was combined with *Panax ginseng* [112]. Future research should consider interactive effects of EGb with other common supplements.

Most EGb used for medical and research purposes (EGb 761) contains 24 % flavone and 6 % terpenoids [113]. It is believed that the flavonoids contribute the antioxidant effects of EGb, thus making it an effective free radical scavenger [113]. This might actually be one of the primary mechanisms through which EGb exerts its effects on dementia and cognition. Oxidative damage to polyunsaturated fatty acids (PUFA) in brain cells results in impaired neurotransmitter uptake, and cellular damage resulting from free radical production appears to be a key contributor to the pathology and neurotoxicity associated with Alzheimer's disease [114]. Research using an animal model for Alzheimer's disease found that both in vivo and in vitro treatment with EGb 761 resulted in significant attenuations in reactive oxygen species (ROS) [115] and enhanced hippocampal neurogenesis [116]. This is consistent with epidemiological findings in humans demonstrating an association between flavonoid [117] and vitamin E [118] intake and cognitive functioning in older adults.

Results of a few, large-scale randomized clinical trials (RCT) have provided somewhat mixed results regarding the effects of EGb administration on symptoms of dementia, though the majority of the evidence supports the efficacy of EGb treatment. In a 24-week study of 156 subjects with Alzheimer-induced dementia or multi-infarct dementia, Kanowski et al. [119] found that EGb 761 administration resulted in improved cognitive performance, behavior (i.e., coping skills, independence), and EEG mapping characteristics compared to placebo. LeBars et al [120] randomly assigned 202 subjects with dementia of mild-to-moderate severity to receive either 120 mg day^{-1} of EGb 761 or a placebo for 1 year. They found that EGb successfully attenuated continued declines in cognitive functioning and the signs and symptoms of the disease compared to placebo, though the effects were relatively modest. There were also some patients that improved while taking EGb. A re-analysis of

the data [121] revealed that the changes in the experimental group were dependent upon severity of the disease at baseline. In those individuals classified as having "mild" cognitive impairment, EGb resulted in improvements. In those individuals having "severe" cognitive impairments, progression of the disease was only stabilized or slowed by EGb, but was still better than placebo [121]. A more recent 24-week placebo-controlled, double-blind EGb trial with 123 patients [122] failed to support the efficacy of two different doses (240 or 160 mg day^{-1}) of EGb for subjects with age-associated memory impairment or dementia. However, these results have been criticized as difficult to interpret due to the mixture of subjects suffering from dementia and subjects with, in some cases, very little cognitive impairment [113]. In light of this criticism, interpretation becomes even more challenging due to the fact that subjects in each of the original EGb dose groups were randomly assigned to continue with EGb or a placebo after 12 weeks. A more recent RCT in over 400 individuals with mild-to-moderate dementia, Alzheimer's disease, or vascular dementia found significant improvements in cognitive function, neuropsychiatric symptoms, and functional abilities over 24 weeks of treatment with 240 mg d^{-1} of EGb [123]. Overall, it appears that EGb has potentially beneficial effects on Alzheimer's disease and dementia symptoms, and further well-designed RCTs should help elucidate long-term efficacy and dose–response effects.

St. John's Wort The use of St. John's wort may be less common for sport or exercise-specific reasons as compared to caffeine, creatine, or EGB. However, this supplement is widely used in the general population [11] and has interesting purported benefits and concerning possible side effects. Also, this supplement has similar purported benefits to alleviate depression as does physical exercise, and its study in conjunction in exercise settings is warranted. Several meta-analytic reviews [124–129], most of which have included only RCTs in their analyses, have supported the efficacy of St. John's wort (SJW; *Hypericum perforatum* L.) for the treatment of depression of mild-to-moderate severity compared to placebo. Many of these meta-analyses [124, 126, 128] have also concluded that SJW is as effective as some of the conventional antidepressants, including tricyclic antidepressants (TCA) and fluoxetine, typically with fewer side effects. However, Whiskey et al. [128] urged caution in interpreting the apparent equivalence due to the low statistical power inherent in most of the RCTs that traditionally compared SJW to antidepressants. A more recent, larger-scale ($N=251$) RCT, however, found that SJW was *at least* as effective as paroxetine for treating moderate to severe major depression and was better tolerated [130]. Nonetheless, most RCTs continue to support the meta-analytic conclusions (see reviews [131, 132]), though evidence for efficacy in treating major depression appears mixed [130, 133–135].

The two primary substances contained in SJW that are believed to be responsible for the antidepressant effect are hyperforin and hypericin [131]. Recent evidence now points to hyperforin being the main contributor to this effect [136, 137]. Various mechanisms have been identified to explain how SJW might exert its antidepressant effects, though the precise mechanism remains unclear [131]. SJW or its isolated components have been shown to inhibit serotonin (5-HT), norepinephrine, and dopamine reuptake [138], inhibit GABA and L-glutamate uptake [136, 139], and inhibit substance-P (SP) production of proinflammatory cytokines (e.g., IL-6) [140] that have been implicated in depressive etiology. Additionally, SJW has been shown to inhibit monoamine oxidase (MAO), though this inhibition appears to be of insufficient magnitude to account for significant antidepressant effects [141]. It is entirely possible that SJW functions to reduce depression through a combined effect of each of these mechanisms.

Despite the established benefits of SJW in the treatment of mild-to-moderate depression, there is a major concern with its use that focuses on apparent drug-interaction effects. There have been various reports of SJW having negative interactions with drugs such as warfarin, cyclosporine, HIV protease inhibitors, digoxin,

theophylline, and oral contraceptives by decreasing their circulating concentrations [142]. The mechanism behind these interactions appears to be the combined result of induction of the cytochrome P450 isoenzymes, particularly CYP3A4 as well as CYP2C9 and CYP1A2, and the transport protein P-glycoprotein by SJW [142]. These effects appear to be primarily related to the degree of hyperforin content, with the least enzyme induction seen for SJW products with <1 % hyperforin [142]. It also appears that SJW can compound the effects of other selective serotonin reuptake inhibitors (SSRIs) and potentially lead to serotonin excess if SJW and SSRIs are combined due to their common pharmacological mechanisms [143, 144]. Considering the commonality of the mechanisms identified above to explain SJWs effects on depression and those that have been advanced to explain the effects of exercise on depression (see review [145]), it is imperative that future studies begin to explore the potential interactions between SJW (as well as many other popular herbal supplements) and exercise. While there might be a synergistic effect, we must also consider the physiological responses induced by exercise and how they might impact the metabolism of these supplements. Dose–response models derived from primarily sedentary populations may not apply to more active groups.

Omega-3 Fatty Acids Omega-3 fatty acids (O3FA) have received considerable attention for their established effects on cardiovascular health, blood lipids, and inflammation. However, there is increasing evidence for impacts of the O3FA constituent components eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) on cognitive- and mood-related issues [146]. Sufficient EPA and, in particular, DHA are absolutely required for development of sensory, perceptual, cognitive, and motor neural systems during brain growth, which is part of the reason that they have begun to receive attention in supplemental form for adults and individuals with certain cognitive-based disorders [146]. There is evidence that O3FAs may be helpful in treating mild Alzheimer's disease [147]. A large-scale double-blind RCT in patients with mild-to-moderate Alzheimer's disease found that a combined DHA/EPA supplement (total 2.3 g day^{-1}) slowed the decline in cognitive function in a subgroup with less severe dysfunction [147]. As noted by the authors, the effect appeared to be primarily driven by DHA. This also makes theoretical sense given that DHA limits production and accumulation of amyloid β peptide toxin, thus protecting against Alzheimer's disease and dementia [148]. It also suppresses several signal transduction pathways induced by amyloid β [148]. Because of this, DHA may be more effective if begun early and used in conjunction with antioxidants. It is also worth noting that even in otherwise healthy subjects, a recent double-blind RCT [149] found that using 4 g fish oil/day (800 mg DHA and 1,600 mg EPA) for 35 days resulted in improved mood, attention, reaction time, and decision-making.

Another area related to cognitive function and development that has received interest as an area of impact with O3FA is attention-deficit/hyperactivity disorder (ADHD), which happens to be the most common childhood development disorder. Prevalence rates in children range between 4 and 15 % [150]. Children with ADHD consistently exhibit abnormal FA status, with pronounced O3FA deficiencies [150]. The low levels of O3FA have been found to be correlated with behavioral problems and learning difficulties [151]. Though results have been mixed [150, 152–155], most RCTs have supported at least some benefits of an EPA/DHA combination (particularly if combined with O6FA) for improving ADHD symptoms and behaviors. From a design standpoint, some of these RCTs have used a potentially "active" placebo in the form of olive oil which may explain some of the small differences noted between groups.

Given the notable cognitive effects of O3FA, it is perhaps not surprising that they have been investigated for their potential contribution to protection or recovery from TBI. Much like we see with creatine, O3FA restore cellular energetics, reduce oxidative stress and inflammation, repair cellular damage, reduce axonal damage, and mitigate the activation of apoptotic processes after TBI [156–159]. Perhaps equally as important,

O3FA also appear to regulate BDNF and maintain brain plasticity [159]. Of critical consideration is that supplementation not only serves as effective treatment from induced TBI in an animal model [158], but it also provides a prophylactic effect when supplemented regularly before the injury [157, 159]. Recovery was to the level of uninjured animals by 30 days in one study [158]. Overall, it appears that O3FA supplementation enhances structural, biochemical, behavioral, and cognitive (i.e., memory) responses to TBI in animal models utilizing mild fluid percussion injury [159] or impact acceleration injury [157, 158] to induce TBI. By increasing axonal regeneration, reducing inflammation, buffering glutamate cytotoxicity, and decreasing lipid peroxidation byproducts, O3FA mitigate much of the pathogenesis resulting from TBI. Unfortunately, human data are generally lacking. Given the promising animal findings, this is an area of research with O3FA that clearly warrants human trials.

One final area of biobehavioral impact of O3FA that has received considerable support in human research is on mental health and, specifically, depression. Not only does epidemiological and correlational evidence support the role of low levels of O3FA in the etiology of depression [156], but supplementation with these compounds has provided generally positive results for mild, moderate, and, in some cases, major depression [146]. In a recent double-blind RCT in individuals with major depression, O3FA only appear to be effective if the depression is not accompanied by comorbid anxiety disorders [160]. There may even be a positive effect for bipolar disorder [146]. It has become increasingly clear that the effects of O3FA on depression are almost solely due to the EPA component (1–4.4 g/day) [161], which may explain mixed findings from some studies if a high DHA component was employed [162]. While a meta-analysis by Bloch and Hannestad [163] concluded that there is no significant benefit of O3FA on depression, it has been heavily criticized [164] for including studies in which depressive disorder was not rigorously diagnosed and one study in particular that represented 31.7 % of the weighted pooled estimate in the meta-analysis but used self-rating to classify depression [165]. A re-analysis of the data after accounting for the questionably included clinical trials resulted in a significant effect for O3FA on depression [164].

It has been suggested that method of delivery may impact O3FA outcomes, with EPA and DHA bound to phospholipids (i.e., omega-3 phosphatidylserine; omega-3 phospholipids via krill oil) potentially being the most effective method of administration due to their ability to target the brain [146]. However, most of this evidence applies to ADHD and dysmenorrhea while direct testing for depression is lacking. Future research is warranted in this area. Additionally, further examination of mechanisms of action for the O3FA biobehavioral effects is needed, particularly considering that DHA and EPA appear to provide different outcomes depending on the condition. Whether the compounds are modulating inflammation, modifying neurotransmitters (especially BDNF), maintaining membrane fluidity, reducing oxidative stress, or providing for axonal protection needs to be elucidated in order to provide sound recommendations for application and potentially enhance effects with other biobehavioral treatments (e.g., exercise, creatine) in a synergistic manner.

2.4 Summary

Though supplement use continues to grow in the United States, little attention has been given to developing a theoretical understanding of the motivational forces at work in this area. Researchers should consider that most individuals in sport and exercise environments are looking for quick results reflected as performance gains, shape change, or health. If supplements provide such changes, they could be said to be reinforced through reward contingencies. Thus, in one sense, the motivation to take supplements is quite simple—those who take supplements are (sometimes) rewarded. This might help to explain why many muscle-building supplements have been shown to contain illegal constituents that would actually lead to a failed drug test [6]. Supplement companies want their products to work very

effectively in order to capitalize upon the motivating properties of reward. On the other hand, we know that the effectiveness of many supplements is not well-established and that it is likely that few supplements can legitimately offer immediate improvement. Therefore, researchers must consider other motivational explanations for supplement use in sport and exercise settings.

Among theories or constructs that may explain supplement use in sport and exercise, the theory of planned behavior, balance theory, achievement goal theory, social physique anxiety, and muscle dysmorphia would be important to consider. The theory of planned behavior considers the importance of norms, attitude and perceived behavioral control as predictors of intent to engage in behavior that is partially under our volitional control. Understanding how supplements are considered good/bad (attitude), commonly used or approved of (subjective norm), and available and easy to use (perceived behavioral control) may allow researchers to understand the pathways directing supplement use. Closely related to the idea of normative influence on behavior, we should consider the persuasive effects of well-liked spokespersons who tout the efficacy of certain supplements. According to balance theory, individuals may change their action (begin to use supplements) or attitudes (condone use) when faced with a situation that causes imbalance of thought and action (i.e., one of their favorite athletes uses supplements). Achievement goal theory proposes that individuals who are motivated to beat others or win (i.e., judge success based on social comparison) will be more likely to use legal or even illegal supplementation to achieve such goals. Individuals driven by personal improvement (i.e., task involved motivation) should be less likely to use supplements. Finally, upon considering the forces driving supplementation in sport and exercise, it is important to consider how body image and social physique anxiety relate to supplement use. This may be one of the more important psychological considerations considering the dramatic findings of Pope and colleagues [42]. If individuals are willing to risk their career to lift weights to change their body shape, it suggests an alarming obsession with body image that has been already linked to supplement use. What seems to be lacking in the literature is an understanding of motivational factors and their relation to supplement use generally, but more importantly to dangerous (i.e., over-supplementation or mixed supplementation) supplementation practices.

Consideration of the psychological outcomes associated with some of the best-selling supplements (e.g., caffeine, creatine, *Ginkgo biloba*, St. John's wort) has revealed encouraging findings for efficacy in improving such things as arousal and attention, neuroprotection, cognitive function, neurological diseases, and mild-to-moderate depression. Furthermore, there is reason to be encouraged by the RCTs and meta-analytic reviews that have been conducted on many of these compounds. Some of these studies, particularly those employing animal models, have provided important evidence for the physiological mechanisms potentially underlying these psychological outcomes. While considerable work remains to be done to continue to clarify these mechanisms and examine their applicability to the human model, biological plausibility for these supplements' psychological utility appears to have been established. Dose–response issues, on the other hand, remain unresolved for many of the substances, and this is an area that warrants further consideration in order to establish optimal use. Along these same lines, effects that might be impacted by exercise need to be evaluated for *Ginkgo biloba* and St. John's wort. This is particularly important for St. John's wort considering the established interaction effects that it has been shown to have with many drugs [133–136]. Some of the effects induced by these drugs have also been found to be induced by exercise [137], and this needs to be considered in future research. Finally, before definitive efficacy conclusions can be reached for creatine and neuroprotection, *Ginkgo biloba* and dementia/Alzheimer's disease, and St. John's wort and depression, larger-scale, long-term RCTs are needed. To this point, trials of these supplements have been too small and too short [55]. Generally speaking, though, there appears to be a positive risk-benefit profile for each of the reviewed supplements, thus

warranting dedication of resources to further examination of their application to enhancing performance as well as to various diseases and conditions.

2.5 Practical Applications

- The use of supplements having obvious efficacy to the user is likely to cause future use.
- Information leading to favorable attitudes about supplements is likely to promote their use. Promotion or data from "experts" can be persuasive in developing (or degrading) favorable attitudes regarding supplements.
- Individuals who perceive that supplement use is common among their peers will be more likely to use supplements. Individuals who believe that they "should" be taking supplements will be more likely to take supplements. One should be aware of the messages sent by coaches, trainers, and professionals regarding frequency of use of supplements and the necessity of supplement use.
- Individuals will be more likely to take supplements if they feel they are easy to use or cheaper.
- Well-liked individuals (e.g., professional athletes, celebrities) who state they use supplements may lead their fans to use supplements.
- Athletes motivated primarily to win may engage in greater supplementation. Care may be taken to ensure that win-focused athletes don't engage in illegal or dangerous supplementation practices.
- There appears to be a portion of the population compulsive about their appearance which may cause an increase in supplementation (either to gain muscle or lose weight). Appearance of these compulsions should be taken seriously, as we are just beginning to learn about the nature of these issues. Professionals working with such individuals should be on the lookout for illegal or dangerous supplementation practices.
- We know little about the overlap of eating disorders and supplementation use, but individuals who work with those attempting to lose weight should consider preoccupation with weight an important risk factor. Studies show that intense and prompt treatment is the best course of action to help individuals with eating disorders. Professionals working in this area should monitor traditional warning signs and supplementation practices alike.
- Caffeine doses in the range of 200 mg appear to produce positive changes in attention, vigilance, and arousal, particularly if the individual is fatigued or sleep deprived. This may be particularly useful to athletes that require sustained vigilance or individuals exposed to extreme conditions and physical and psychological demands (i.e., military, firefighters).
- Creatine not only enhances physical performance but also has apparent neuroprotective effects. Its use as a prophylactic might be beneficial to athletes involved in sports where incidence of TBI is high (i.e., mixed martial arts, football, soccer, boxing). Additionally, creatine use might be beneficial for individuals suffering from Huntington's disease in order to help attenuate neurodegeneration. Moderate doses appear to be most effective.
- *Ginkgo biloba* supplementation might help attenuate or even reverse some of the cognitive symptoms of Alzheimer-related dementia. It appears to do this through a reduction in oxidative stress at the level of the brain cells.
- St. John's wort can be used to help reduce symptoms of mild-to-moderate depression. However, caution must be observed if the individual is taking other drugs, such as warfarin, cyclosporine, HIV protease inhibitors, digoxin, theophylline, or oral contraceptives because it may interact with these drugs and lower their circulating levels. Combination with SSRIs can exacerbate their effects. Interactions with exercise also need to be considered because of many overlapping mechanisms.
- O3FA improve cognition in health individuals and those with Alzheimer's disease, reduce problems associated with ADHD, serve as a prophylactic and treatment for TBI, and reduce depression. The DHA and EPA components appear to have different effects

depending on the desired outcome, with DHA contributing primarily to cognitive benefits and EPA contributing to antidepressant effects. Doses from 1.5 to 4 g day^{-1} appear to be well-tolerated and most effective.

References

1. Dietary Supplement Health and Education Act of 1994. Public Law 103-417. 103rd Congress. Downloaded from http://www.fda.gov/opacom/laws/dshea.html on 7 May 2007.
2. Nutrition Business Journal's Supplement Business Report. Downloaded from http://www.nutritionbusiness.com on 7 May 2013.
3. Radimer KL, Subar AF, Thompson FE. Nonvitamin, nonmineral dietary supplements: issues and findings from NHANES III. J Am Diet Assoc. 2000;100(4):447–54.
4. Perkin JE, Wilson WJ, Schuster K, Rodriguez J, Allen-Chabot A. Prevalence of non-vitamin, non-mineral supplement usage among university students. J Am Diet Assoc. 2002;102:412–4.
5. 2013-14 NCAA Banned Drugs. Downloaded from http://www.ncaa.org/health-and-safety/policy/2013-14-ncaa-banned-drugs on 1 May 2014.
6. Geyer H, Parr MK, Mareck U, Reinhart U, Schrader Y, Schanzer W. Analysis of non-hormonal nutritional supplements for anabolic-androgenic steroids—results of an international study. Int J Sports Med. 2004;25:124–9.
7. Almeida JC, Grimsley EW. Coma from the health food store: interaction between kava and alprazolam. Ann Intern Med. 1996;125(11):940–1.
8. Fennell D. Determinants of supplement usage. Prev Med. 2004;39:932–9.
9. Egger G, Cameron-Smith D, Stanton R. The effectiveness of popular, non-prescription weight loss supplements. Med J Aust. 1999;171:604–8.
10. Popkin BM, Doak C. The obesity epidemic is a worldwide phenomenon. Nutr Rev. 1998;56:106–14.
11. Kaufman DW, Kelly JP, Rosenberg L, Anderson TE, Mitchell AA. Recent patterns of medication use in the ambulatory adult population of the United States: the Slone Survey. JAMA. 2002;287:337–44.
12. Bailey RL, Gahche JJ, Lentino CV, Dwyer JT, Engel JS, Thomas PR, Betz JM, Sempos CT, Picciano MF. Dietary supplement use in the United States, 2003-2006. J Nutr. 2011;141:261–6.
13. Foote JA, Murphy SP, Wilkens LR, Hankin JH, Henderson BE, Kolonel LN. Factors associated with dietary supplement use among healthy adults of five ethnicities: the Multiethnic Cohort Study. Am J Epidemiol. 2003;157:888–97.
14. Harrison RA, Holt D, Pattison D, Elton PJ. Who and how many people are taking herbal supplements? A survey of 21,923 adults. Int J Vitam Nutr Res. 2004;74:183–6.
15. Sobal J, Marquart LF. Vitamin/mineral supplement use among athletes: a review of the literature. Int J Sport Nutr. 1994;4:320–34.
16. Froiland K, Koszewski W, Hingst J, Kopecky L. Nutritional supplement use among college athletes and their sources of information. Int J Sport Nutr Exerc Metab. 2004;14:104–20.
17. Scofield DE, Unruh S. Dietary supplement use among adolescent athletes in central Nebraska and their sources of information. J Strength Cond Res. 2006;20:452–5.
18. Huang SH, Johnson K, Pipe AL. The use of dietary supplements and medications by Canadian athletes at the Atlanta and Sydney Olympic Games. Clin J Sport Med. 2006;16:27–33.
19. Nieper A. Nutritional supplement practices in UK junior national track and field athletes. Br J Sports Med. 2005;39:645–9.
20. Perko MA, Eddy JM, Bartee RT, Dunn MS. Giving new meaning to the term "Taking one for the team": influences on use/non-use of dietary supplements among adolescent athletes. J Am Health Stud. 2000;16:99–106.
21. Martin G, Pear J. Behavior modification: what it is and how to do it. 6th ed. Englewood Cliffs, NJ: Prentice-Hall; 1998.
22. Watson JB. Psychology as the behaviorist views it. Psychol Rev. 1913;20:158–77.
23. Moses E. An athlete's Rx for the drug problem. *Newsweek.* 1988;Oct. 10:57.
24. Asch SE. Opinions and social pressures. Sci Am. 1955;193:31–5.
25. Okun MA, Karoly P, Lutz R. Clarifying the contribution of subjective norm to predicting leisure-time exercise. Am J Health Behav. 2002;26:296–305.
26. Reno RR, Cialdini RB, Kallgren CA. The transsituational influence of norms. J Pers Soc Psychol. 1993;64:104–12.
27. Ajzen I, Fishbein M. The influence of attitudes on behavior. In: Albarracin D, Johnson BT, Zanna MP, editors. The handbook of attitudes. Mahwah, NJ: Erlbaum; 2005. p. 173–221.
28. Conner M, Kirk SF, Cade JE, Barrett JH. Why do women use dietary supplements? The use of the theory of planned behaviour to explore beliefs about their use. Soc Sci Med. 2001;52:621–33.
29. Perloff RM. The dynamics of persuasion. Hillsdale, NJ: Lawrence Erlbaum; 1993.
30. Rosenthal R. The "file drawer problem" and tolerance for null results. Psychol Bull. 1979;86:638–41.
31. Scargle JD. Publication bias: the "file-drawer" problem in scientific inference. J Sci Explor. 2000;14:91–106.
32. Heider F. The psychology of interpersonal relations. New York: Wiley; 1958.

33. Ames C. Classrooms: goals, structures, and student motivation. J Educ Psychol. 1993;84:261–71.
34. Dweck C. Motivational processes affecting learning. Am Psychol. 1986;41:1040–8.
35. Nicholls JG. The competitive ethos and democratic education. Cambridge, MA: Harvard University Press; 1989.
36. Sarrazin P, Biddle S, Famose JP, Cury F, Fox K, Durand M. Goal orientations and conceptions of the nature of sport ability in children: a social cognitive approach. Br J Soc Psychol. 1996;35:399–414.
37. Duda JL, Olson LK, Templin TJ. The relationship of task and ego orientation to sportsmanship attitudes and the perceived legitimacy of injurious acts. Res Q Exerc Sport. 1991;62:79–87.
38. Flegal KM, Carroll MD, Ogden CL, Johnson CL. Prevalence and trends in obesity among US adults, 1999-2000. JAMA. 2002;288:1723–7.
39. Owen PR, Laurel-Seller E. Weight and shape ideals: thin is dangerously in. J App Soc Psychol. 2000;30:979–90.
40. Hart EH, Leary MR, Rejeski WJ. The measurement of social physique anxiety. J Sport Exerc Psychol. 1989;11:94–104.
41. Hausenblas HA, Fallon EA. Relationship among body image, exercise behavior, and exercise dependence symptoms. Int J Eat Disord. 2002;32: 179–85.
42. Martin Ginis KA, Strong HA, Arent SM, Bray SR. The effects of threatened social evaluation of the physique on cortisol activity. Psychol Health. 2012; 27:990–1007.
43. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Washington, DC: American Psychiatric Association; 1994.
44. Celio CI, Luce KH, Bryson SW, Winzelberg AJ, Cunning D, Rockwell R, Celio Doyle AA, Wilfley DE, Taylor CB. Use of diet pills and other dieting aids in a college population with high weight and shape concerns. Int J Eat Disord. 2006;39:492–7.
45. Pope Jr HG, Phillips KA, Olivardia R. The Adonis complex: the secret crisis of male body obsession. New York: Free; 2000.
46. Pope Jr HG, Katz DL, Hudson JI. Anorexia nervosa and "reverse anorexia" among 108 male bodybuilders. Compr Psychiatry. 1993;34:406–9.
47. Pope Jr HG, Gruber AJ, Choi P, Olivardia R, Phillips KA. Muscle dysmorphia: an underrecognized form of body dysmorphic disorder. Psychosomatics. 1997;38:548–57.
48. Hildebrandt T, Langenbucher J, Schlundt DG. Muscularity concerns among men: development of attitudinal and perceptual measures. Body Image. 2004;1:169–81.
49. Raevuori A, Keski-Rahkonen A, Bulik CM, Rose RJ, Rissanen A, Kaprio J. Muscle dissatisfaction in young adult men. Clin Pract Epidemiol Ment Health. 2006;2:6.
50. Chittester NI, Hausenblas HA. Correlates of drive for muscularity: the role of anthropometric measures and psychological factors. J Health Psychol. 2009; 14:872–7.
51. Bond A, Choi PYL, Pope HG. Assessment of attentional bias and mood in users and non-users of anabolic-androgenic steroids. Drug Alchol Depend. 1995;37:241–5.
52. Choi PY. Alarming effects of anabolic steroids. Psychologist. 1993;6:258–60.
53. Dalby JT. Brief anabolic steroid use and sustained behavioral reaction. Am J Psychiatry. 1992;149: 271–2.
54. Pope HG, Katz DL. Psychiatric and medical effects of anabolic-androgenic steroid use. Arch Gen Psychiatry. 1994;51:375–82.
55. Su T, Pagliaro M, Schmidt PJ, Pickar D, Wolkowitz O, Rubinow DR. Neuropsychiatric effects of anabolic steroid in male normal volunteers. JAMA. 1993;269:2760–4.
56. O'Connor DB, Archer J, Hair WM, Wu FCW. Exogenous testosterone, aggression, and mood in eugonadal and hypogonadal men. Physiol Behav. 2002;75:557–66.
57. Pope HG, Kouri EM, Hudson JI. Effects of supraphysiological doses of testosterone on mood and aggression in normal men. Arch Gen Psychiatry. 2000;57:133–40.
58. Tricker R, Casaburi R, Storer TW, Clevenger B, Berman N, Shirazi A, Bhasin S. The effects of supraphysiological doses of testosterone on angry behavior in healthy eugonadal men: a clinical research center study. J Clin Endocrinol Metab. 1996;81:3754–8.
59. Ernst E. The risk-benefit profile of commonly used herbal therapies: Ginkgo, St. John's Wort, ginseng, echinacea, saw palmetto, and Kava. Ann Intern Med. 2002;136:42–53.
60. Kruk B, Chmura J, Krzeminski K, Ziemba AW, Nazar K, Pekkarinen H, Kaciuba-Uscilko H. Influence of caffeine, cold and exercise on multiple choice reaction time. Psychopharmacology (Berl). 2001;157:197–201.
61. Sinclair CJ, Geiger JD. Caffeine use in sports: a pharmacological review. J Sports Med Phys Fitness. 2000;40:71–9.
62. Doyle T, Arent SM, Lutz RS. Dose-response effects of caffeine on performance in college fencers. J Strength Cond Res. 2006;20, e41.
63. Kenemans JL, Lorist MM. Caffeine and selective visual processing. Pharmacol Biochem Behav. 1995; 52:461–71.
64. Rees K, Allen D, Lader M. The influences of age and caffeine on psychomotor and cognitive function. Psychopharmacology. 1999;145:181–8.
65. Fine BJ, Kobrick L, Lieberman HR, Marlowe B, Riley RH, Tharion WJ. Effects of caffeine or diphenhydramine on visual vigilance. Psychopharmacology (Berl). 1994;114:233–8.
66. Koelega HS. Stimulant drugs and vigilance performance: a review. Psychopharmacology (Berl). 1993; 111:1–16.

67. Reyner LA, Horne JA. Early morning driver sleepiness: effectiveness of 200 mg caffeine. Psychophysiology. 2000;37:251–6.
68. Lorist MM, Snel J, Kok A, Mulder G. Influence of caffeine on selective attention in well-rested and fatigued subjects. Psychophysiology. 1994;31:525–34.
69. Patat A, Rosenzwieg P, Enslen M, Trocherie S, Miget N, Bozon MC, Allain H, Gandon JM. Effects of a new slow release formulation of caffeine on EEG, psychomotor and cognitive functions in sleep deprived subjects. Hum Psychopharmacol Clin Exp. 2000;15:153–70.
70. Smith A. Effects of repeated doses of caffeine on mood and performance of alert and fatigued volunteers. J Psychopharmacol. 2005;19:620–6.
71. Lieberman HR, Tharion WJ, Shukitt-Hale B, Speckman KL, Tulley R. Effects of caffeine, sleep loss, and stress on cognitive performance and mood during U.S. Navy SEAL training. Psychopharmacology (Berl). 2002;164:250–61.
72. Bovim G, Naess P, Helle J, Sand T. Caffeine influence on the motor steadiness battery in neuropsychological tests. J Clin Exp Neuropsychol. 1995; 17:472–6.
73. Loke WH, Hinrichs JV, Ghoneim MM. Caffeine and diazepam: separate and combined effects on mood, memory, and psychomotor performance. Psychopharmacology (Berl). 1985;87:344–50.
74. Tikuisis P, Keefe AA, McLellan TM, Kamimori G. Caffeine restores engagement speed but not shooting precision following 22 h of active wakefulness. Aviat Space Environ Med. 2004;75:771–6.
75. Gillingham RL, Keefe AA, Tikuisis P. Acute caffeine intake before and after fatiguing exercise improves target shooting engagement time. Aviat Space Environ Med. 2004;75:865–71.
76. Ferrauti A, Weber K, Struder HK. Metabolic and ergogenic effects of carbohydrate and caffeine beverages in tennis. J Sports Med Phys Fitness. 1997; 37:258–66.
77. Hogervorst E, Bandelow S, Schmitt J, Jentjens R, Oliveira M, Allgrove J, Carter T, Gleeson M. Caffeine improves physical and cognitive performance during exhaustive exercise. Med Sci Sports Exerc. 2008;40:1841–51.
78. Ruijter J, Lorist LM, Snel J, De Ruiter M. The influence of caffeine on sustained attention: an ERP study. Pharmacol Biochem Behav. 2000;66:29–37.
79. Huang Z-L, Qu W-M, Eguchi N, et al. Adenosine A2A, but not A1, receptors mediate the arousal effect of caffeine. Nat Neurosci. 2005;8:858–9.
80. Ross GW, Abbott RD, Petrovich H, et al. Relationship between caffeine intake and Parkinson's disease. JAMA. 2000;283:2674–9.
81. Ferré S, Fredholm BB, Morelli M, Popoli P, Fuxe K. Adenosine-dopamine receptor-receptor interactions as an integrative mechanism in the basal ganglia. Trends Neurosci. 1997;20:482–7.
82. Garrett BE, Griffiths RR. The role of dopamine in the behavioral effects of caffeine in animals and humans. Pharmacol Biochem Behav. 1997;57: 533–41.
83. Schwarzschild MA, Chen J-F, Ascherio A. Caffeinated clues and the promise of adenosine A2A antagonists in PD. Neurology. 2002;58:1154–60.
84. Kitagawa M, Houzen H, Tashiro K. Effects of caffeine on the freezing of gait in Parkinson's disease. Mov Disord. 2007;22:710–2.
85. Gilbert DG, Dibb WD, Plath LC, Hiyane SG. Effects of nicotine and caffeine, separately and in combination, on EEG topography, mood, heart rate, cortisol, and vigilance. Psychophysiology. 2000;37:583–95.
86. Lovallo WR, al'Absi M, Blick K, et al. Stress-like adrenocorticotropin responses to caffeine in young healthy men. Pharmacol Biochem Behav. 1996;55: 365–9.
87. al'Absi M, Lovallo WR, Sung BH, et al. Persistent adrenocortical sensitivity to caffeine in borderline hypertensive men. FASEB J. 1993;7:A552.
88. al'Absi M, Lovallo WR, McKey B, Sung BH, Whitsett TL, Wilson MF. Hypothalamic-pituitary-adrenocortical responses to psychological stress and caffeine in men at high and low risk for hypertension. Psychosom Med. 1998;60:521–7.
89. Blanchard J, Sawers SJA. Comparative pharmacokinetics of caffeine in young and elderly men. J Pharmacokinet Biopharm. 1983;11:109–26.
90. Jacobson BH, Thurman-Lacey SR. Effect of caffeine on motor performance by caffeine-naïve and -familiar subjects. Percept Mot Skills. 1992;74:151–7.
91. Mikalsen A, Bertelsen B, Flaten MA. Effects of caffeine, caffeine-associated stimuli, and caffeine-related information on physiological and psychological arousal. Psychopharmacology (Berl). 2001;157: 373–80.
92. Wyss M, Schulze A. Health implications of creatine: can oral creatine supplementation protect against neurological and atherosclerotic disease? Neuroscience. 2002;112:243–60.
93. Faul M, Xu L, Wald MM, Coronado VG. Traumatic brain injury in the United States: emergency department visits, hospitalizations, and deaths. Atlanta, GA: Centers for Disease Control and Prevention, National Center for Injury Prevention and Control; 2010.
94. Gilchrist J, Thomas KE, Xu L, McGuire LC, Coronado VG. Nonfatal sports and recreation related traumatic brain injuries among children and adolescents treated in emergency departments in the United States, 2001-2009. MMWR. 2011;60:1337–42.
95. Sullivan PG, Geiger JD, Mattson MP, Scheff SW. Dietary supplement creatine protects against traumatic brain injury. Ann Neurol. 2000;48:723–9.
96. Klivenyi P, Ferrante RJ, Matthews RT, et al. Neuroprotective effects of creatine in a transgenic animal model of amyotrophic lateral sclerosis. Nat Med. 1999;5:347–50.
97. Klivenyi P, Calingasan NY, Starkov A, et al. Neuroprotective mechanisms of creatine occur in the absence of mitochondrial creatine kinase. Neurobiol Dis. 2004;15:610–7.

98. Rae C, Digney AL, McEwan SR, Bates TC. Oral creatine monohydrate supplementation improves brain performance: a double-blind, placebo-controlled, cross-over trial. Proc R Soc Lond [Biol]. 2003;270:2147–50.
99. Watanabe A, Kato N, Kato T. Effects of creatine on mental fatigue and cerebral hemoglobin oxygenation. Neurosci Res. 2002;42(4):279–85.
100. Jacobus WE, Diffley DM. Creatine kinase of heart mitochondria: control of oxidative phosphorylation by the extramitochondrial concentrations of creatine and phosphocreatine. J Biol Chem. 1986;261: 16579–83.
101. Sakellaris GS, Partalis NI, Nasis GD, Kotsiou ME, Tamiolaki MD, Bouloukaki EH, Evangeliou AN. Outcome of traumatic dysarthria and lingual problems of understanding with creatine administration. An open label randomized pilot study. J Trauma Treat. 2012;1:120.
102. Ferrante RJ, Andreassen OA, Jenkins BG, et al. Neuroprotective effects of creatine in a transgenic mouse model of Huntington's disease. J Neurosci. 2000;20:4389–97.
103. Mangiarini L, Sathasivam K, Seller M, et al. Exon 1 of the HD gene with an expanded CAG repeat is sufficient to cause a progressive neurological phenotype in transgenic mice. Cell. 1996;87:493–506.
104. Matthews RT, Yang L, Jenkins BG, et al. Neuroprotective effects of creatine and cyclocreatine in animal models of Huntington's disease. J Neurosci. 1998;18:156–63.
105. Verbessem P, Lemiere J, Eijnde BO, et al. Creatine supplementation in Huntington's disease: a placebo-controlled pilot trial. Neurology. 2003;61:925–30.
106. Mahady GB. Ginkgo biloba: a review of quality, safety, and efficacy. Nutr Clin Care. 2001;4:140–7.
107. Kleijnen J, Knipschild P. Ginkgo biloba for cerebral insufficiency. Br J Clin Pharmacol. 1992;34:352–8.
108. Lingaerde O, Foreland AR, Magnusson A. Can winter depression be prevented by Ginkgo biloba extract? A placebo-controlled trial. Acta Psychiatr Scand. 1999;100:62–6.
109. Hopfenmüller W. Evidence for a therapeutic effect of Ginkgo biloba special extract: meta-analysis of 11 clinical studies in patients with cerebrovascular insufficiency in old age. Arzneimittelforschung. 1994;44:1005–13.
110. Oken BS, Storzbach DM, Kaye JA. The efficacy of Ginkgo biloba on cognitive function in Alzheimer's disease. Arch Neurol. 1998;55:1409–15.
111. Birks J, Grimly Evans J. Ginkgo biloba for cognitive impairment and dementia. Cochrane Database Syst Rev. 2007;(2):CD003120.
112. Scholey AB, Kennedy DO. Acute, dose-dependent cognitive effects of Ginkgo biloba, Panax ginseng and their combination in healthy young volunteers: differential interactions with cognitive demand. Hum Psychopharmacol Clin Exp. 2002;17:35–44.
113. Gertz H-J, Kiefer M. Review about Ginkgo biloba special extract EGb 761 (Ginkgo). Curr Pharm Des. 2004;10:261–4.
114. Butterfield DA, Howard B, Yatin S, et al. Elevated oxidative stress in models of normal brain aging and Alzheimer's disease. Life Sci. 1999;65:1883–92.
115. Vining Smith J, Luo Y. Elevation of oxidative free radicals in Alzheimer's disease models can be attenuated by Ginkgo biloba extract EGb 761. J Alzheimers Dis. 2003;5:287–300.
116. Tchantchou F, Xu Y, Wu Y, Christen Y, Luo Y. EGb 761 enhances adult hippocampal neurogenesis and phosphorylation of CREB in transgenic mouse model of Alzheimer's disease. FASEB J. 2007;21: 2400–8.
117. Letenneur L, Proust-Lima C, Le Gouge A, Dartigues JF, Barberger-Gateau P. Flavonoid intake and cognitive decline over a 10-year period. Am J Epidemiol. 2007;165(12):1364–71 [Epub ahead of print].
118. Grodstein F, Chen J, Willett WC. High-dose antioxidant supplements and cognitive function in community-dwelling elderly women. Am J Clin Nutr. 2003;77:975–84.
119. Kanowski S, Herrmann WM, Stephan K, Wierich W, Horr R. Proof of efficacy of the Ginkgo biloba special extract EGb 761 in outpatients suffering from mild to moderate primary degenerative dementia of Alzheimer type or multi-infarct dementia. Pharmacopsychiatria. 1996;29:47–56.
120. LeBars PL, Katz MM, Berman N, Itil TM, Freedman AM, Schatzberg A. A placebo-controlled, double-blind, randomized trial of an extract of Ginkgo biloba for dementia. JAMA. 1997;278:1327–32.
121. LeBars PL, Velasco FM, Ferguson JM, Dessain EC, Kieser M, Hoerr R. Influence of the severity of cognitive impairment on the effect of the Ginkgo biloba extract EGB 761 in Alzheimer's disease. Neuropsychobiology. 2002;45:19–26.
122. van Dongen M, van Rossum E, Kessels A, Sielhorst H, Knipschild P. Ginkgo for elderly people with dementia and age-associated memory impairment: a randomized clinical trial. J Clin Epidemiol. 2003; 56:367–76.
123. Ihl R, Tribanek M, Bachinskaya N. Efficacy and tolerability of a once daily formulation of Ginkgo biloba extract EGb 761 in Alzheimer's disease and vascular dementia: results from a randomized controlled trial. Pharmacopsychiatry. 2012;45:41–6.
124. Kim HL, Streltzer J, Goebert D. St. John's wort for depression: a meta-analysis of well-defined clinical trials. J Nerv Ment Dis. 1999;187:532–9.
125. Linde K, Ramirez G, Mulrow CD, Pauls A, Weidenhammer W, Melchart D. St. John's wort for depression—an overview and meta-analysis of randomized clinical trials. BMJ. 1996;313:253–8.
126. Linde K, Mulrow CD. St. John's wort for depression (Cochrane Review). Cochrane Database Syst Rev. 1998;(4):CD000448.

127. Gaster B. Holroyd. St. John's wort for depression: a systematic review. Arch Intern Med. 2000;160: 152–6.
128. Whiskey E, Werneke U, Taylor D. A systematic review and meta-analysis of Hypericum perforatum in depression: a comprehensive clinical review. Int Clin Psychopharmacol. 2001;16:239–52.
129. Williams JW, Mulrow CD, Chiquette E. A systematic review of new pharmacotherapies for depression in adults. Ann Intern Med. 2000;132:743–56.
130. Szegedi A, Kohnen R, Dienel A, Kieser M. Acute treatment of moderate to severe depression with hypericum extract WS 5570 (St John's wort): randomized controlled double blind non-inferiority trial versus paroxetine. BMJ. 2005. doi:10.1136/bmj.38356.655266.82.
131. Barnes J, Anderson LA, Phillipson JD. St. John's wort (Hypericum perforatum L.): a review of its chemistry, pharmacology and clinical properties. J Pharm Pharmacol. 2001;53:583–600.
132. Bilia AR, Gallori S, Vincieri FF. St. John's wort and depression: efficacy, safety, and tolerability—an update. Life Sci. 2002;70(26):3077–96.
133. Shelton RC, Keller MB, Gelenberg A, et al. Effectiveness of St. John's wort in major depression: a randomized controlled trial. JAMA. 2001;285: 1978–86.
134. Lecrubier Y, Clerc G, Didi R, Kieser M. Efficacy of St. John's wort extract WS 5570 in major depression: a double-blind, placebo-controlled trial. Am J Psychiatry. 2002;159:1361–6.
135. Fava M, Alpert J, Nierenberg AA, et al. A double-blind, randomized trial of St. John's wort, fluoxetine, and placebo in major depressive disorder. J Clin Psychopharmacol. 2005;25:441–7.
136. Chatterjee SS, Nolder M, Koch E, Erdelmeier C. Antidepressant activity of hypericum perforatum and hyperforin: the neglected possibility. Pharmacopsychiatry. 1998;31:7–15.
137. Müller WE, Singer A, Wonnemann M, Hafner U, Rolli M, Schäfer C. Hyperforin represents the neurotransmitter reuptake inhibiting constituent of hypericum extract. Pharmacopsychiatry. 1998;31: 16–21.
138. Müller WE, Rolli M, Schäfer C, Hafner U. Effects of hypericum extract in biochemical models of antidepressant activity. Pharmacopsychiatry. 1997;30: 102–7.
139. Wonnemann M, Singer A, Müller WE. Inhibition of synaptosomal uptake of 3H-L-glutamate and 3H-GABA by hyperforin, a major constituent of St. John's wort: the role of amiloride sensitive sodium conductive pathways. Neuropsychopharmacology. 2000;23:188–97.
140. Fiebich BL, Höllig A, Lieb K. Inhibition of substance P-induced cytokine synthesis by St. John's wort extracts. Pharmacopsychiatry. 2001;34:S26–8.
141. Cott JM. In vitro receptor binding and enzyme inhibition by Hypericum perforatum extract. Pharmacopsychiatry. 1997;30:108–12.
142. Madabushi R, Frank B, Drewelow B, Derendorf H, Butterweck V. Hyperforin in St. John's wort drug interactions. Eur J Clin Pharmacol. 2006;62: 225–33.
143. Müller WE, Rolli M, Schäfer C, Hafner U. Effects of Hypericum extract on the expression of serotonin receptors. J Geriatr Psychiatry Neurol. 1994;7:63–4.
144. Demmott K. St. John's wort tied to serotonin syndrome. Clin Psychiatry News. 1998;26:28.
145. Landers DM, Arent SM. Exercise and mental health. In: Eklund RC, Tenenbaum G, editors. The handbook of sport psychology. 3rd ed. New York: Wiley; 2007. p. 469–91.
146. Kidd PM. Omega-3 DHA and EPA for cognition, behavior, and mood: clinical findings and structural-functional synergies with cell membrane phospholipids. Altern Med Rev. 2007;12:207–27.
147. Freund-Levi Y, Eriksdotter-Jönhagen M, Cederholm T, Basun H, Faxén-Irving G, Garlind A, Vedin I, Vessby B, Wahlund L, Palmblad J. ω-3 fatty acid treatment in 174 patients with mild to moderate Alzheimer's disease: OmegAD study. A randomized double-blind trial. Arch Neurol. 2006;63:1402–8.
148. Cole GM, Ma Q-L, Frautschy SA. Omega-3 fatty acids and dementia. Prostaglandins Leukot Essent Fatty Acids. 2009;81:213–21.
149. Fontani G, Corradeschi F, Felici A, Alfatti F, Migliorini S, Lodi L. Cognitive and physiological effects of Omega-3 polyunsaturated fatty acid supplementation in healthy subjects. Eur J Clin Invest. 2005;35:691–9.
150. Richardson AJ, Puri BK. A randomized double-blind, placebo-controlled study of the effects of supplementation with highly unsaturated fatty acids on ADHD-related symptoms in children with specific learning difficulties. Prog Neuropsychopharmacol Biol Psychiatry. 2002;26:233–9.
151. Stevens LJ, Zentall SS, Abate ML, Kuczek T, Burges JR. Omega-3 fatty acids in boys with behavior, learning, and health problems. Physiol Behav. 1996;59:915–20.
152. Voigt RG, Llorente AM, Jensen CL, Fraley JK, Berretta MC, Heird WC. A randomized, double-blind, placebo-controlled trial of docosahexaenoic acid supplementation in children with attention-deficit/hyperactivity disorder. J Pediatr. 2001;139: 189–96.
153. Hirayama S, Hamazaki T, Terasawa K. Effects of docosahexaenoic acid-containing food administration on symptoms of attention-deficit/hyperactivity disorder—a placebo-controlled double-blind study. Eur J Clin Nutr. 2004;58:467–73.
154. Hamazaki T, Hirayama S. The effect of docosahexaenoic acid-containing food administration on

symptoms of attention-deficit/hyperactivity disorder—a placebo-controlled double-blind study. Eur J Clin Nutr. 2004;58:838.
155. Stevens L, Zhang W, Peck L, Kuczek T, Grevstad N, Mahon A, Zentall SS, Arnold LE, Burgess JR. EFA supplementation in children with inattention, hyperactivity, and other disruptive behaviors. Lipids. 2003;38:1007–21.
156. Sinclair AJ, Begg D, Mathai M, Weisinger RS. Omega 3 fatty acids and the brain: review of studies in depression. Asia Pac J Clin Nutr. 2007;16:391–7.
157. Mills JD, Hadley K, Bailes JE. Dietary supplementation with the omega-3 fatty acid docosahexaenoic acid in traumatic brain injury. Neurosurgery. 2011;68:474–81.
158. Mills JD, Bailes JE, Sedney CL, Hutchins H, Sears B. Omega-3 fatty acid supplementation and reduction of traumatic axonal injury in a rodent head injury model. J Neurosurg. 2011;114:77–84.
159. Wu A, Ying Z, Gomez-Pinilla F. Dietary omega-3 fatty acids normalize BDNF levels, reduce oxidative damage, and counteract learning disability after traumatic brain injury in rats. J Neurotrauma. 2004;21:1457–67.
160. Lespérance F, Frasure-Smith N, St-André E, Turecki G, Lespérance P, Wisniewski SR. The efficacy of omega-3 supplementation for major depression: a randomized controlled trial. J Clin Psychiatry. 2011;72:1054–62.
161. Martins JG. EPA but not DHA appears to be responsible for the efficacy of omega-3 long chain polyunsaturated fatty acid supplementation in depression: evidence from a meta-analysis of randomized controlled trials. J Am Coll Nutr. 2009;28:525–42.
162. Marangell LB, Martinez JM, Zboyan HA, Kertz B, Seung Kim HF, Puryear LJ. A double-blind, placebo-controlled study of the omega-3 fatty acid docosahexaenoic acid in the treatment of major depression. Am J Psychiatry. 2003;160:996–8.
163. Bloch MH, Hannestad J. Omega-3 fatty acids for the treatment of depression: systematic review and meta-analysis. Mol Psychiatry. 2012;17:1272–82.
164. Lin P-Y, Mischoulon D, Freeman MP, Matsuoka Y, Hibbeln J, Belmaker RH, Su K-P. Are omega-3 fatty acids anti-depressants or just mood-improving agents? Mol Psychiatry. 2012;17:1161–3.
165. Rogers PJ, Appleton KM, Kessler D, Peters TJ, Gunnell D, Hayward RC, Heatherley SV, Christian LM, McNaughton SA, Ness AR. No effect of n-3 long-chain polyunsaturated fatty acid (EPA and DHA) supplementation on depressed mood and cognitive function: a randomised controlled trial. Br J Nutr. 2008;99:421–31.

Part II

Nutritional Basics First

3 The Role of Nutritional Supplements Complementing Nutrient-Dense Diets: General Versus Sport/Exercise-Specific Dietary Guidelines Related to Energy Expenditure

Susan M. Kleiner and Mike Greenwood

Abstract

A nutrient-dense diet is a critical aspect in attaining optimal exercise training, recovery, and athletic performance outcomes. While including safe and effective nutritional supplements in the dietary design can be extremely helpful in promoting adequate caloric and nutrient ingestion, they are not a complete cure in promoting adequate caloric ingestion based on individualized caloric expenditure needs without the proper diet. Specifically, a strategic and scientifically based nutrient-dense dietary profile should be created by qualified professionals to meet the sport/exercise-specific energy and nutrient demands of any individual involved in select training intensity protocols. Finally, ingesting the right quantity and quality of nutrient-dense calories at precise windows of opportunity becomes vital in attaining desired training and/or competitive performance outcomes.

Keywords

Nutrient dense • Nutritional Supplements • Caloric intake • Caloric expenditure • Nutrient timing • Restoration • Macronutrient profiles

3.1 Establishing Adequate Dietary Foundations

One of the important differences between any athlete and a champion is the keen ability to pay attention to details regarding a variety of training categories. While one might think that the important details of sports nutrition center on targeting the right supplements, that assumption could not be further from the truth. Nothing is more important than a good nutritional foundation.

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This chapter focuses on the details of nutrient density, how to pack in the most nutrition for every calorie that you eat from food, putting your food to work for you. By maximizing nutrient density, your body will be primed to respond to the supplements that you may choose to add to enhance your nutrition program. Build a strong nutritional foundation and your optimal health, fitness, and performance outcomes will follow.

3.2 Nutrient Density Defined

The most important factor in an athlete's diet is the amount of energy available. Calories (or joules) are the key to activity, to feeling energized, to building muscle, to increasing power, and to fueling endurance. Hand in hand with calories are the nutrients that you consume per calorie. If one just focuses on getting enough calories to fuel activity, foods high in simple sugars and fats would be the ideal choices. There is no doubt that this would fuel exercise. However, a diet robust in calories, along with the right composition of proteins, carbohydrates, healthy fats, vitamins, minerals, and other notable food factors, will catalyze metabolism and tissue building, getting the athlete further in training at a faster rate, with a superior outcome.

A common example of nutrient density is comparing a sports drink to orange juice and water (see Table 3.1). Even if you doubled the amount of sports drink to make the calories equivalent to orange juice, the nutrient density is not even close.

Table 3.1 Nutrient density fluid comparisons

	8 oz. sports drink	8 oz. orange juice	8 oz. water
Calories	50	112	0
Protein (g)	0	2	0
Carb (g)	14	27	0
Fat (g)	0	0	0
Vit A (IU)	0	266	0
Vit C (mg)	0	97	0
Folate (mg)	0	110	0
Ca (mg)	0	0	5
Mg (mg)	0	0	2
K (mg)	30	473	0
Na (mg)	110	2	5

The sports drink is the performance beverage of choice during exercise to promote rehydration and glucose/electrolyte replenishment. If a sports drink is the beverage of choice all day long, then many calories will add up without any further nutrition. If orange juice is chosen as a beverage during the day, there is greater density of nutrients per calorie, building the nutritional foundation throughout the day. Finally, water adds no calories and a minor amount of nutrients, but the ongoing fluid replacement is essential for an athlete. By eliminating "empty calories" from sports drinks during non-exercise times, the athlete can eat more nutrient-dense foods, allowing for a greater amount and variety of nutrients in the diet and enhancing the nutritional foundation for performance.

3.3 The Nutrient-Dense Diet

It is often assumed that a nutrient-dense diet is also a diet full of variety, but this should not be taken for granted. One could easily have a diet that is high in certain nutrients, but missing others due to the elimination of an entire food group. For instance, if dairy is eliminated from the diet, one could easily consume enough of most nutrients, but it would be difficult to consume enough calcium and vitamin D. Along with choosing foods that are dense in nutrients, a nutrient-dense diet must also be rich in a variety of foods from all the food groups to be most readily and efficiently both nutritionally dense and complete (see Table 3.2).

In addition to choosing a variety of foods from all of the food groups, a variety of foods from within each food group should also be selected. For example, one could select only wheat bread, apples, celery, yogurt, hamburger, and butter to create a diet that includes foods from all the food groups. But if this is what was eaten each day it would not provide a nutritionally complete diet, despite representation from all of the food groups. Selecting apples, peaches, and grapefruits from the fruit group, celery, broccoli, and onions from

Table 3.2 Foundational food group categories

Grains, breads, and starches
Fruit
Non-starchy vegetables
Milk/dairy
Meat and meat substitutes
Very lean
Lean
Medium-fat
High-fat
Fats

the vegetable group, wheat, buckwheat, quinoa, peas, and winter squash from the grains and starches group, etc., represents variety among the food groups as well as from within each group.

3.4 Nutritional Supplements Defined

Within the area of sports, performance-enhancing aids have been defined and classified by Dr. Melvin H. Williams. Describing them as sports ergogenics, Dr. Williams categorizes them into nutritional aids, pharmacological aids, and physiological aids. Nutritional supplements would fall under the category of nutritional aids and serve to "increase muscle tissue, muscle energy supplies, and the rate of energy production in the muscle." Some nutritional supplements are also used to enhance mental focus and energy [1].

Most nutritional supplements are obvious, but some are not as clear. Supplements included in the broad nutritional aids category include fluid replacements, carbohydrates, fats, protein/amino acids and their metabolites, vitamins, minerals, plant extracts, miscellaneous food factors, phytochemicals, probiotics, prebiotics, and engineered dietary supplements.

3.5 The Role of Supplements in a Nutrient-Dense Diet

There are many circumstances where nutritional supplementation plays a very important role in both health and performance. The most common instance is when food groups or key foods in the diet must be eliminated intentionally due to food allergies or intolerances. Supplementation with the minerals and vitamins associated with bone health is essential when individuals are allergic to cow's milk protein. Supplementation may come in the form of food fortification, as with the addition of calcium and vitamins A and D to soymilk. Supplementation can also be in a daily dose of the nutrients through liquids, pills, or capsules.

Oftentimes the diet is unintentionally incomplete due to lack of nutritional knowledge, hectic lifestyle, or other reasons. In this case, daily multivitamin–mineral supplementation has been suggested as an "insurance policy" for health promotion and disease prevention [2].

The use of nutritional supplementation in sports is pursued with the goal of enhancing performance. As stated above, in this case nothing can substitute for a complete, nutrient-dense diet from foods. However, there are circumstances where athletes benefit from supplementation due to increased requirements but an inability to consume increased amounts of nutrients from foods. An example of this may be protein. The protein requirements of a lightweight or middleweight strength and power athlete may be difficult to meet with food alone. Since dense sources of protein most often occur with fats and/or carbohydrates (egg whites are the exception here), the total caloric intake for the diet may be too high, or the foods too inconvenient to eat throughout the day. A powdered protein supplement can offer just pure protein that can be easily mixed with water anywhere during the athlete's day. For any athlete, the convenience of dietary supplements used in a targeted way in the diet, of which protein is one good example, is often the driving force for their use.

Athletes may also benefit from increased amounts of specific nutrients, but will not necessarily benefit from consuming increasing amounts of the whole foods that are the source of those nutrients. Creatine is an excellent example of this notion. While the research is clear that many athletes will benefit from creatine supplementation, consuming enough creatine from food (meat) to achieve dose requirements would be both difficult and unhealthy.

In both of the above examples, nutritional supplementation plays an important role in performance enhancement. However, neither of the supplements will be as effective if used in place of a nutrient-dense diet, rather an addition to a nutrient-dense diet.

3.6 Designing a Nutrient-Dense Diet

3.6.1 Establishing Viable Energy Requirements

Signs and symptoms associated with decrements in performance and health that are related to clinical safety markers have been linked to a number of aspects including chronic caloric restrictions [3, 4]. In relation to establishing a solid nutritional foundation, to adequately set the stage for reaching optimal training/performance outcomes one need not look any further than establishing a properly designed dietary plan. While this may seem to be an easy goal to accomplish, the commitment, time, and costs often associated with a quality dietary strategy often make it difficult to attain this option. It is a widely accepted fact that athletes involved with high-intensity training and competition do not ingest the right type and/or amounts of macronutrients to offset their energy expenditure. Confirming this premise, utilizing a self-report measure, researchers recently reported that 405 Division I strength and power athletes' {male = 191; female = 214} caloric intake did not match the recommended caloric intake requirements compared to their caloric expenditure during their annual peroidized training cycles [5]. Specifically, 86 % of the participants surveyed reported being drastically below the scientifically based recommended macronutrient intake for strength/power athletes [3–5]. In fact over 79 % of the athletes reported being hungry during practice/training sessions and competitive events [5]. Finally, with the noted undernourished macronutrient levels, one could also question these athletes' micronutrient dietary status, especially when 74 % of these participants reported never ingesting a multivitamin during the academic training year.

While nutritional supplementation is a viable alternative for athletes to consume and meet their dietary needs, it should be noted that this practice is not a healthy option to completely replace a quality nutrient-dense diet. This is exactly why it is referred to as nutritional supplementation, to complement/supplement a properly designed nutrient-dense diet. In this section, nutritional necessities surrounding an "eat to compete" philosophy are addressed in relation to strategies to promote recovery of athletic and exercise populations.

The most critical aspect of establishing a properly implemented dietary strategy to accomplish optimal performance outcomes is to insure that exercise participants ingest quality caloric needs to balance specific energy expenditure [3, 4]. When considering this nutritional approach, it is always important to include and calculate individual differences regarding select exercise training intensities. While RDA guidelines have been established regarding daily dietary consumption for general populations, these suggested initiatives really do not apply to athletic or exercise populations involved with intense training protocols because of greater caloric requirements. For example, daily caloric intake needs for untrained individuals are based on the number of kilocalories per kilogram of body weight per day which usually averages between 1,900 and 3,000 kcal daily [6–8]. Without question, when adding various factors of exercise into the equation, the frequency, duration, and intensity demands of the training protocol require increased nutritional intake to maintain an effective energy balance. Individuals involved in low-intensity exercise lasting 30–40 min a day that is performed three times per week typically require 1,800–2,400 kilocalories per day due to minimal physical exertion and energy expenditure [4, 7, 8]. Athletes undertaking moderate exercise protocols defined as 5–6 times a week for 2–3 h a day or intense training 5–6 days a week 3–6 h a day obviously require greater dietary needs (2,500–8,000 kcal/day depending on body weight) compared to individuals involved in light exercise protocols [4, 8, 9]. When accurately evaluating the amount of caloric values needed for individuals involved in the previously mentioned levels of

exercise training, it becomes increasingly evident that athletes have a difficult time maintaining ingestion of enough calories by simply consuming a well-balanced diet. Due to the enormous energy expenditure for high volume intensity training the combination of nutritional supplementation to a quality nutritional dietary profile makes it much more feasible for athletes to consume enough energy to replace caloric needs. The proper replacement of caloric needs based on energy expenditure not only helps control a person's health status but heightens the recovery process needed for adaption to the exercise session and future optimal training/performance bouts. While a balanced energy status is vital for all athletes in formalized training, this aspect becomes even more imperative for larger athletes who must consume huge amounts of quality calories to offset the energy expenditures acquired from high volume and intensity training. Obviously the ramifications of inappropriate dietary strategies can not only lead to tremendous weight loss but make the athlete more susceptible to the various signs and symptoms of physiological and psychological decline. Further, there is scientific evidence that the athlete who undertakes intense training has a greater preponderance to display suppressed appetites which increases the possibility of health risk factors and ultimately promotes performance decrements [10]. A great strategic plan is to develop a multidisciplinary team approach that combines athletic coaches, athletic trainers, sports nutritionists, strength and conditioning coaches, parents, and physicians to closely monitor and evaluate the athlete's nutrient-dense dietary status in an effort to maintain body weight and promote restoration, thereby promoting optimal performance outcomes.

While caloric ingestion concerns of larger athletes were previously mentioned, there are additional athletic groups that require close monitoring in relation to meeting caloric energy demands. Specifically, female athletes such as gymnasts, figure skaters, and distance runners can be highly susceptible to eating disorders and therefore place themselves in jeopardy of not meeting specific energy caloric needs. This can also hold true for athletes who participate in sports like horse racing (jockeys), boxing, and wrestling and select unsafe dietary strategies in order to make a particular weight class for competition.

3.7 Determining Macronutrient Profiles

The goals of training and competition will guide the determination of dietary macronutrient profiles. While the differences in the dietary recommendations may appear small, research has shown that they lead to significant differences in outcomes in endurance enhancement, muscle growth, strength building, and power output. In all cases, adequate energy consumption is the most critical factor, with macronutrient distribution following close behind. For a very detailed discussion of research and nutrient-dense recommendations for energy and macronutrient profiles and diet plans, see Power Eating, 4th Edition [11].

3.7.1 Endurance Enhancement

Carbohydrates and fats are long-distance fuels. A diet low in either one will temper performance advancement. Protein is essential for repair and recovery of damaged tissues and to keep the body healthy as it is driven in distance and duration. Typical recommendations for carbohydrate are 5–7 g/kg body weight per day for general training. With exercise of increased distance and duration, a carbohydrate intake of 8–10 g/kg/day has been shown to be a successful dietary strategy for fueling performance. Male athletes are more likely to achieve these recommendations than female athletes. Due to their lower energy requirements, it is often difficult to consume this much carbohydrate and maintain control of body weight, an essential factor in long-distance sports [12]. These calorie and carbohydrate deficits can lead to disruption of metabolic control and are therefore essential to monitor in female and male athletes [13].

The protein needs of endurance athletes are close to twice the Dietary Reference Intakes for the general population. According to research studies, an intake of 1.4–1.8 g/kg/day of protein is an important target for support of endurance exercise [14, 15].

The difficulty with these recommendations is that once you add up the carbohydrate and protein needs of the diet, there is little room left for fat. However, the critical role that monounsaturated and polyunsaturated fats play in health promotion, disease prevention, hormone production, weight control, mood, and cognitive function requires their adequate inclusion in the diet. The proportion of calories from fat in the diet should not go below 25 % for any extensive length of time. The role of fats is so important that if calories are restricted it is advisable to reduce the proportion of carbohydrates in the diet to leave room for adequate protein and fat [16]. However, with appreciable energy restriction, a lowering of energy output is advisable to avoid gross metabolic disturbances [13].

3.7.2 Weight Gain and Muscle Growth

There is little disagreement on the nutritional requirements of building strength and power. Carbohydrate is required to fuel muscle building and sports-specific exercise, protein is essential to tissue recovery, repair, and growth, and fat is essential for production of the hormones that allow the entire anabolic process to move forward.

The protein needs of strength trainers and bodybuilders are higher than those of endurance athletes. When energy intake is adequate, protein needs during a building phase range from 2.0 to 2.5 g/kg body weight per day and are closely linked to total energy consumption. Carbohydrate needs are lower than those of endurance athletes and range from 4.5 to 7.0 g/kg/day depending on intensity and frequency of training. Depending on energy intake, 25–30 % of total calories will come from healthy fats [11].

3.8 Nutritionally Dense Restoration Timing Consideration

The issue of rest and recovery for athletes involved with specific training intensities and competitive situations involves so much more than adhering to adequate sleep patterns. Specifically, sport nutritionists and researchers have placed tremendous emphasis on the value of adequate dietary timing to promote viable recovery ingestion strategies. Understanding the value of select but quality nutritional timing is critical for athletes to not only increase strength and muscle mass but to enhance optimal performance outcomes.

Notable researchers in the Exercise and Sport Nutrition Laboratory at **Texas A & M** University promote the following guidelines for nutritional timing for athletic and exercise populations. In order to enhance the digestive process, athletes are encouraged to eat a full meal complete with high-energy carbohydrates 4–6 h before practice or competition. An example of this could include the ingestion of a high carbohydrate breakfast for afternoon training sessions and a carbohydrate snack for events prior to noon. Thirty to 60 min before practice/competition athletes should consume a combination carbohydrate (30–50 g)/protein (5–10 g) snack or shake to help provide needed energy and reduce catabolism. Ready to drink products and bars are convenient options for pre-training and pre-competition events which can help control markers of overtraining. One concern associated with post-training and competition dietary ingestion is that select athletes just are not hungry after the intense event. However, this is one of the most critical times to replenish dietary energy balance to offset tremendous energy expenditure. A viable recommendation is to ingest a post-workout snack within 30–60 min after the event comprised of a light carbohydrate/protein (50–100 g of carbohydrates and 30–40 g of protein) snack until the individual is ready to consume a complete dietary meal within the 2 h supported nutritional recovery window.

Further, the scientific based recommendation is to ingest low to moderate glycemic index and/or glycemic load carbohydrates prior to and during training/competition with an emphasis on high glycemic index/load carbohydrate ingestion options post-workout [5]. The post-workout/competition meal should be high in carbohydrates and protein because this is the period that body is most receptive to energy replenishment which helps sustain the critical energy repletion and balance. Overall, the general dietary suggested guidelines for athletes during heavy training periods include 55–65 % calories from carbohydrates, 15 % from protein, and less than 30 % from fat [3]. Sport nutritionists and researchers recommend that athletes involved in heavy intense training eat as frequently as 4–6 meals daily. However, it is recommended that power and/or strength athletes do not need as much carbohydrates as suggested in these guidelines.

In a recent book entitled "Nutrient Timing," the authors further drive home the importance of proper dietary ingestion based on a finely tuned nutritional schedule [17]. This exceptionally written and scientific based reading promotes the importance of a "Nutritional Timing System" that is comprised of three vital phases: (1) Energy, (2) Anabolic, and (3) Growth. While the majority of nutritional research has been centered on what to eat, this cutting-edge contribution places tremendous emphasis on what and when to eat. The primary concepts of this book not only allow the athlete to reach optimal potentials but prepare for the next training or competitive bout.

There are numerous formulae for determining energy needs. Table 3.3 is a representation of accumulated data translated into an easy-to-use format [18]. Under circumstances of endurance and ultra-endurance training, energy demands may be significantly higher, and the sport-specific energy demand should be added to the energy estimation (see Table 3.3). Numerous charts of energy expenditure during exercise are available from exercise physiology texts, as well as within online sites and nutrient analysis software.

Table 3.3 Men and women's estimation of daily energy needs based on activity intensity [16]

Level of activity	Estimated energy expenditure (kcal/kg/day)
Very light	
Men	31
Women	30
Light	
Men	38
Women	35
Moderate	
Men	41
Women	37
Heavy	
Men	50
Women	44

Very light: walking/standing, light: walking up to 3.0 mph; housecleaning, moderate: walking 3.5–4.0 mph; heavy housecleaning, heavy: football, soccer, other serious athletic endeavors; manual labor

3.9 Translating Nutrients into Food

Once macronutrient numbers are determined, they must be applied to the design of a meal plan and a menu. Meal plans can be based on accepted dietary guidelines but will need to be broadened and increased based on the needs of athletes. For a sedentary population, dietary guidelines often serve as a complete meal plan since calorie and nutrient needs are relatively low. In an active population, dietary guidelines serve as the scaffolding upon which a diet more dense in calories and nutrients can be built. Without the guidelines, it becomes more cumbersome to determine a basic outline of foods to include in the diet. The guidelines also ensure food group variety in the diet.

Several dietary guidelines are in use. The USDA MyPlate Food Guide is the most widely disseminated food guide in the United States (www.myplate.gov) [19]. Worldwide many countries have developed their own dietary guidelines based on cultural preferences and regional foods. The Healthy Eating Plate from Harvard School of Public Health (http://www.hsph.harvard.edu/nutritionsource/healthy-eating-plate/) [20],

The Mediterranean Diet Pyramid and Heritage Diet Pyramids from Oldways Preservation and Exchange Trust (www.oldwayspt.org) [21], and the Healing Foods Pyramid 2010 from the University of Michigan Integrative Medicine Clinic (http://med.umich.edu/umim/food-pyramid/index.htm) [22] are also well-accepted and scientifically founded food guides.

An adjunct to the food guides is the use of an accepted database of calories and macronutrients in foods. This can be done by hand using a rough equivalency chart based on The Exchange Lists for Meal Planning from the American Dietetic Association and The American Diabetes Association (see Table 3.4) [23]. Added to this chart is the notation for a teaspoon of added sugar. In all food guides, sugar is an optionally added food that should be controlled to avoid diluting the nutrient density of the diet. Rapidly and comfortably digested and utilized carbohydrates should be used by an athlete around exercise to gain the greatest fuel advantage.

One can determine the amount of added sugar in foods by first selecting a sugar-free prepared food, such as shredded wheat cereal, and observing the amount of sugar listed per serving on the Nutrition Facts label. This sugar-free cereal contains 0 g of sugar. Therefore, any cereal that contains sugar has it added as an ingredient (unless fruit is added as an ingredient, and even then the fruit will add a minor amount of sugar). You can determine the number of teaspoons of added sugar in foods by using this strategy and knowing that one teaspoon of sugar contains 4 g. Note that certain foods contain a natural amount of sugar: milk, for instance, contains 12 g of milk sugar per one cup serving. This should be subtracted from any amount greater than 12 g per cup in a milk product with added sugar [11].

Nutrient database software is also available for meal planning and menu design. There are a number of options available, from free and subscription online services to personal and professional software programs. Take the time to investigate the quality of the software and the nutrient database used for establishing nutrient values of foods consumed. The database should be research quality from reputable sources. The USDA Nutrient Database for Standard Reference is the gold standard used by nearly all modern software programs. Release 26 is the most recent edition. Other research quality databases may specialize in certain nutrients. For instance, the University of Minnesota Nutrition Coordinating

Table 3.4 Nutrients and calories per serving of food from each food group and from teaspoons of added sugar

Food groups	Carbohydrates (g)	Protein (g)	Fat (g)	Calories
Grains, breads, and starches	15	3	0–1	72–81
Fruit	15	–	–	60
Milk				
Fat-free	12	8	0	80
Reduced-fat	12	8	1–5	89–120
Whole	12	8	8	152
Non-starchy vegetables	5	2	–	28
Meat and meat substitutes				
Very Lean	–	7	0–1	28–37
Lean	–	7	3	55
Medium-fat	–	7	5	73
High-fat	–	7	8	100
Fat	–	–	5	45
Added sugars (1 teaspoon)	4	–	–	16

Adapted from: American Dietetic Association, American Diabetes Association. Exchange lists for meal planning. 2003 and Kleiner SM, Greenwood-Robinson M. Power eating, 3rd ed. Champaign, IL: Human Kinetics; 2014

Center Database is well known for its collection of foods important in the research of lipid metabolism, cancers, and other disease states.

If you are going to use the software for meal planning, then it must be versatile enough to allow for customization of calorie levels and nutrient composition. Many software programs will generate menus based on guidelines that you enter; others can use only preset guidelines. Editing should be easy and fairly intuitive. Files should be able to be exported and used in word processing or calendar programs, or compressed for email or other online utilities [24].

3.9.1 Example Diet Plans

Creating an effective diet plan requires an understanding of the goals of the athlete and their sport. When training and competition seasons alter energy and nutrient requirements, one diet plan may not be enough. Many athletes, especially youth athletes, participate in more than one sport and move quickly from a strength and power sport to the next season where speed and agility are primary. They frequently request a weight gain diet prior to the first season and a weight loss diet prior to the second.

For some athletes, the diet during the competitive season is lower in calories than in the preseason. During the preseason for football, increases in weight and strength can be desirable. Training activity is high, especially during training camps when two-a-day practices are common, along with strength training and position-specific drills. Energy needs are high. Once the season begins, activity levels decrease so calorie intakes must decrease to avoid fat gain.

Reset calorie and nutrient levels based on physical goals and seasonal changes. Diets can be designed for weight maintenance, muscle building, or fat loss. Macronutrient composition can be set to enhance endurance capacity or strength and power. Refer to other chapters in this text for sport-specific macronutrient breakdowns.

Once the calorie and macronutrient composition is set, choose a food guide system to start the distribution of nutrients into foods, portions, and servings.

Table 3.5 Percent calculation of macronutrients ingestion according to food groups

Maintenance diet for a male athlete training 5 or more days per week [11]	
Body weight: 180 lb./81.5 kg; height: 6′2″/188 cm; age: 25 years	
Calories: 42 calories/kg/day	3,423 calories
Protein: 1.4 g/kg/day	115 g
Carbohydrate: 6.0 g/kg/day	486 g
Fat: ~1.4 g/kg/day	~114 g

Table 3.6 Food group distributions via USDA "My Food Plate Guide" SuperTracker

Grains, breads, and starches	10 servings
Fruit	5 servings
Milk	3 servings
Nonstarchy vegetables	4 servings
Meat and meat substitutes	7 servings (ounces)
Fats	11 servings

Use the values in Table 3.5 to calculate the amount of calories and macronutrients gained from the number of portions from each food group. In most cases, the number of servings suggested in the food guide will not add up to the calorie and macronutrient levels set for your diet plan. At this point, begin to fill out the plan by adding more servings from the different food groups to yield your set values and still allow for variety among all the food groups. An example follows.

If you now use the USDA My Plate Food Guide SuperTracker at www.myplate.gov and enter this personal data, the results are actually quite close in calories: 3,200 [19]. The distribution of food groups from the SuperTracker **is noted directly in Table** 3.6.

Now the actual distribution of macronutrients must be calculated and food group servings adjusted to meet guidelines set for the maintenance diet for the actual athlete. More detail must be added to the meat group and the servings adjusted to control for unhealthy saturated fats, leaving room for healthy and essential monounsaturated and polyunsaturated fats. More carbohydrate in the form of added sugar or fast starches must be added to allow for proper fueling before, during, and after exercise. While the final numbers

Table 3.7 Example final meal plan for maintenance diet

Food groups	Number of servings	Carbohydrate (g)	Protein (g)	Fat (g)	Calories
Grains, breads, and starches	11	165	32	0–11	880
Fruit	9	135	–	–	540
Nonfat Milk	3	36	24	0	240
Non-starchy Vegetables	11	55	22[a]	–	275
Meat and meat substitutes					
Very lean	4	–	28	0–5	140
Lean	3	–	21	9	165
Medium fat	1	–	7	5	75
Fat	18	–	–	90	810
Tsp of added sugar	23	92	–	–	368
Totals (goal)		483	132[a]	104	3,493

[a]Protein quality in non-starchy vegetables is low; so to maintain a high nutrient density from vegetables and a high-quality overall protein consumption, a larger margin is allowed for total protein consumption. While this augments total calorie consumption, it is not a substantial amount of calories for a highly active athlete

are not exactly the same as the goal, they are very close. It is often very difficult to create a diet that exactly meets the goal values (see Table 3.7).

The next step is to distribute these foods throughout the day, creating a meal plan that follows the principles of food combinations and timing of eating that enhance sports performance and that is also practical and palatable for the athlete (see Table 3.8). Then the food group categories will be translated into actual food selections to create a day's menu.

3.10 Summary

- A nutrient-dense diet is the foundation to athletic performance and optimal results.
- The most important factor in an athlete's diet is the amount of energy available.
- Nutrient density is defined as a rich amount of nutrients per calorie consumed.
- To attain optimal performance outcomes via quality nutritional intake, exercise and athletic populations must match caloric ingestion with caloric expenditure.
- It is a widely accepted fact that athletes involved with high-intensity training and competition do not ingest the right type and/or amounts of macronutrients to offset their energy expenditure.
- Along with choosing foods that are dense in nutrients, a nutrient-dense diet must also be rich in a variety of foods from all the food groups to be both nutritionally dense and complete.
- Nutritional supplements are not a complete substitute for a well-balanced nutrient-dense diet. However, nutritional supplementation strategies, in addition to a nutrient-dense diet, are vital in assisting the athlete in replacing the necessary caloric requirements lost through high-intensity energy expenditure.
- Because matching caloric intake to energy expenditure is critical, athletes engaged in intense training to build performance (2–3 h/day) should ingest between 60 and 80 kcal/kg/day. The quality caloric requirement should be based on the intensity of training and the total energy expenditure.
- Because it is difficult to consume large quantities of food in one setting and difficult to maintain a quality energy balance, athletes are encouraged to eat 4–6 meals per day. Ingesting carbohydrate/protein snacks between meals helps offset energy expenditure.

Table 3.8 Example daily meal plan for adequate nutrient timing and food combinations enhancing sport performance

Food group servings	Menu
Pre-workout snack	
	Water
1 milk	1 c plain yogurt
1 fruit	¾ cup fresh blueberries
1 tsp added sugar	1 tsp honey
Workout	
	Water
18 tsp added sugar	~70 g carbohydrate from sports drink
Breakfast	
	Water
2 grain/bread/starch	2 slices whole-grain bread
1 vegetable	Sliced tomato to garnish eggs
1 milk	1 c fat-free milk
3 fruit	1 c orange juice
	1 c melon cubes
2 tsp added sugar	2 tsp 100 % fruit spread for bread
1 medium-fat meat/ substitute	1 whole egg, scrambled
5 fat	½ avocado cooked with eggs
	1 tsp heart healthy spread for cooking eggs
Snack	
2 grains/bread/starch	8 whole grain crackers or 1 cup quinoa
2 vegetable	2 c vegetable sticks
6 fat	3 Tbsp natural peanut butter
Lunch	
5 grains/bread/starch	Foot-long Subway sandwich (choose from "6 grams of fat or less" list)
2 vegetable	Fill sandwich with vegetable choices
1 fruit	1 banana
4 very lean meat/ substitute	4 oz. meat included in sandwich
2 fat	2 tsp olive oil or 2 tbsp salad dressing
Snack	
2 fruit	8 dried apricots
1 milk	1 tall nonfat latte
1 tsp added sugar	1 tsp sugar in latte
3 fat	18 almonds
Snack (before or after dinner)	
3 vegetables	Plate of fresh vegetable crudité
Dinner	
	Green tea or other tea
2 grains/bread/starch	1 baked sweet potato
2 fruit	6 oz. or about 30 red grapes
1 tsp added sugar	1 tsp. sugar or honey for tea
3 vegetable	½ c steamed asparagus
	2 c mixed green salad
3 lean mean/substitute	3 oz. grilled salmon
3 fat	2 tbsp. olive oil-based salad dressing
	1 tsp olive oil for grilling salmon

- Because athletes are susceptible to negative energy balance during intense training periods, dietary options should be comprised of the following combinations: carbohydrate (8–10 g/kg/day), high-quality protein (1.5–2.5 g/kg/day), and low to moderate fat intake (less than or equal to 30 % of diet). This recommendation is suggested 4–6 h before training whenever possible. Recommended fat intake for athletes attempting to lose weight is 0.5–1 g/kg/day.
- Nutritional timing is imperative as a dietary strategy. To help maintain energy balance and reduce catabolic states, athletes are encouraged to consume the following 30–60 min prior to exercise: 50–100 g of carbohydrate and 30–40 g of protein.

References

1. Williams MH. The ergogenics edge. Champaign, IL: Human Kinetics; 1998. p. 12.
2. Fletcher RH, Fairfield KM. Vitamins for chronic disease prevention in adults. JAMA. 2002;287:3127–9.
3. Kreider RB, Leutoholtz B. Nutritional considerations for preventing overtraining. In: Antonio J, Stout JR, editors. Sports supplements. Philadelphia, PA: Lippincott Williams & Wilkins; 2001. p. 199–208.
4. Kreider RB, Almada AL, Antonio J, et al. ISSN exercise and sport nutrition review: research recommendations. Sports Nutr Rev J. 2004;1(1):1–44.

5. Greenwood M, Jones M, Carter J, et al. Sport nutrition eating habits of NCAA-division I athletes. In: NSCA annual national conference, Las Vegas, NV, 10–13 July 2013. http://NSCA.allenpress.com
6. Berning JR. Energy intake, diet, and muscle wasting. In: Kreider RB, Fry AC, O'Toole ML, editors. Overtraining in sport. Champaign, IL: Human Kinetics; 1998. p. 275–88.
7. American College of Sports Medicine. Encyclopedia of sports sciences and medicine. New York: Macmillan; 1999. p. 1128–9.
8. Leutholtz B, Kreider RB. Exercise and sport nutrition. In: Temple N, Wilson T, editors. Nutritional health. Totowa NJ: Humana; 2001. p. 207–39.
9. Bloomstrand E, Hassmen P, Newsholme E. Effect of branch-chain amino acid supplementation on mental performance. Acta Physiol Scand. 1991;143:225–6.
10. Blomstrand E, Celsing F, Newshome EA. Changes in plasma concentrations of aromatic and branch-chain amino acids during sustained exercise in man and their possible role in fatigue. Acta Physiol Scand. 1988;133:115–21.
11. Kleiner SM, Greenwood-Robinson M. Power eating. 4th ed. Champaign, IL: Human Kinetics; 2014.
12. Burke LM, Cox GR, Culmmings NK, Desbrow B. Guidelines for daily carbohydrate intake: do athletes achieve them? Sports Med. 2001;31(4):267–99.
13. Trexler ET, Smith-Ryan AE, Norton LE. Metabolic adaptation to weight loss: implications for the athlete. J Int Soc Sports Nutr. 2014;11:7.
14. Lemon PW. Beyond the zone: protein needs of active individuals. J Am Coll Nutr. 2000;19(5 Suppl): 513S–21.
15. Pasiakos SM, Martin WF, Sharma CS, Pikosky MA, Gaine PC, Bolster DR, Bennett BT, Rodriguez NR. Level of dietary protein intake affects glucose turnover in endurance-trained men. J Int Soc Sports Nutr. 2011;8:20. doi:10.1186/1550-2783-8-20.
16. Wells A, Read NW, Macdonald IA. Effects of carbohydrate and lipid on resting energy expenditure, heart rate, sleepiness and mood. Physiol Behav. 1998;63(4): 621–8.
17. Ivy J, Portman P. The future of sports nutrition: nutrient timing. North Bergen, NJ: Basic Health; 2004. p. 7–14.
18. Food and Nutrition Board, Institute of Medicine of the National Academies. Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids (macronutrients). Washington, DC: National Academies Press; 2005.
19. United States Department of Agriculture, Center for Nutrition Policy and Promotion. Choose My Plate. 2013. www.myplate.gov
20. Harvard School of Public Health. The Nutrition Source. 2014. Healthy eating plate and healthy eating pyramid. http://www.hsph.harvard.edu/nutritionsource/healthy-eating-plate/
21. Oldways Preservation and Exchange Trust. The Mediterranean diet pyramid. 1999. www.oldwayspt.org
22. The University of Michigan Integrative Medicine Clinic. The healing foods pyramid. 2004. http://med.umich.edu/umim/food-pyramid/index.htm
23. American Dietetic Association, American Diabetes Association. Exchange lists for meal planning. 2008.
24. Prestwood E. Nutrition software: 101 questions to ask before you buy. Today's Dietitian. 2000;2(2).

Macronutrient Intake for Physical Activity

4

Elfego Galvan

Abstract

Appropriate nutritional guidelines are an essential component of optimal training programs to aid in adaptations, peak sports performance, and injury prevention. Understanding the latest macronutrient guidelines set forth by the latest research findings and position stands from credible professional organizations that have a specialty with applied sports nutrition can assist dietitians, nutritionists, coaches, and athletes develop suitable nutrition plans that are strategically timed around an athlete's training schedule. Furthermore, it is important to recognize the three main energy systems used to yield adenosine triphosphate (ATP) and the bioenergetics involved in strength–power events, speed events, and endurance events. To develop a nutrition plan, you must determine the total daily needs for both calories and macronutrients.

Keywords

Macronutrients • Protein • Carbohydrate • Fats • Estimating energy expenditure

4.1 Introduction

Appropriate nutrition guidelines are an essential component of athletic performance, body composition goals, and health. While natural variability between persons makes it inappropriate to create one diet to recommend to all, examining scientific principles makes it easier for athletes and other physically active persons to eat a diet that will prepare them for successful training or athletic competition. The purpose of this chapter is to discuss the three macronutrients (i.e., protein, carbohydrate, and fat) that provide energy (e.g., calories) and how they can promote and maintain athletic nutrition. Throughout the chapter, the term athlete will be used to refer to anyone who exercises consistently.

Designing a nutritional program for an athlete can be viewed much like the process of

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exercise prescription. The nutritional design should be individualized and account for factors such as age, height, weight, gender, body composition, training regimen, and bioenergetics demands of the activity or sport. Much like the concept of sport-specific training, to maximize the benefits of training and/or exercise performance, one needs to implement a system of performance nutrition for sport and recovery. To do this, it is necessary to understand the primary energy systems used during a particular activity. Furthermore, it is necessary to understand an athlete's goals. Only then can kilocalorie requirements, macronutrient ratios, and nutrient timing issues be addressed.

The aim of this chapter is to provide a framework to allow athletes, coaches, and sports nutritionists to make successful food and supplement choices and recommendations. These choices will enable the athlete to train and compete at maximal capacity and reach their fitness goals. Each individual responds differently to a given diet; athletes must take these recommendations and make adjustments if their body does not respond as they would wish.

4.2 The Macronutrients

Macronutrients consist of the three nutrients that are required in large quantities in an individual's diet: protein, carbohydrate, and fat. These nutrients provide the energy or kilocalories required to maintain the body's functions during exercise and rest. Whether in energy production or cellular structure, these nutrients play a vital role in athletic performance as well as the overall health of an individual.

4.2.1 Protein

In the human body, skeletal muscle consists of approximately half of total body weight [1]. Proteins may be mainly associated with playing a role in skeletal muscle hypertrophy, but they play a role in every cell of the body. They are needed to support normal growth and repair of tissues and cells. Furthermore, proteins have structural and regulatory (e.g., hormones) roles. Proteins provide structure to bodily tissues such as skeletal muscle, connective tissue, bone, and organs. In addition, nonstructural proteins act as hormones, catalysts (enzymes), buffer systems, cellular water balance regulators, and lubricants. Noting these numerous functions, the value of proteins in the body cannot be underestimated. In contrast to carbohydrates and fat, the body has no physiologic reserve of protein stores. Therefore, if the body is not sufficiently supplied with protein, it will catabolize tissue proteins, and cellular function will be lost.

Proteins are nitrogen-containing compounds composed of dozens, hundreds, or thousands of amino acids. Amino acids are joined by peptide bonds, and several amino acids joined together become a polypeptide. Polypeptide chains then bond together and form various proteins. Chemically, proteins can be divided into groups: simple or conjugated. Simple proteins contain only amino acids or their derivatives. More recognizable to some are conjugated proteins, which contain some nonprotein substances such as sugar molecules (glycoproteins), lipids (lipoproteins), or phosphate groups (phosphoproteins). One protein category that is most important to the nutritionist and the athlete alike is essential versus nonessential and complete versus incomplete proteins.

For nutritional purposes, amino acids (AA) can be divided into several groups: essential, conditionally essential, and nonessential. It is important to understand that all AA (i.e., essential, conditionally essential, and nonessential AA) are necessary for normal growth and general health [2]. Essential amino acids (EAA) must be provided by the diet as the body cannot synthesize them [3]. Generally, protein from animal sources contains a greater concentration of EAA than protein from plant sources [3]. Conditionally essential amino acids (CEAA) are needed in greater amounts under certain physiologically stressful situations. Under certain stressful situations, nonessential amino acids (NEAA) can become CEAA. For example, proline, a NEAA

Table 4.1 Nonessential, essential, and conditionally essential amino acids

Nonessential	Essential	Conditionally essential
Alanine	Isoleucine	Arginine
Asparagine	Leucine	Cysteine
Aspartic acid	Lysine	Glutamine
Glutamic acid	Methionine	Histidine
Glycine	Phenylalanine	Proline
Serine	Threonine	Tyrosine
	Tryptophan	
	Valine	

Adapted from [5, 6]

under normal physiological conditions, becomes a CEAA in burn victims [4, 5]. NEAA does not need to be provided by dietary protein as they are AA that our body can synthesize de novo [5]. Some argue that serine and glutamic acid are the only truly NEAA as they are the only AA that can be synthesized de novo from non-amino acid sources of nitrogen [5]. EAA, CEAA, and NEAA are listed in Table 4.1.

Furthermore, it is also useful to know if a certain dietary protein is categorized as a complete or incomplete protein. A complete protein is one containing all AA within one serving. Complete proteins are primarily found in animal products and are proteins that contain the proper quantity of EAA. Meat, fish, eggs, milk, and cheese are all good sources of complete proteins. Incomplete proteins, on the other hand, lack one or more EAA. A few animal products may be considered incomplete proteins, but they are primarily found in plant protein sources such as grains, legumes, or vegetables. It can be challenging for vegetarian and vegan athletes to obtain proper amounts of all essential amino acids when forced to eat many plant sources in combination. An option is to combine two or more incomplete proteins (i.e., complementary proteins) in order to ingest all of the EAA. For example, combining legumes (limited in methionine) with corn (limited in lysine) results in the ingestion of all EAA [7]. Thus, an athlete following a vegetarian or vegan diet can obtain the EAA by combining foods of complementary AA composition.

4.2.2 Carbohydrates

Carbohydrates have a wide range of functions, but they are most known for providing kilocalories (i.e., energy) and a storage form of energy in the body. Simpler carbohydrates are known to have the empirical formula $(CH_2O)_n$, hence the name "hydrate of carbon" [8]. Carbohydrates are usually classified into three major groups: monosaccharides, disaccharides, and polysaccharides.

Monosaccharides are single sugar molecules and include glucose, fructose, and galactose. Monosaccharides can bond to form disaccharides and polysaccharides. Disaccharides, as the prefix suggests, are two sugar units and include sucrose (glucose + fructose), lactose (glucose + galactose), and maltose (glucose + glucose). Monosaccharides and disaccharides are better known as simple carbohydrates or simple sugars. Polysaccharides are commonly referred to as complex carbohydrates. Important polysaccharides include starch, fiber, and glycogen. Glycogen is also the storage form of glucose in the body and is found primarily in the liver and skeletal muscle.

Over the last few decades, simple carbohydrates have received an overwhelming amount of negative attention. Beverages such as sodas, fruit juices, energy drinks, and functional waters are sweetened with simple sugars [9], and these sugar-sweetened beverages are associated with an increased risk of weight gain, metabolic syndrome, and type 2 diabetes in both children and adults [10–12]. Furthermore, simple carbohydrates have also been associated with a greater risk for certain cancers [10]. It may sound like simple carbohydrates are vastly inferior to complex, but a mix of carbohydrate types is beneficial for supplying athletes with energy. While the majority of the sedentary population should cut back and even avoid sugar-sweetened beverages, the athletic population has better use of short-term simple sugar-containing beverages to enhance training adaptations and exercise performance during competition [13]. With that said, athlete should consume simple sugars before, during, and after exercise training (this will be further discussed in the nutrient timing section).

Polysaccharides are generally promoted because of their ability to be absorbed more slowly and provide greater nutrient value overtime. Starch is the storage form of carbohydrate in plants, and starch can be found in grains, nuts, legumes, and vegetables. It is a viable energy source because it digests slowly and provides energy for longer periods than does simple carbohydrate. Fiber on the other hand, is indigestible, and is useful in slowing the digestive rate of food, adding bulk to the feces, reducing appetite and is associated with health benefits [14, 15]. It is found in foods such as vegetables, fruits, nuts, and legumes. Current recommendations suggest that ~20–40 g/day, depending on age and gender, of dietary fiber be consumed for proper health [16].

Although first developed for use with diabetics, the glycemic index (GI) provides a useful tool for helping athletes with food choices. The GI is a measurement of the response of blood glucose concentration after a 50-g bolus of a carbohydrate-containing food [17, 18]. The values are based on a standard of 100, which is the value for glucose or white bread (common food found globally). Often, people mistake the GI as a function of whether foods are simple or complex. However, some complex carbohydrates (e.g., baked potatoes) may increase glucose levels similarly to glucose. These values can be helpful for athletes to determine food choices when they quickly want to increase glucose/glycogen levels. A food is considered to have a low GI when its value is less than 55, a medium GI when it is 55–70, and a high GI when its value is over 70 [19].

Glycemic load (GL) is often confused with the glycemic index. Although GL is related to GI, the latter is thought to be a better indicator of dietary insulin demand [20]. GL is related to GI, yet its value represents the effect it will have on blood sugar after an average serving of a particular food [19]. It is calculated by dividing the product of the grams of carbohydrate in a typical serving of a food and its GI value by 100 [19]. A low, medium, and high GL is represented by a score of 10 or less, 11–19, and 20 or more, respectively [19]. Table 4.2 lists common foods and data derived from subjects with normal glucose tolerance [21].

4.2.3 Fat

Lipids are a broad group of energy dense compounds made up of carbon, hydrogen, and oxygen that are insoluble in water. Often, the terms fat and lipid are used interchangeably, although they are indeed different——all fats are lipids, but not all lipids are fats. Lipids include triglycerides, sterols, and phospholipids. Triglycerides are the primary fat found in our food and our body. They are the primary storage form of fat within the human body. Sterols are found in both plant and animal sources. In animal and plant sources, sterols are referred to as cholesterol and plant sterols, respectively. Although many associate cholesterol with negative health outcomes, it plays an import role as a structural component of all cell membranes and is a precursor of bile acids, steroid hormones, and vitamin D. Phospholipids are the predominate lipids of cell membranes. Phospholipids play a role in intracellular communication as well as structural support of the cell membrane. Many other lipids exist and are significant in the diet. For the purposes of this chapter, the terms fat/fats will be used to refer to dietary lipids.

Weight gain is often attributed to dietary fats because they contain far more energy per gram than does carbohydrate or protein. Dietary fats provide 9 calories per gram, while carbohydrates and proteins provide 4 calories per gram. Fats are often viewed in a negative light due to the association with weight gain and their role in disease development. However, fats serve many functions in the body. These include providing energy for tissues and organs as well as playing a role in cell membrane makeup, nerve signal transmission, vitamin transport, and cushioning and insulation for internal organs. In addition, for endurance athletes, they are a vital fuel source for skeletal muscles.

The primary fats found in large quantities in foods are triglycerides. Triglycerides are composed of three fatty acids and one glycerol molecule. Fatty acids can be grouped by the amount of hydrogen they contain, otherwise known as saturation. Saturated fatty acid chains contain no double bonds; monounsaturated fatty acids

Table 4.2 Glycemic index (GI) and glycemic load (GL) values determined in subjects with normal glucose tolerance: 2008

Food item	GI (glucose = 100)	GI (bread = 100)	Serve size (g)	GL per serving
Coca Cola®, soft drink	63	90	250 ml	16
V8® 100 % vegetable juice	43 ± 4	61	250 ml	4
V8® Splash, tropical blend fruit drink	47 ± 4	67	250 ml	13
Bagel, white	69	99	70	24
100 % whole wheat burger bun	62 ± 6	89	30	7
Rye bread (50 % rye flour + 50 % wheat flour)	50	72 ± 5	30	7
Wonder™, enriched white bread	71 ± 9	101 ± 13	30	10
Rice, Arborio, risotto rice, boiled (SunRice brand)	69 ± 7	99	150	36
Rice, brown, steamed	50	72	150	21
Ice cream, premium, French vanilla, 16 % fat	38 ± 3	54	50	3
Milk, full fat	41 ± 2	59	250 ml	5
Milk, reduced fat (1.4 %)	30 ± 6	43	250 ml	4
Milk, skim	32	46	250 ml	4
Soy milk, full fat (3 %)	44 ± 5	63	250 ml	8
Soy milk, reduced fat (1.5 %), light	17 ± 3	24	250 ml	8
Yoplait™ no fat yogurt, various flavors	18 ± 3	26	200	3
Grapes, black	59	84	120	11
Raisins	64 ± 11	91	60	28
Pineapple, raw	66 ± 7	94	120	6
Watermelon, raw	72 ± 13	103	120	4
Apple juice, unsweetened, reconstituted	39 ± 5	55 ± 7	250 ml	10
Carrot juice, freshly made	43 ± 3	61	250 ml	10
Peanut butter	23 ± 3	33	50	1
Filet-O-Fish™ burger (fish patty, cheese, and tartar sauce on a burger bun)	66 ± 10	94	128	20
Pizza, Super Supreme, pan (Pizza Hut, Sydney, NSW, Australia)	36 ± 6	51	100	9

Adapted from International Tables of Glycemic Index and Glycemic Load Values: 2008 [21]

contain one double bond; and polyunsaturated fats have two or more double bonds. The fatty acid makeup of the triglycerides is important to its metabolism in the body. For example, saturated fats may increase cholesterol in the body, while unsaturated fats may have no effect or lower cholesterol.

Cholesterol is found in food and even synthesized by the body. High-density lipoproteins (HDLs) are a type of cholesterol composed of a high protein-to-fat ratio. HDL is typically known as good cholesterol because of its protective nature against heart disease, while elevated low-density lipoproteins (LDLs) are a risk factor for heart disease. LDL is primarily fat with lower amounts of protein. However, recent research suggests that lipoprotein size, regardless of whether the lipoprotein is high or low density, is more important to cardiovascular health [22]. Small particle LDL and HDL may both have a negative effect on the cardiovascular system [22]. A recent prospective study of 26,332 initially healthy women evaluated the association between HDL particle size, determined via nuclear magnetic resonance spectroscopy, and the risk of coronary heart disease (CHD) [23]. Researchers observed a positive association in CHD and both small and very small HDL particles.

Dietary fats also provide a source of essential fatty acids. These fatty acids are essential as the body cannot synthesize them from endogenous sources. There are two types of fatty acids to pay special attention to in the diet. The essential fatty acids are linoleic (omega-6) and linolenic (omega-3), both 18-carbon fatty acids. Linoleic acid is found in oils of plant origin, while marine oils are a good source of linolenic acid. Although both linoleic and linolenic are essential fatty acids, they have very different roles in the body. Linoleic acids are generally associated with the promotion of inflammation [24] and certain cancers [25], while linolenic are anti-inflammatory and associated with a decreased risk of heart disease [26] and cancers [25].

Trans fatty acids should receive considerable attention as well due to their relationship with health status. Trans fats, as they are commonly known, are often oils that are solidified through a process known as dehydrogenation, although some amounts are found naturally. Dr. Paul Sabatier, a French chemist, received the Nobel Prize in Chemistry in 1912 for developing a method to convert oils, via hydrogenation, to saturated fats. Trans fats are now used in foods such as margarine, shortening, and some dairy products. These fats are beneficial to the food industry as they are inexpensive to make and promote product shelf life. The reduction of trans fats has become a point of public scrutiny in places such as fast food and packaged foods because, although they are unsaturated fats, they behave like saturated fats in the body. Trans fatty acids have been shown to have a negative effect on blood cholesterol markers of health, increase inflammatory markers, and promote endothelial dysfunction [27]. Research suggests that trans fatty acids should have no place in our food supply as they have no health value and pose substantial health risks [28]. In 2013, the Food and Drug Administration took their initial steps to potentially eliminate trans fats from our processed-food supply as ample evidence suggested that trans fats are no longer safe for consumption.

Generally, fruits and vegetables contain little fat. Animal products such as meat, milk, cheese, and eggs, as well as baked goods, generally contain high amounts of saturated fats. Nuts and peanut/canola oils can be good sources of monounsaturated fats. Polyunsaturated fats, including the essential fatty acids, can be found in fish, nuts, corn, soy, and sunflower oils. Lastly, margarine, shortening, cookies, pastries, and fried foods have high levels of trans fats.

4.2.4 Metabolic Usage

Paramount to understanding sport-specific eating and proper food decisions is a basic knowledge of the metabolic usage of the macronutrients within the body. This chapter will give only a cursory overview of the bioenergetics of activity and exercise, yet these principles are essential to a proper nutritional design. The discussion here will be limited to energy production from carbohydrates and fats.

The primary energy systems used during exercise depend on the intensity and duration of the exercise. Most exercise activity can be categorized as power–strength events (e.g., discus throw), speed events (e.g., 100-m sprint), and endurance events (e.g., triathlons). Short quick bursts such as a discus throw and vertical jump are fueled by the phosphagen system (adenosine triphosphate [ATP] system and creatine phosphate [CP]). The glycolytic system is mainly responsible for supplying energy derivative during speed events such as a 100-m and 400-m sprints. Endurance events are mainly supported by the substrates metabolized by the oxidative phosphorylation system. It is important to realize that all of the energy systems work in unison, but under certain conditions, one energy system may be more dominant in providing energy substrates. In terms of energy metabolism for exercise, it is agreed that fats provide the dominant energy source during low- to moderate-intensity exercise [29]. As exercise intensity increases, there is a greater reliance on carbohydrate (e.g., muscle and liver glycogen; blood glucose; blood, muscle, and liver lactate) oxidation for fuel. In addition, the longer the duration, the more fat will be utilized. This means that even activity that begins at high or

moderate levels will taper off due to glycogen depletion, and fat will be the primary fuel derivative after 20–30 min of continual exercise. These basic concepts are essential to determine proper dietary guidelines for an activity or event.

When comparing energy reserves, the human body has far more fat than glycogen stores. Skeletal muscle glycogen stores approximately 400 g for an 80-kg individual, with an additional 100 g stored in the liver. In comparison, that same 80-kg individual may have over 12,000 g of fat stored in adipose tissue! When factoring in the fact that fat is more than twice as calorie dense than carbohydrate, the energy stores are quite unbalanced. However, while each fatty acid provides 147 ATP and each triglyceride provides 460 ATP, glucose metabolism (36 ATP/molecule) is more efficient per unit of oxygen at providing energy. In addition, it takes roughly 20 min for free fatty acids to be liberated for use through lipolysis. Therefore, per unit of time glucose is more efficient and thus the preferred fuel for high-intensity exercise. These data help to briefly detail the merits of both fats and carbohydrates as fuel sources. The importance of both of these fuels should not be underestimated by the athlete, when considering intake or expenditure.

4.3 Determining Intake Needs

Possibly, the most important piece of the nutritional puzzle for athletes is the understanding of how to determine the right amount of calories and macronutrients to consume. After all, what good is an understanding of what the nutrients are for an athlete if they do not know how much they need to take in?

The initial consideration when determining macronutrient needs is to determine the goal of the nutritional design. Is the goal to improve muscular strength and power, lose fat mass, or simply improve body composition? Secondly, one must then consider the bioenergetics of the event or training required to meet the established goal. For example, a high-intensity, high-frequency resistance training will require higher dietary protein intake than other forms of exercise. Finally, physiologic factors such as size, age, and gender will play a role in caloric needs as well as the macronutrient distribution of those calories. For example, older athletes may need higher protein intake to prevent muscle loss and/or bone resorption, while highly active women at risk for amenorrhea may need to increase caloric intake and fat consumption.

4.3.1 Determining Caloric Needs

Meeting caloric needs of an athlete should be a nutritional priority. To determine macronutrient intake needs, one must begin by determining the caloric needs of the individual. Total energy expenditure (TEE) is composed of four factors: resting metabolic rate (RMR), exercise energy expenditure, thermogenesis, and activities of daily living.

RMR accounts for the greatest percentage of calorie expenditure. RMR is positively correlated with total body surface area and lean body mass. The percentage of TEE from RMR depends on the fitness and activity level of the individual, but it generally accounts for 60–70 % of daily energy expenditure. As a person becomes more active, RMR will begin to account for slightly lower percentages of energy expenditure. RMR values below 50 % of TEE have even been reported in male endurance athletes [30].

When direct or indirect calorimetry is not available to determine RMR, the next best method is using a predictive equation to estimate an athlete's RMR. Two predictive equations recommended by several professional organizations [31] include the Harris–Benedict equation [32] and the Cunningham equation [33]. It is suggested that the Cunningham equation, which requires fat-free mass information, is the most appropriate predictive equation to use when working with endurance athletes [34]. If accurate fat-free mass data is not available, then the Harris–Benedict equation may be more appropriate. The Harris–Benedict equation requires information of total body weight, height, and gender. It is important to note that neither the Cunningham nor the Harris–Benedict equations

Table 4.3 Various predictive equations

Harris–Benedict: Males	RMR (kcal/day) =	66.47 + 13.75 (wt. in kg) + 5 (ht. in cm) − 6.76 (age in years)
Harris–Benedict: Females	RMR (kcal/day) =	655.1 + 9.56 (wt. in kg) + 1.85(ht. in cm) − 4.68(age in years)
Cunningham:	RMR (kcal/day) =	500 + 22 (LBM [lean body mass] in kg)
De Lorenzo:	RMR (kcal/day) =	−857 + 9.0 (wt. in kg) + 11.7 (ht. in cm)

were developed using athletic test subjects; rather, they were developed using healthy untrained subjects. The De Lorenzo equation did, however, use male athletes to predict RMR [35]. Numeric guidelines such as these only provide an approximation of the average energy needs of an individual athlete (Table 4.3).

While most of these equations do not take into account fat-free mass, they have been reported to predict RMR within 200 kcal/day in endurance athletes of both genders [34].

Exercise energy expenditure and activities of daily living are often combined into physical activity. It is important to remember to factor in daily activities such as walking up/down stairs, yard work, or even shopping. These activities take small amounts of energy to complete, but energy nonetheless. Then, the athlete's training routine must be taken into account. Once the RMR has been established by using a predictive equation or by measurement, the next step is to determine the daily energy expenditure from physical activity. This is accomplished by multiplying the RMR value by the physical activity level factor that most closely represents the athlete's current physical activity level. Although no standard physical activity level factor exists, the values below in Table 4.4 are common ranges for the sedentary and active population [36].

The final component of TEE is thermogenesis, which is energy expenditure not accounted for by RMR or physical activity. The most important form of thermogenesis is the thermic effect of food, which accounts for the energy cost of digestion, absorption, transportation, and storage of the macronutrients. The measured thermic effects

Table 4.4 Physical activity level based on doubly labeled water

Lifestyle and level of activity	Physical activity level
Chair bound/bed bound	1.2
Seated work with no option of moving around and little or no strenuous leisure activity	1.4–1.5
Seated work with discretion and requirement to move around but little or no strenuous leisure activity	1.6–1.7
Standing work (e.g., housework, shop assistant)	1.8–1.9
Significant amounts of sport or strenuous leisure activity (30–60 min 4–5 times per week	2.1–2.3
Strenuous work or highly active leisure time	2.0–2.4

Adapted from Human energy expenditure in affluent societies: An analysis of 574 doubly-labelled water measurements [30]

of fat, carbohydrates, and proteins are 0–3 %, 5–10 %, and 20–30 %, respectively [37]. In other words, it does not take much energy to breakdown, transport, and store dietary fat, whereas much more energy is required to do the same for dietary protein. The thermic effect of food generally accounts for 5–10 % of TEE.

We know TEE determines the number of calories that the athlete needs per day to stabilize his/her body weight. If, however, a change in body weight is desired, as in the case of weight-dependent or muscle-building sports, the daily caloric intake will need to be adjusted as such. Dietitians and nutritionists often recommend a 500 calorie per day reduction, which will lead to 3,500 calorie deficit over the course of 1 week. It is generally assumed that this 3,500 calorie reduction will result in the loss of one pound of fat. One pound of fat is worth approximately 3,500 calories. If all weight loss came in the form of lost fat mass, then the previous assumption would be true [36]. However, this is not the case. Approximately 25 % of skeletal muscle mass is also lost when body mass is reduced [38]. Under certain conditions such as rapid weight loss and at altitude, the loss of lean muscle mass can be even greater.

4.3.2 Determining Macronutrient Intake

Once daily caloric intake is determined, the macronutrient composition distribution of the diet must be considered. The first thing to consider is the type of athlete you are working with. Are you working with a strength and power athlete or an endurance athlete? From there, you can start with the general recommendations for protein, carbohydrate, and fat for that specific type of athlete. A second consideration should be the athlete's goal. Is the goal to lose fat mass, gain lean body mass, or maintain current body composition?

Beginning with protein, the general guideline for sedentary individuals is to intake ~0.8 g/kg of body weight [39]. This recommendation of protein intake is estimated to be sufficient for most (~98 %) healthy, adult men and women. The International Society of Sports Nutrition recommends a protein intake of 1.4–2.0 g/kg/day for the athletic population [40]. It was suggested that protein consumption for endurance athletes occur on the lower range (i.e., 1.4 g/kg/day), athletes in intermittent sports such as soccer and basketball in the middle range (i.e., 1.7 g/kg/day), and strength and power athletes on the higher range (i.e., 2 g/kg/day). Other researchers have also recommended the upper range of daily protein intake to prevent lean muscle mass losses during periods of caloric restriction [41]. In addition, BCAAs may be important for endurance athletes in delaying fatigue in respect to the central fatigue hypothesis. New research reports that dietary protein intake as high as 1.8 g/kg stimulates protein synthesis following endurance exercise, but further research is needed [42]. For athletes participating in regular resistance training, greater amounts of protein are needed in order to maintain an anabolic environment and increase muscle mass.

Carbohydrate intake is of great importance to endurance athletes who train for longer than 90 min/day in order to replenish muscle and liver glycogen levels. However, each gram of glycogen requires extra water to be stored and may inhibit performance in training or events shorter than 90 min. Generally, individuals need between 6 and 10 g/kg of carbohydrates daily to restore muscle and liver glycogen levels, but athletes training for periods longer than 90 min may require 8–10 g/kg daily [42]. In fact, Fallowfield and Williams [43] determined that even when isocaloric diets were consumed, a high-carbohydrate (8.8 g/kg) diet was significantly better at maintaining running time than a low-carbohydrate (5.8 g/kg) diet. However, benefits vary between individuals, and some may experience gastrointestinal problems on a high-carbohydrate diet. Therefore, it is important for athletes to determine what works best for them.

Once the total grams of protein and carbohydrate have been determined, multiply each factor by 4 to find the total number of calories from each of the respective substrates. Once this is completed, subtract the number from the total energy needs determined earlier. The remainder of the necessary calories will come from fat. Divide the fat calories by 9 to determine the total number of fat grams to be consumed per day.

Though fats are the last macronutrient to be prescribed in the diet, they are not simply throw-away calories. It is not the unimportance of fats but rather the importance of protein and carbohydrate that makes dietary fat the final consideration. It is not recommended for an athlete to consume less than 20 % of calories from fat as it can promote immune system dysfunction and deteriorate health status [44–46]. Generally, it is accepted that athletes consume approximately 30 % of their calories from fat [47]. Additionally, athletes participating in high-volume training can safely ingest up to 50 % of their calories from fat [47]. In fact, higher fat diets (~35 % kcal) have been reported to enhance endurance performance in some athletes [48]. The effects of a high-fat diet also vary between individuals; caution should be used in recommending such a diet. For athletes attempting to lose fat mass, a dietary fat intake of 0.5–1 g/kg body weight/day is recommended [47].

Since the daily recommendations are ranges, these should be reconciled with the percentages. For example, if the values of 9 g/kg of carbohydrate and 1.4 g/kg of protein breakdown to 80 % carbohydrate, 12 % protein, and 8 % fat, then they need to be adjusted to lower the carbohydrate intake and increase the fat and protein.

4.3.3 Case Study

Ellen is an endurance athlete who comes to you for nutrition counseling. She is 27 years old, 5 ft., 4 in. (163 cm) tall, weighs 121 lb. (55 kg), and her body fat percentage is 23 % according to her latest DEXA (dual energy X-ray absorptiometry). During her training, she performs well at the beginning of her sessions, but she feels fatigued sooner than she would like or expect. She trains 5–6 days/week for 90 min per session at a 7 mph pace. She informs you that she consumes 2,197 calories per day with 302 g of carbohydrate, 83 g of protein, and 73 g of fat.

Since Ellen is an endurance athlete and we have her body fat percentage information, we will use the Cunningham equation (RMR = 500 + 22 [LBM in kg]). If we did not have Ellen's body fat percentage information, we would not be able to use the Cunningham equation, and thus it would be more appropriate to use either the De Lorenzo or the Harris–Benedict equation. Using Ellen's information, we get an RMR value of ~1,430 calories (500 + 22 [42.25 kg of LBM]). Using a physical activity level factor of 2.1 (based on her training frequency per week), we multiply the calculated RMR value by 2.1, which gives us approximately 3,000 calories per day. You inform Ellen that she first needs to consume more calories; based on her RMR (1,430 kcal) and her physical activity level factor (2.1), her calorie intake during regular training periods should be approximately 3,000 calories per day. The added calories should help her to improve her endurance. Frequent nutrition counseling and body composition assessment of an athlete will help determine any undesirable body composition changes. If unwanted weight gain occurs, then reducing caloric intake would be appropriate.

Now that we have her total daily caloric needs, we can work on setting dietary guidelines for protein, carbohydrate, and fat. Based on the dietary protein recommendations mentioned earlier, we can recommend Ellen to consume 1.4 g of protein/kg body weight/day. This gives us a total dietary protein intake of 77 (1.4 × 55) grams of protein per day. Now, following with carbohydrate guidelines, we would recommend 8 g of carbohydrate/kg body weight per day. Ellen would be recommended to consume approximately 440 g (8 × 55) of carbohydrate per day. Right now, we have protein contributing approximately 308 calories (77 g of protein × 4 calories per gram of protein) and carbohydrates contributing 1,760 calories (440 g of carbohydrate × 4 calories per gram of carbohydrate), which gives us a total of 2,068 calories. Since we are recommending Ellen to consume approximately 3,000 calories, the remaining 932 calories (3,000 − 2,068 = 932) will come from dietary fat. This amount of dietary fat (~31 % calories from fat) puts us well within the fat recommendations mentioned above. Remember that these are simply guidelines that can be adjusted at any time to better suit the athlete.

You inform her that this diet should help to maximize muscle glycogen stores while still providing enough fat for oxidation and protein for contractile protein repair. After beginning this new diet, Ellen discovers that her ability to maintain intensity during the ends of her workouts improves and that she recovers more readily from her training bouts.

4.4 Nutrient Timing

One of the hottest topics in the sports nutrition field is the concept of "nutrient timing." Nutrient timing suggests that it is not merely what you eat and how much, but also when. To properly build lean mass, replace glycogen stores, or simply maximize athletic performance, one needs to be conscious of the proper time to ingest food or macronutrient supplements. Not only is the timing an issue in terms of proper metabolic usage, but improper timing can also cause gastrointestinal or psychological discomfort. In general, pre- and postexercise supplements are preferred to be in liquid form to limit gastrointestinal discomfort.

Aside from improving performance, the primary nutritional goal for endurance athletes is to maximize (pre) and replenish (post) glycogen stores. For many years, endurance athletes have used "carbohydrate loading" as a tool for increasing muscle glycogen stores. Variations of carbohydrate

loading regimens exist, but it requires several days of high-carbohydrate intake combined with tapered exercise the week before competition. Yet, endurance athletes should not forget about the importance of fats as a fuel either. For muscle glycogen to be spared during long-duration endurance training, fats must be metabolized preferentially to glycogen. Depending on the intensity of exercise, carbohydrate supplementation immediately before or during exercise may inhibit lipolysis due to increases in insulin. Fat oxidation seems to be inhibited by carbohydrate intake during lower-intensity exercise (~45 % VO_2max), but not during moderate-intensity exercise [49, 50]. In contrast, increased dietary fat appears to increase lipolysis and fat oxidation during exercise [51]. Therefore, it may be advisable to consume carbohydrate prior to moderate- to high-intensity exercise so muscle glycogen is maximized, but to consume small amounts of fat prior to low-intensity exercise to increase fat oxidation.

To maximize glycogen replenishment after exercise, it is necessary to ingest a carbohydrate supplement immediately after and every 2 h (up to 6 h) following exercise [52]. In addition, adding protein to the carbohydrate supplement appears to increase glycogen storage by acting synergistically on insulin secretion [53]. Restoring the glycogen levels properly after exercise will allow for proper recovery and support the next day's training or competition.

For resistance-training athletes, the goals are to increase amino acid uptake and anabolic hormone release to enhance protein synthesis as well as to replenish glycogen stores. At present, it appears that providing protein and/or carbohydrate immediately before and after resistance exercise may provide the optimal environment for enhanced muscle growth [54]. While consumption of protein [55] or carbohydrate [56] following exercise has been shown to increase protein synthesis, the combination of the two has shown even greater success before and after exercise [57, 58]. The protein–carbohydrate combination consumed prior to and after a workout has also been shown to significantly increase growth hormone levels [59, 60]. In addition, it currently appears that consuming the postexercise supplement as soon as possible is extremely important and more effective than waiting for extended periods [54, 61].

Research in the area of nutrient timing and its connection with athletic performance is greatly expanding. As more research is completed, further information on the proper timing of macronutrient intake will most certainly come to light.

4.5 Summary

Proper macronutrient nutrition is part of the basis of any successful training and competition program. Although it is suggested that prior to using nutritional supplements, an athlete must properly regiment their diet, it is not imperative. Most dietary supplementation studies do not control nutritional intake. A fitting nutritional design is an essential part of an athlete's training program. A proper meal plan will help manage body composition, promote training adaptations and exercise performance, improve recovery, and prevent fatigue and injury. When designing a nutritional program, you must know what type of athlete you are working with. Once that is established, you can set total caloric needs, followed by total daily grams of proteins, carbohydrates, and fats. Additionally, we know that the timing of protein and carbohydrate in relation to exercise training is important to training adaptations. Each of these factors plays a critical role in the development of peak athletic performance.

References

1. Wagenmakers AJM. Muscle amino acid metabolism at rest and during exercise: role in human physiology and metabolism. Exerc Sport Sci Rev. 1998;26:287–314.
2. Elango R, Ball RO, Pencharz PB. Amino acid requirements in humans: with a special emphasis on the metabolic availability of amino acids. Amino Acids. 2009;37:19–27.
3. Wilson JM, Wilson SMC, Loenneke JP, Wray M, Norton LE, Campbell BI, Lowery RP, Stout JR. Effects of amino acids and their metabolites on aerobic and anaerobic sports. Strength Cond J. 2012; 34:33–48.

4. Jaksic T, Wagner DA, Burke JF, Young VR. Proline metabolism in adult male burned patients and healthy control subjects. Am J Clin Nutr. 1991;54:408–13.
5. Reeds PJ. Dispensable and indispensable amino acids for humans. J Nutr. 2000;130:1835S–40S.
6. Darmaun D. What is an essential amino acid in 2008? Nutrition Clinique Et Metabolisme. 2008;22:142–50.
7. St. Jeor ST, Howard BV, Prewitt TE, Bovee V, Bazzarre T, Eckel RH. Dietary protein and weight reduction: a statement for healthcare professionals from the nutrition committee of the council on nutrition, physical activity, and metabolism of the American Heart Association. Circulation. 2001;104: 1869–74.
8. Champe PC, Harvey RA, Ferrier DR. Biochemistry. Lippincott Williams & Wilkins, 2005; 83.
9. Moeller SM, Fryhofer SA, Osbahr AJ, Robinowitz CB, Amer Med A. The effects of high fructose syrup. J Am Coll Nutr. 2009;28:619–26.
10. Larsson SC, Bergkvist L, Wolk A. Consumption of sugar and sugar-sweetened foods and the risk of pancreatic cancer in a prospective study. Am J Clin Nutr. 2006;84:1171–6.
11. Malik VS, Popkin BM, Bray GA, Despres JP, Hu FB. Sugar-sweetened beverages, obesity, type 2 diabetes mellitus, and cardiovascular disease risk. Circulation. 2010;121:1356–64.
12. Malik VS, Popkin BM, Bray GA, Despres JP, Willett WC, Hu FB. Sugar-sweetened beverages and risk of metabolic syndrome and type 2 diabetes. Diabetes Care. 2010;33:2477–83.
13. Kerksick C, Harvey T, Stout J, Campbell B, Wilborn C, Kreider R, Kalman D, Ziegenfuss T, Lopez H, Landis J, Ivy JL, Antonio J. International Society of Sports Nutrition position stand: nutrient timing. J Int Soc Sports Nutr. 2008;5:12.
14. Johansson-Persson A, Ulmius M, Cloetens L, Karhu T, Herzig K-H, Onning G. A high intake of dietary fiber influences C-reactive protein and fibrinogen, but not glucose and lipid metabolism, in mildly hypercholesterolemic subjects. Eur J Nutr. 2014;53(1):39–48.
15. Wanders AJ, Feskens EJ, Jonathan MC, Schols HA, de Graaf C, Mars M. Pectin is not pectin: a randomized trial on the effect of different physicochemical properties of dietary fiber on appetite and energy intake. Physiol Behav. 2014;128:212–9.
16. Trumbo P, Schlicker S, Yates AA, Poos M. Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein and amino acids. J Am Diet Assoc. 2002;102:1621–30.
17. Ludwig DS. Dietary glycemic index and obesity. J Nutr. 2000;130:280S–3S.
18. Roberts SB. High-glycemic index foods, hunger, and obesity: is there a connection? Nutr Rev. 2000;58:163–9.
19. Gagne L. The glycemic index and glycemic, load in clinical practice. Explore. 2008;4:66–9.
20. Salmeron J, Manson JE, Stampfer MJ, Colditz GA, Wing AL, Willett WC. Dietary fiber, glycemic load, and risk of non-insulin-dependent diabetes mellitus in women. JAMA. 1997;277:472–7.
21. Atkinson FS, Foster-Powell K, Brand-Miller JC. International tables of Glycemic Index and Glycemic Load values: 2008. Diabetes Care. 2008;31:2281–3.
22. Krauss RM, Blanche PJ, Rawlings RS, Fernstrom HS, Williams PT. Separate effects of reduced carbohydrate intake and weight loss on atherogenic dyslipidemia. Am J Clin Nutr. 2006;83:1025–31.
23. Akinkuolie AO, Paynter NP, Padmanabhan L, Mora S. High-density lipoprotein particle subclass heterogeneity and incident coronary heart disease. Circ Cardiovasc Qual Outcomes. 2014;7:55–63.
24. Simopoulos AP. The importance of the omega-6/omega-3 fatty acid ratio in cardiovascular disease and other chronic diseases. Exp Biol Med. 2008;233: 674–88.
25. Ibiebele TI, Nagle CM, Bain CJ, Webb PM. Intake of omega-3 and omega-6 fatty acids and risk of ovarian cancer. Cancer Causes Control. 2012;23:1775–83.
26. Chowdhury R, Warnakula S, Kunutsor S, Crowe F, Ward HA, Johnson L, Franco OH, Butterworth AS, Forouhi NG, Thompson SG, Khaw KT, Mozaffarian D, Danesh J, Di Angelantonio E. Association of dietary, circulating, and supplement fatty acids with coronary risk: a systematic review and meta-analysis. Ann Intern Med. 2014;160:398–408.
27. Mozaffarian D, Katan MB, Ascherio A, Stampfer MJ, Willett WC. Medical progress—trans fatty acids and cardiovascular disease. N Engl J Med. 2006;354: 1601–13.
28. Michas G, Micha R, Zampelas A. Dietary fats and cardiovascular disease: putting together the pieces of a complicated puzzle. Atherosclerosis. 2014;234(2): 320–8.
29. Brooks GA, Mercier J. Balance of carbohydrate and lipid utilization during exercise - the crossover concept. J Appl Physiol. 1994;76:2253–61.
30. Black AE, Coward WA, Cole TJ, Prentice AM. Human energy expenditure in affluent societies: an analysis of 574 doubly-labelled water measurements. Eur J Clin Nutr. 1996;50:72–92.
31. Position of the American Dietetic Association, Dietitians of Canada, and the American College of Sports Medicine. Nutrition and athletic performance. J Am Diet Assoc. 2009;109:509–27.
32. Harris J, Benedict F. A biometric study of basal metabolism in man. Philadelphia: J.B. Lippincott; 1919.
33. Cunningham JJ. A reanalysis of the factors influencing basal metabolic-rate in normal adults. Am J Clin Nutr. 1980;33:2372–4.
34. Thompson J, Manore MM. Predicted and measured resting metabolic rate of male and female endurance athletes. J Am Diet Assoc. 1996;96:30–4.
35. De Lorenzo A, Bertini I, Candeloro N, Piccinelli R, Innocente I, Brancati A. A new predictive equation to calculate resting metabolic rate in athletes. J Sports Med Phys Fitness. 1999;39:213–9.
36. Campbell B. Sports nutrition: enhancing athletic performance. Boca Raton, FL: Taylor & Francis; 2013. p. 338.

37. Tappy L. Thermic effect of food and sympathetic nervous system activity in humans. Reprod Nutr Dev. 1996;36:391–7.
38. Heymsfield SB, Gonzalez M, Shen W, Redman L, Thomas D. Weight loss composition is one-fourth fat-free mass: a critical review and critique of this widely cited rule. Obes Rev. 2014;15(4):310–21.
39. Zello GA. Dietary Reference Intakes for the macronutrients and energy: considerations for physical activity. Appl Physiol Nutr Metab. 2006;31:74–9.
40. Campbell B, Kreider RB, Ziegenfuss T, La Bounty P, Roberts M, Burke D, Landis J, Lopez H, Antonio J. International Society of Sports Nutrition position stand: protein and exercise. J Int Soc Sports Nutr. 2007;4:7.
41. Phillips SM, Van Loon LJC. Dietary protein for athletes: from requirements to optimum adaptation. J Sports Sci. 2011;29:S29–38.
42. Costill DL, Sherman WM, Fink WJ, Maresh C, Witten M, Miller JM. The role of dietary carbohydrates in muscle glycogen resynthesis after strenuous running. Am J Clin Nutr. 1981;34:1831–6.
43. Fallowfield JL, Williams C. Carbohydrate intake and recovery from prolonged exercise. Int J Sport Nutr. 1993;3:150–64.
44. Loucks AB. Energy balance and body composition in sports and exercise. J Sports Sci. 2004;22:1–14.
45. Loucks AB. Low energy availability in the marathon and other endurance sports. Sports Med. 2007;37:348–52.
46. Venkatraman JT, Leddy J, Pendergast D. Dietary fats and immune status in athletes: clinical implications. Med Sci Sports Exerc. 2000;32:S389–95.
47. Kreider RB, Wilborn CD, Taylor L, Campbell B, Almada AL, Collins R, Cooke M, Earnest CP, Greenwood M, Kalman DS, Kerksick CM, Kleiner SM, Leutholtz B, Lopez H, Lowery LM, Mendel R, Smith A, Spano M, Wildman R, Willoughby DS, Ziegenfuss TN, Antonio J. ISSN exercise & sport nutrition review: research & recommendations. J Int Soc Sports Nutr. 2010;7:43.
48. Muoio DM, Leddy JJ, Horvath PJ, Awad AB, Pendergast DR. Effect of dietary-fat on metabolic adjustments to maximal VO2 and endurance in runners. Med Sci Sports Exerc. 1994;26:81–8.
49. Horowitz JF, Mora-Rodriguez R, Byerley LO, Coyle EF. Substrate metabolism when subjects are fed carbohydrate during exercise. Am J Physiol Endocrinol Metab. 1999;276:E828–35.
50. Horowitz JF, MoraRodriguez R, Byerley LO, Coyle EF. Lipolytic suppression following carbohydrate ingestion limits fat oxidation during exercise. Am J Physiol Endocrinol Metab. 1997;273:E768–75.
51. Zderic TW, Davidson CJ, Schenk S, Byerley LO, Coyle EF. High-fat diet elevates resting intramuscular triglyceride concentration and whole body lipolysis during exercise. Am J Physiol Endocrinol Metab. 2004;286:E217–25.
52. Ivy JL. Glycogen resynthesis after exercise: effect of carbohydrate intake. Int J Sports Med. 1998;19:S142–5.
53. Williams MB, Raven PB, Fogt DL, Ivy JL. Effects of recovery beverages on glycogen restoration and endurance exercise performance. J Strength Cond Res. 2003;17:12–9.
54. Volek JS. Influence of nutrition on responses to resistance training. Med Sci Sports Exerc. 2004;36:689–96.
55. Tipton KD, Ferrando AA, Phillips SM, Doyle D, Wolfe RR. Postexercise net protein synthesis in human muscle from orally administered amino acids. Am J Physiol Endocrinol Metab. 1999;276:E628–34.
56. Roy BD, Tarnopolsky MA, MacDougall JD, Fowles J, Yarasheski KE. Effect of glucose supplement timing on protein metabolism after resistance training. J Appl Physiol. 1997;82:1882–8.
57. Rasmussen BB, Tipton KD, Miller SL, Wolf SE, Wolfe RR. An oral essential amino acid-carbohydrate supplement enhances muscle protein anabolism after resistance exercise. J Appl Physiol. 2000;88:386–92.
58. Tipton KD, Rasmussen BB, Miller SL, Wolf SE, Owens-Stovall SK, Petrini BE, Wolfe RR. Timing of amino acid-carbohydrate ingestion alters anabolic response of muscle to resistance exercise. Am J Physiol Endocrinol Metab. 2001;281:E197–206.
59. Chandler RM, Byrne HK, Patterson JG, Ivy JL. Dietary-supplements affect the anabolic hormones after weight-training exercise. J Appl Physiol. 1994;76:839–45.
60. Kraemer WJ, Volek JS, Bush JA, Putukian M, Sebastianelli WJ. Hormonal responses to consecutive days of heavy-resistance exercise with or without nutritional supplementation. J Appl Physiol. 1998;85:1544–55.
61. Esmarck B, Andersen JL, Olsen S, Richter EA, Mizuno M, Kjaer M. Timing of postexercise protein intake is important for muscle hypertrophy with resistance training in elderly humans. J Physiol. 2001;535:301–11.

Essential and Nonessential Micronutrients and Sport

5

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Abstract

The purpose of this chapter is to review the role of micronutrients in sport. Attention is given to the function of micronutrients in the body, examples of quality dietary sources of each micronutrient, and an assessment of the literature examining how the recommended daily intake of a micronutrient may or may not change with exercise. The discussion includes plausible biological mechanisms of proposed performance enhancement and current research to support or negate these claims. Water-soluble vitamins, fat-soluble vitamins, macrominerals, and select microminerals are discussed in detail, and a comprehensive table reviewing all micronutrient recommendations for the athletes is provided. Practical applications for professionals working with athletes conclude the chapter.

Keywords

Micronutrients • Vitamins • Minerals • Ergogenic aid • Physical performance

5.1 Chapter Introduction

In order to maintain normal health, a wide range of vitamins, minerals, and trace elements must be present in adequate amounts in the body. Micronutrients play many important roles in the body, including hemoglobin synthesis, maintenance of bone health, adequate immune function, and protection of body tissues from oxidative damage [1]. In addition to this, and of interest to the athlete, micronutrients are integral in the process of energy metabolism. While macronutrients (carbohydrate, protein, and fat) constitute the

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sources of fuel for our bodies, micronutrients allow for the breakdown and use of these fuels.

To help quantify which micronutrients we need and in what amounts, the Food and Nutrition Board, along with the Institute of Medicine, provides reference values, known as Dietary Reference Intakes (DRIs: Tables 5.1 and 5.2), of suggested intake of micronutrients to prevent deficiency and provide optimal nutrition [2]. The DRIs consist of four categories: recommended dietary allowance (RDA), adequate intake (AI), estimated average requirement (EAR), and tolerable upper intake level (UL). The goal of the RDA is to provide a dietary intake level that is sufficient to meet the requirement for 98 % of healthy individuals. The AI is used when no RDA has been determined, while the EAR is used to satisfy the needs of 50 % of individuals within a particular group. The UL is the maximum recommended intake that individuals can consume of a particular nutrient, without the risk of adverse effects. The DRIs vary among gender and age groups, and importantly, these values represent what is needed for the "normal" individual. Thus, if and how micronutrient needs change with increased physical activity is still a matter of debate. It appears logical that regular intense exercise training increases all nutrient requirements by increasing turnover and decreasing absorption. Moreover, high intakes of micronutrients may be required to cover needs related to tissue maintenance and repair.

The purpose of this chapter is to review the function of micronutrients in the body, provide examples of quality dietary sources of each micronutrient, and assess the literature examining how the recommended daily intake of a micronutrient may or may not change with exercise.

5.2 Vitamin Introduction

Vitamins are organic compounds naturally found in small amounts in food products. They are designated as essential nutrients because they cannot be synthesized by the body in amounts that are necessary to support normal physiological function. Generally, vitamins are classified as either water soluble or fat soluble, based on the medium needed for their absorption. Water-soluble vitamins include the B complex (thiamin, riboflavin, niacin, pantothenic acid, pyridoxine, biotin, folic acid, cyanocobalamin) and ascorbic acid (vitamin C), and fat-soluble vitamins include vitamins A, D, E, and K. Each group and its associated vitamins will be examined in detail in the paragraphs that follow.

5.2.1 Water-Soluble Vitamins

As their name suggests, water-soluble vitamins dissolve readily in water and are lost daily in the urine. Because of this, most water-soluble vitamins are not stored in the body, necessitating their regular dietary consumption. The largest contributors to the water-soluble vitamins are the B complex vitamins, including thiamin (B_1), riboflavin (B_2), niacin (B_3), pantothenic acid, pyridoxine (B_6), biotin, folic acid, and cyanocobalamin (B_{12}). B vitamins act primarily as coenzymes, facilitating hundreds of chemical reactions in our bodies. Ascorbic acid, or vitamin C, is also a water-soluble vitamin and plays a major role as an antioxidant.

5.2.1.1 Vitamin B_1 (Thiamin)

Thiamine monophosphate (TMP), thiamine pyrophosphate (TPP), and thiamine triphosphate (TTP) are the three most studied forms of thiamin. The TPP form makes up ~80 % of thiamin in the body, while TMP and TTP each contribute ~10 %. TPP functions in the metabolism of carbohydrates, by serving as a cofactor in the conversion of pyruvate to acetyl-CoA and in the transketolase reaction, which synthesizes NADPH, deoxyribose, and ribose sugars in the pentose phosphate pathway. Thiamin also plays a role in branch chain amino acid metabolism and may serve a role in nerve conduction and transmission. Although found in a variety of animal products and vegetables, an abundance of thiamin is found in only a few foods (see Table 5.3). There are no known adverse effects associated with thiamin supplementation; therefore, no UL has been set. Deficiency of thiamin may lead to cardiac failure, muscle weakness, neuropathy, and gastrointestinal disturbances (all hallmarks of the thiamin-deficiency disease: beriberi).

Table 5.1 Dietary reference intakes (DRIs): recommended dietary allowances and adequate intakes of vitamins. Food and Nutrition Board, Institute of Medicine, National Academies

Life stage group	Vitamin A (μg/day)[a]	Vitamin C (mg/day)	Vitamin D (μg/day)[b,c]	Vitamin E (mg/day)[d]	Vitamin K (μg/day)	Thiamin (mg/day)	Riboflavin (mg/day)	Niacin (mg/day)[e]	Vitamin B6 (mg/day)	Folate (μg/day)[f]	Vitamin B12 (μg/day)	Pantothenic acid (mg/day)	Biotin (μg/day)	Choline (mg/day)[g]
Infants														
0–6 months	400*	40*	10	4*	2.0*	0.2*	0.3*	2*	0.1*	65*	0.4*	1.7*	5*	125*
6–12 months	500*	50*	10	5*	2.5*	0.3*	0.4*	4*	0.3*	80*	0.5*	1.8*	6*	150*
Children														
1–3 years	**300**	**15**	**15**	**6**	30*	**0.5**	**0.5**	**6**	**0.5**	**150**	**0.9**	2*	8*	200*
4–8 years	**400**	**25**	**15**	**7**	55*	**0.6**	**0.6**	**8**	**0.6**	**200**	**1.2**	3*	12*	250*
Males														
9–13 years	**600**	**45**	**15**	**11**	60*	**0.9**	**0.9**	**12**	**1.0**	**300**	**1.8**	4*	20*	375*
14–18 years	**900**	**75**	**15**	**15**	75*	**1.2**	**1.3**	**16**	**1.3**	**400**	**2.4**	5*	25*	550*
19–30 years	**900**	**90**	**15**	**15**	120*	**1.2**	**1.3**	**16**	**1.3**	**400**	**2.4**	5*	30*	550*
31–50 years	**900**	**90**	**15**	**15**	120*	**1.2**	**1.3**	**16**	**1.3**	**400**	**2.4**	5*	30*	550*
51–70 years	**900**	**90**	**15**	**15**	120*	**1.2**	**1.3**	**16**	**1.7**	**400**	**2.4**[h]	5*	30*	550*
> 70 years	**900**	**90**	**20**	**15**	120*	**1.2**	**1.3**	**16**	**1.7**	**400**	**2.4**[h]	5*	30*	550*
Females														
9–13 years	**600**	**45**	**15**	**11**	60*	**0.9**	**0.9**	**12**	**1.0**	**300**	**1.8**	4*	20*	375*
14–18 years	**700**	**65**	**15**	**15**	75*	**1.0**	**1.0**	**14**	**1.2**	**400**[i]	**2.4**	5*	25*	400*
19–30 years	**700**	**75**	**15**	**15**	90*	**1.1**	**1.1**	**14**	**1.3**	**400**[i]	**2.4**	5*	30*	425*
31–50 years	**700**	**75**	**15**	**15**	90*	**1.1**	**1.1**	**14**	**1.3**	**400**[i]	**2.4**	5*	30*	425*
51–70 years	**700**	**75**	**15**	**15**	90*	**1.1**	**1.1**	**14**	**1.5**	**400**	**2.4**[h]	5*	30*	425*
> 70 years	**700**	**75**	**20**	**15**	90*	**1.1**	**1.1**	**14**	**1.5**	**400**	**2.4**[h]	5*	30*	425*
Pregnancy														
14–18 years	**750**	**80**	**15**	**15**	75*	**1.4**	**1.4**	**18**	**1.9**	**600**[j]	**2.6**	6*	30*	450*
19–30 years	**770**	**85**	**15**	**15**	90*	**1.4**	**1.4**	**18**	**1.9**	**600**[j]	**2.6**	6*	30*	450*
31–50 years	**770**	**85**	**15**	**15**	90*	**1.4**	**1.4**	**18**	**1.9**	**600**[j]	**2.6**	6*	30*	450*

(continued)

Table 5.1 (continued)

Life stage group	Vitamin A (μg/day)[a]	Vitamin C (mg/day)	Vitamin D (μg/day)[b,c]	Vitamin E (mg/day)[d]	Vitamin K (μg/day)	Thiamin (mg/day)	Riboflavin (mg/day)	Niacin (mg/day)[e]	Vitamin B6 (mg/day)	Folate (μg/day)[f]	Vitamin B12 (μg/day)	Pantothenic acid (mg/day)	Biotin (μg/day)	Choline (mg/day)[g]
Lactation														
14–18 years	**1,200**	**115**	**15**	**19**	75*	**1.4**	**1.6**	**17**	**2.0**	**500**	**2.8**	7*	35*	550*
19–30 years	**1,300**	**120**	**15**	**19**	90*	**1.4**	**1.6**	**17**	**2.0**	**500**	**2.8**	7*	35*	550*
31–50 years	**1,300**	**120**	**15**	**19**	90*	**1.4**	**1.6**	**17**	**2.0**	**500**	**2.8**	7*	35*	550*

Note: This table (taken from the DRI reports, see www.nap.edu) presents recommended dietary allowances (RDAs) in **bold type** and adequate intakes (AIs) in ordinary type followed by an asterisk (*). An RDA is the average daily dietary intake level, sufficient to meet the nutrient requirements of nearly all (97–98 %) healthy individuals in a group. It is calculated from an estimated average requirement (EAR). If sufficient scientific evidence is not available to establish an EAR and thus calculate an RDA, an AI is usually developed. For healthy breast-fed infants, an AI is the mean intake. The AI for other life stage and gender groups is believed to cover the needs of all healthy individuals in the groups, but lack of data or uncertainty in the data prevents being able to specify with confidence the percentage of individuals covered by this intake

Sources: Dietary reference intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride (1997); Dietary reference intakes for thiamin, riboflavin, niacin, vitamin B_6, folate, vitamin B_{12}, pantothenic acid, biotin, and choline (1998); Dietary reference intakes for vitamin C, vitamin E, selenium, and carotenoids (2000); Dietary reference intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc (2001); Dietary reference intakes for water, potassium, sodium, chloride, and sulfate (2005); and Dietary reference intakes for calcium and vitamin D (2011). These reports may be accessed via www.nap.edu

[a]As retinol activity equivalents (RAEs). 1 RAE = 1 μg retinol, 12 μg β-carotene, 24 μg α-carotene, or 24 μg β-cryptoxanthin. The RAE for dietary provitamin A carotenoids is twofold greater than retinol equivalents (RE), whereas the RAE for preformed vitamin A is the same as RE

[b]As cholecalciferol. 1 μg cholecalciferol = 40 IU vitamin D

[c]Under the assumption of minimal sunlight

[d]As α-tocopherol. α-Tocopherol includes *RRR*-α-tocopherol, the only form of α-tocopherol that occurs naturally in foods, and the *2R*-stereoisomeric forms of α-tocopherol (*RRR*-, *RSR*-, *RRS*-, and *RSS*-α-tocopherol) that occur in fortified foods and supplements. It does not include the *2S*-stereoisomeric forms of α-tocopherol (*SRR*-, *SSR*-, *SRS*-, and *SSS*-α-tocopherol), also found in fortified foods and supplements

[e]As niacin equivalents (NE). 1 mg of niacin = 60 mg of tryptophan; 0–6 months = preformed niacin (not NE)

[f]As dietary folate equivalents (DFE). 1 DFE = 1 μg food folate = 0.6 μg of folic acid from fortified food or as a supplement consumed with food = 0.5 μg of a supplement taken on an empty stomach

[g]Although AIs have been set for choline, there are few data to assess whether a dietary supply of choline is needed at all stages of the life cycle, and it may be that the choline requirement can be met by endogenous synthesis at some of these stages

[h]Because 10–30 % of older people may malabsorb food-bound B_{12}, it is advisable for those older than 50 years to meet their RDA mainly by consuming foods fortified with B_{12} or a supplement containing B_{12}

[i]In view of evidence linking folate intake with neural tube defects in the fetus, it is recommended that all women capable of becoming pregnant consume 400 μg from supplements or fortified foods in addition to intake of food folate from a varied diet

[j]It is assumed that women will continue consuming 400 μg from supplements or fortified food until their pregnancy is confirmed, and they enter prenatal care, which ordinarily occurs after the end of the periconceptional period—the critical time for formation of the neural tube

Table 5.2 Dietary reference intakes (DRIs): recommended dietary allowances and adequate intakes of elements. Food and Nutrition Board, Institute of Medicine, National Academies

Life stage group	Calcium (mg/day)	Chromium (μg/day)	Copper (μg/day)	Fluoride (mg/day)	Iodine (μg/day)	Iron (mg/day)	Magnesium (mg/day)	Manganese (mg/day)	Molybdenum (μg/day)	Phosphorus (mg/day)	Selenium (μg/day)	Zinc (mg/day)	Potassium (g/day)	Sodium (g/day)	Chloride (g/day)
Infants															
0–6 months	200*	0.2*	200*	0.01*	110*	0.27*	30*	0.003*	2*	100*	15*	2*	0.4*	0.12*	0.18*
6–12 months	260*	5.5*	220*	0.5*	130*	**11**	75*	0.6*	3*	275*	20*	**3**	0.7*	0.37*	0.57*
Children															
1–3 years	**700**	11*	**340**	0.7*	**90**	**7**	**80**	1.2*	**17**	**460**	**20**	**3**	3.0*	1.0*	1.5*
4–8 years	**1,000**	15*	**440**	1*	**90**	**10**	**130**	1.5*	**22**	**500**	**30**	**5**	3.8*	1.2*	1.9*
Males															
9–13 years	**1,300**	25*	**700**	2*	**120**	**8**	**240**	1.9*	**34**	**1,250**	**40**	**8**	4.5*	1.5*	2.3*
14–18 years	**1,300**	35*	**890**	3*	**150**	**11**	**410**	2.2*	**43**	**1,250**	**55**	**11**	4.7*	1.5*	2.3*
19–30 years	**1,000**	35*	**900**	4*	**150**	**8**	**400**	2.3*	**45**	**700**	**55**	**11**	4.7*	1.5*	2.3*
31–50 years	**1,000**	35*	**900**	4*	**150**	**8**	**420**	2.3*	**45**	**700**	**55**	**11**	4.7*	1.5*	2.3*
51–70 years	**1,000**	30*	**900**	4*	**150**	**8**	**420**	2.3*	**45**	**700**	**55**	**11**	4.7*	1.3*	2.0*
> 70 years	**1,200**	30*	**900**	4*	**150**	**8**	**420**	2.3*	**45**	**700**	**55**	**11**	4.7*	1.2*	1.8*
Females															
9–13 years	**1,300**	21*	**700**	2*	**120**	**8**	**240**	1.6*	**34**	**1,250**	**40**	**8**	4.5*	1.5*	2.3*
14–18 years	**1,300**	24*	**890**	3*	**150**	**15**	**360**	1.6*	**43**	**1,250**	**55**	**9**	4.7*	1.5*	2.3*
19–30 years	**1,000**	25*	**900**	3*	**150**	**18**	**310**	1.8*	**45**	**700**	**55**	**8**	4.7*	1.5*	2.3*
31–50 years	**1,000**	25*	**900**	3*	**150**	**18**	**320**	1.8*	**45**	**700**	**55**	**8**	4.7*	1.5*	2.3*
51–70 years	**1,200**	20*	**900**	3*	**150**	**8**	**320**	1.8*	**45**	**700**	**55**	**8**	4.7*	1.3*	2.0*
> 70 years	**1,200**	20*	**900**	3*	**150**	**8**	**320**	1.8*	**45**	**700**	**55**	**8**	4.7*	1.2*	1.8*
Pregnancy															
14–18 years	**1,300**	29*	**1,000**	3*	**220**	**27**	**400**	2.0*	**50**	**1,250**	**60**	**12**	4.7*	1.5*	2.3*
19–30 years	**1,000**	30*	**1,000**	3*	**220**	**27**	**350**	2.0*	**50**	**700**	**60**	**11**	4.7*	1.5*	2.3*
31–50 years	**1,000**	30*	**1,000**	3*	**220**	**27**	**360**	2.0*	**50**	**700**	**60**	**11**	4.7*	1.5*	2.3*

(continued)

Table 5.2 (continued)

Life stage group	Calcium (mg/day)	Chromium (µg/day)	Copper (µg/day)	Fluoride (mg/day)	Iodine (µg/day)	Iron (mg/day)	Magnesium (mg/day)	Manganese (mg/day)	Molybdenum (µg/day)	Phosphorus (mg/day)	Selenium (µg/day)	Zinc (mg/day)	Potassium (g/day)	Sodium (g/day)	Chloride (g/day)
Lactation															
14–18 years	**1,300**	44*	**1,300**	3*	**290**	**10**	**360**	2.6*	**50**	**1,250**	**70**	**13**	5.1*	1.5*	2.3*
19–30 years	**1,000**	45*	**1,300**	3*	**290**	**9**	**310**	2.6*	**50**	**700**	**70**	**12**	5.1*	1.5*	2.3*
31–50 years	**1,000**	45*	**1,300**	3*	**290**	**9**	**320**	2.6*	**50**	**700**	**70**	**12**	5.1*	1.5*	2.3*

Note: This table (taken from the DRI reports, see www.nap.edu) presents recommended dietary allowances (RDAs) in **bold type** and adequate intakes (AIs) in ordinary type followed by an asterisk (*). An RDA is the average daily dietary intake level, sufficient to meet the nutrient requirements of nearly all (97–98 %) healthy individuals in a group. It is calculated from an estimated average requirement (EAR). If sufficient scientific evidence is not available to establish an EAR and thus calculate an RDA, an AI is usually developed. For healthy breast-fed infants, an AI is the mean intake. The AI for other life stage and gender groups is believed to cover the needs of all healthy individuals in the groups, but lack of data or uncertainty in the data prevents being able to specify with confidence the percentage of individuals covered by this intake

Sources: Dietary reference intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride (1997); Dietary reference intakes for thiamin, riboflavin, niacin, vitamin B_6, folate, vitamin B_{12}, pantothenic acid, biotin, and choline (1998); Dietary reference intakes for vitamin C, vitamin E, selenium, and carotenoids (2000); and Dietary reference intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc (2001); Dietary reference intakes for water, potassium, sodium, chloride, and sulfate (2005); and Dietary reference intakes for calcium and vitamin D (2011). These reports may be accessed via www.nap.edu

Table 5.3 Summary of water-soluble vitamins

Nutrient	Function	Adult (nonpregnant) recommended intake	Food sources	Comments for the athlete
Thiamin (B_1)	Carbohydrate and amino acid metabolism	• UL: N/A • Deficiency: weakness, decreased endurance, weight loss	Yeast, pork, fortified grains, cereals, legumes	Studies indicate that there is no need for additional thiamin supplementation above the DRI recommendations with exercise
Riboflavin (B_2)	Oxidative metabolism, electron transport system	• UL: N/A • Deficiency: altered skin and mucous membrane and nervous system function	Milk, almonds, liver, eggs, bread, fortified cereals	Athletes who consume adequate levels through the diet do not require supplementation above the DRI
Niacin (B_3)	Oxidative metabolism, electron transport system	• UL: 35 mg/day • Deficiency: irritability, diarrhea	Meats, fish, legumes, peanuts, some cereals	All persons should obtain the DRI for niacin intake to ensure adequate intake and performance
Pantothenic acid	Essential to the metabolism of fatty acids, amino acids, and carbohydrates	• UL: N/A • Deficiency: muscle cramps, fatigue, apathy, malaise, nausea, vomiting	Liver, egg yolk, sunflower seeds, mushrooms, peanuts, brewer's yeast, yogurt, broccoli	Limited research exists on pantothenic acid supplementation and exercise performance
Vitamin B_6	Gluconeogenesis	• UL: 100 mg/day • Deficiency: dermatitis, convulsions	Meats, whole grain products, vegetables, nuts	Exercise has been shown to increase the loss of vitamin B_6
Biotin	Cofactor in synthesis of fatty acids, gluconeogenesis, and the metabolism of leucine	• UL: N/A • Deficiency: dermatitis, alopecia, conjunctivitis	Liver, egg yolk, soybeans, yeast, cereals, legumes, nuts	Not enough information to make a recommendation regarding supplementation and exercise
Folate	Hemoglobin and nucleic acid formation	• UL:1,000 μg/day • Deficiency: anemia, fatigue	Yeast, liver, fresh green vegetables, strawberries	Exercise does not appear to increase needs
Vitamin B_{12}	Hemoglobin formation	• UL: N/A • Deficiency: anemia, neurologic symptoms	Organ meats, shellfish, dairy products	Supplemental vitamin B_{12} does not appear to benefit performance unless a nutritional deficit is present
Vitamin C	Antioxidant	• UL: 2,000 mg/day • Deficiency: fatigue, loss of appetite	Citrus fruits, green vegetables, peppers, tomatoes, berries, potatoes	Results of supplementation on performance are equivocal; possible benefits of supplementation include enhanced immune function, antioxidant effects, and decreasing body temperature

Because of the role thiamin plays in energy (particularly carbohydrate) metabolism, it is speculated that needs increase with exercise. Indeed, the differential RDA for thiamin for men and women (1.1 mg/day for adult women and 1.2 mg/day for adult men) is based on increased energy requirements and carbohydrate intake in men than women. Further, exercise has been suggested to affect thiamin status by decreasing absorption of minerals, increasing turnover and metabolism of the nutrients, increasing thiamin-dependent mitochondrial enzymes, increasing needs through tissue repair and maintenance, and varying biochemical adaptations through exercise training [3].

Suzuki et al. [4] determined that 100 mg/day of thiamin supplementation significantly decreased self-reported fatigue (compared to a placebo) after 30 min on a bicycle ergometer. Additionally, one mg/kg of intravenous TPP, administered 24 h prior to a submaximal exercise bout, resulted in reduced serum lactate and postexercise heart rate, as well as improved VO_2max compared to a placebo [5]. However, other studies examining supplementation of thiamin derivatives have been unsuccessful at showing improvements in exercise performance [6, 7]. Despite a plausible biological mechanism, the current literature does not support thiamin supplementation above the DRI recommendations with exercise.

5.2.1.2 Vitamin B_2 (Riboflavin)

Riboflavin functions as a catalyst for redox reactions in energy production and many metabolic pathways, mainly as a component of flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD) [8]. Also, riboflavin is required for the conversion of other nutrients to their active forms, including niacin, folic acid, and vitamin B_6. FAD is part of the electron transport chain, which is central to energy production. Signs and symptoms of deficiency include sore throat, cracked and red lips, inflammation of the tongue and lining of the mouth, and bloodshot eyes, although overt riboflavin deficiency (ariboflavinosis) is rare. Excess intake of riboflavin is eliminated in the urine; therefore, no UL exists. Most plant and animal food sources contain riboflavin, with milk, liver, whole and enriched grains, and fortified cereals among the best dietary sources.

Nutritional surveys provided to athletes suggest that most athletes consume the DRI recommended amount of riboflavin [9, 10]; however, whether current recommendations are adequate for athletes has been debated. Although conflicting data exists as to whether exercise affects the biochemical status of riboflavin in the blood [3, 11], potentially due to increased losses [3, 12], supplementation does not appear to improve physical fitness if baseline values are within the normal range [13, 14]. If riboflavin deficiency is present, however, limited data suggest that supplementation may improve fitness performance [13]. The current consensus is that individuals who consume adequate levels through the diet do not require supplementation above the DRI.

5.2.1.3 Vitamin B_3 (Niacin)

Niacin is a water-soluble vitamin whose derivatives, such as NADH, NAD, NAD+, and NADP, play vital roles in substrate metabolism. There is growing evidence that NAD+ plays an important role in mitochondrial function and energy metabolism, calcium homeostasis, and inflammation [15]. Deficiencies of this vitamin can result in a condition known as pellagra, a disease characterized by scaly skin sores, diarrhea, inflamed mucous membranes, mental confusion, delusions, and ultimately death. Although pellagra has almost disappeared from industrialized countries, it is still common in regions that subsist primarily on a corn-based diet, as corn is a very poor source of niacin. (It is now known that treating corn products in an alkali bath, typically limewater, will increase the bioavailability of niacin.)

Although critical to the oxidation of fuel sources, and thus exercise metabolism, studies assessing the role of niacin on metabolic responses during acute exercise are limited. With small doses of niacin (<1 g/day), supplementation has been shown to improve agility [16], but not endurance [17]. Large doses of niacin (typically supplemented in the form of nicotinic acid) have been shown to adversely affect plasma free fatty acid concentrations during exercise [18, 19], and thus, it is hypothesized that large doses

may negatively impact lower-intensity exercise. However, to date, large niacin supplementation doses have only been shown to decrease performance when carbohydrate availability is low [20, 21]. Surveys of athletic populations show that niacin consumption is adequate, with only athletes participating in weight-restrictive behaviors falling below recommended levels [9, 10]. At present, it is recommended that all persons obtain the DRI for niacin intake to ensure adequate intake and performance.

5.2.1.4 Vitamin B_5 (Pantothenic Acid)

Pantothenic acid performs multiple roles in cellular metabolism and regulation as an integral part of two acylation factors: coenzyme A (CoA) and acyl carrier protein (ACP). In these forms, pantothenic acid is essential to the metabolism of fatty acids, amino acids, and carbohydrates, as well as the synthesis of cholesterol, steroid hormones, vitamin A, and vitamin D [22]. Although human studies looking at the effect of pantothenic acid and exercise performance are limited, two studies suggest that supplementation with pantothenic acid (or vitamin B_5 derivative) does not alter exercise metabolism or exercise performance [23, 24].

5.2.1.5 Vitamin B_6 (Pyridoxine and Related Compounds)

Vitamin B_6 collectively refers to all biologically active forms of vitamin B_6 (including pyridoxal, pyridoxamine, and pyridoxine) although the metabolically active form of the vitamin is pyridoxal phosphate or PLP. B_6 is involved in many different cellular processes including gluconeogenesis, niacin formation, lipid metabolism, erythrocyte function and metabolism, and hormone modulation [22]. All persons, including athletes, consume adequate amounts of this vitamin [10, 25]. Vitamin B_6 is widely distributed in foods (see Table 5.3 to view foods with the greatest concentrations of vitamin B_6) and commonly found in multivitamin and mineral supplements.

Because exercise has been shown to increase the loss of vitamin B_6 as 4-pyridoxic acid [26] and because PLP acts as a cofactor in both gluconeogenesis and glycogenolysis, it has been postulated that supplementation of the vitamin may increase exercise performance. Studies show that time to exhaustion does not improve following B_6 supplementation [27, 28], and thus supplementation above the DRI does not appear to improve performance.

5.2.1.6 Vitamin B_7 (Biotin)

Biotin, also known as vitamin H, plays an important role in the catalysis of many essential metabolic reactions, including the synthesis of fatty acids, gluconeogenesis, and metabolism of leucine. To date no studies have been conducted looking at the role of biotin in exercise performance in humans.

5.2.1.7 Folic Acid

Named for the abundance of the vitamin in green, leafy vegetables (or foliage), folic acid plays several important roles in energy metabolism. Folic acid is the synthetic form of folate and is needed for DNA production and erythropoiesis. Deficiencies, common among athletes [10, 26, 29], can cause errors in cellular replication, particularly affecting the red blood cells; as a result of folate deficiency, megaloblastic anemia can occur. The DRI for folate is 400 μg/day for women and men. Due to its prominent role in cellular growth and differentiation, this value increases to 600 and 500 μg/day during pregnancy and lactation, respectively [2]. Folate is ubiquitous in nature and found in most all natural foods. However, the vitamin is highly susceptible to oxidative damage, and thus the folate content of foods is easily destroyed by heat.

Due to its role in erythrocyte production, it is not surprising that researchers question whether folic acid supplementation can increase athletic performance. Results of one study showed that while folate supplementation in an athletic population did significantly increase circulating levels of serum folate, this increase did not translate into increased performance [30]. The authors of this study speculate that changes in circulating concentrations of folate may not reflect changes in cellular folate status; thus, over-supplementation cannot be justified. At present recommended intake of folate follows the DRI for normal individuals.

5.2.1.8 Vitamin B_{12} (Cyanocobalamin)

Cyanocobalamin, or vitamin B_{12}, is unlike other B vitamins in that plants do not provide it and the body is capable of storing it in the liver. Vitamin B_{12} is involved in fat and carbohydrate metabolism, as well as protein synthesis. Additionally, vitamin B_{12} is responsible for the conversion of homocysteine to methionine, and deficiencies in the vitamin have been linked to hyperhomocysteinemia, an independent risk factor for cardiovascular disease [31]. In nature, this vitamin is synthesized by microorganisms, and thus it is not found in plant foods, except when they are contaminated by microorganisms. Small amounts of vitamin B_{12} are found in legumes, which contain microorganisms, and may provide the only dietary source of vitamin B_{12} for vegans.

Although older studies have shown that supplemental B_{12} does not benefit performance unless a nutritional deficit is present [32, 33], controlled, well-designed studies utilizing modern technology are needed to determine whether Vitamin B_{12} is needed in larger amounts by individuals who exercise.

5.2.1.9 Vitamin C (Ascorbic Acid)

The functions of vitamin C are based primarily on its biological reductant capabilities. As such, vitamin C is involved in collagen formation, cortisol synthesis, neurotransmitter synthesis, and iron absorption. Vitamin C has also been shown to promote resistance to infection through the immunologic activity of leukocytes, production of interferon, process of inflammatory reaction, and/or integrity of the mucous membranes [22]. When dietary intake of ascorbic acid is insufficient, a set of conditions occur (e.g., malaise, lethargy, petechiae, gum disease, poor wound healing) that are collectively known as scurvy.

Important to the athlete, vitamin C has certain biological functions that can influence physical performance. Due to its requirement in the synthesis of carnitine (the enzyme responsible for the transport of long-chain fatty acids into the mitochondria), it is thought to play a major role in lipid energy availability. Additionally, it may act as an antioxidant, along with vitamins A and E, preventing cellular damage caused by free radical intermediates. In general, intakes of 0.2–1.0 g/day reduce oxidative stress, but do not improve athletic performance [34]. Large doses (>1.0 g/day) may possibly impair athletic performance through reduced mitochondrial biogenesis or alterations in vascular function [34].

5.2.2 Fat-Soluble Vitamins

The fat-soluble vitamins include vitamins A, D, E, and K. Vitamins A and E function as antioxidants, and vitamins D and K play a role in bone metabolism. Because fat-soluble vitamins are stored for extended periods when consumed in excess, they create a greater risk for toxicity than water-soluble vitamins. Disease states affecting the absorption or storage of fat could cause deficiency of these vitamins.

5.2.2.1 Vitamin A

The roles of vitamin A within the body are vast, including immune function, vision, growth, and gene expression. Vitamin A comprises a group of compounds, including retinol, retinal, retinoic acid, or retinyl ester. Provitamin A carotenoids (i.e., α-carotene and β-carotene) are precursors to retinol, one of the most active forms of vitamin A. Some provitamin A carotenoids have been found to have antioxidant activity, with β-carotene suggested to be the primary anticancer agent in fruits and vegetables [35].

Dietary carotenoids are consumed primarily through oils and brightly colored fruits and vegetables, whereas preformed vitamin A is found only in animal products. The RDA requirements for vitamin A are expressed in retinol activity equivalents (RAE). A UL of preformed vitamin A has been recommended because retinol is stored and metabolized in the liver; however, the liver has a protective mechanism for reducing vitamin A metabolites by excreting the metabolites in bile. Adverse effects associated with an overdose of vitamin A include acute effects such as vertigo, blurred vision, and nausea, as well as chronic effects such as bone loss and liver abnormalities [36].

To date, there is very little research examining the effects of β-carotene supplementation alone

on muscular strength or endurance. Although there is potential for vitamin A supplementation to decrease oxidative stresses from exercise, research is limited, predominantly because vitamins C and E have greater antioxidant capabilities. Further, evidence of vitamin A deficiency in athletic individuals is lacking, likely because body storage is appreciable [37]. Due to the fat solubility properties, supplementation of β-carotene is not recommended.

5.2.2.2 Vitamin D (Calciferol)

Although many forms of calciferol (vitamin D) exist, the two main forms are ergocalciferol (vitamin D_2) and cholecalciferol (vitamin D_3). Vitamin D_2 is produced from ergosterol in the diet, while vitamin D_3 is synthesized by ultraviolet radiation from a precursor of cholesterol in the skin. Both forms are biologically inert and must be converted to the biologically active form, 1,25-dihydroxyvitamin D (1,25 $(OH)_2D$). The major source of vitamin D for humans is sunlight. This source is especially important because few dietary sources contain vitamin D naturally (see Table 5.4). In the United States, many dairy foods (i.e., milk and cheese) are fortified with vitamin D to avoid deficiency in latitudes where exposure to sunlight is limited during the winter months.

Excess amounts of vitamin D (hypervitaminosis D) can lead to high blood pressure, bone loss, and kidney damage. These effects are thought to be caused, for the most part, by hypercalcemia that may occur with hypervitaminosis D [38]. This is because the function of vitamin D is to maintain serum calcium and phosphorus levels within the body by enhancing their absorption from the gastrointestinal tract and promoting their release from the bones. Active vitamin D provides such a role by working in combination with the parathyroid hormone (PTH) to mobilize calcium and, indirectly, phosphorus from the bone to maintain serum concentrations as needed.

Studies suggest that serum 25-hydroxyvitamin (25(OH)D) concentrations <50 nmol/L is common among athletes [39–41], with serum profiles often worse depending upon winter season, unfavorable latitude of training, and indoor training routine [42]. Decreased vitamin D is associated with increased inflammation in athletes [43]. In subjects with elevated baseline inflammation, the addition of vitamin D supplementation to

Table 5.4 Summary of fat-soluble vitamins

Nutrient	Function	Adult (nonpregnant) recommended intake	Food sources	Comments for the athlete
Vitamin A	Vision, immune response, epithelial cell growth and repair	• UL: 3,000 μg preformed vitamin A/day • Deficiency: dry skin, dry hair, broken fingernails, susceptibility to infections	Broccoli, squash, sweet potatoes, pumpkin, cantaloupe, liver, milk, eggs	Supplementation of β-carotene is not recommended
Vitamin D	Bone remodeling and maintaining serum calcium and phosphorus concentrations	• UL: 100 μg/day • Deficiency: osteomalacia, osteoporosis, heart disease, hypertension	*Natural sources*: fatty fish, egg yolks *Fortified sources*: milk, cereals	May influence bone mineralization and help prevent fractures
Vitamin E	Antioxidant	• UL: 1,000 mg α-tocopherol/day • Deficiency: retinopathy, neuropathy, and myopathy	Vegetable oils, unprocessed cereal grains, green leafy vegetables, nuts	Antioxidant properties may be beneficial in decreasing oxidative stress during exercise bouts
Vitamin K	Essential for normal blood clotting	• UL: N/A • Deficiency: increase in blood clotting time and decrease in bone mineral density	Green leafy vegetables, cereal, organ meats, dairy products, eggs	Supplementation may be needed for formation of bone

exercise has been shown to reduce inflammation beyond that of exercise alone [44]. Further, insufficient vitamin D may increase risk for injuries, such as stress fractures, which are quite common among athletes. In older adults, increasing serum 25(OH)D levels from 53 to 74 nmol/L by supplementation reduced fracture risk by 33 % over 5 years [45]. In a large sample of active female military recruits, supplementation with 800 IU/day of vitamin D for 8 weeks resulted in 20 % lower incidence of stress fractures than the placebo group [46].

With regard to athletic and muscular performance, studies examining the effects of vitamin D supplementation in young athletes are sparse. A recent study examining the effects of 5,000 IU/day of vitamin D_3 supplementation for 8 weeks showed that supplementation resulted in improved 10 m sprint time and vertical jump height [39]. In older adults (>50 years of age), beneficial effects of vitamin D treatment have been observed on muscle function, including muscle strength [47, 48] and physical function [49, 50], when vitamin D status is low prior to supplementation. However, the beneficial effect of supplementation on physical function is not universally observed. A recent review showed that over half of the previously published papers examining the effects of vitamin D supplementation on muscle function show a lack of an effect versus beneficial results [51].

In conclusion, and much like the other micronutrients, while randomized controlled trial evidence is not strong enough to suggest vitamin D as an ergogenic aid, insufficient levels of vitamin D can contribute to decreased athletic performance, potentially by increasing the risk of debilitating stress fractures. Thus, obtaining optimal 25(OH)D levels (i.e., ≥50 ng/mL) through diet and UV exposure is recommended.

5.2.2.3 Vitamin E

Unlike the other fat-soluble vitamins, vitamin E has no specific metabolic function. Instead, its major function is as an antioxidant of polyunsaturated fatty acids, preventing free radical damage in biological membranes caused by lipid peroxidation. Because vitamin E is absorbed similarly to dietary fat, changes in pancreatic function, chylomicron transport of lipids, and bile production are known to impair vitamin E absorption [52]. The majority of vitamin E is stored in the adipose tissue, while smaller amounts are stored in the heart, liver, lungs, brain, muscles, and adrenal glands. Eight naturally occurring isomers of vitamin E exist; however, only the α-tocopherol form is maintained in human plasma [53]. Adverse effects of vitamin E deficiency include retinopathy, neuropathy, and myopathy; however, deficiency occurs rarely in humans. There are no adverse effects noted with ingestion of naturally occurring vitamin E in foods. As a nutritional supplement, side effects include fatigue, gastrointestinal disturbances, and altered lipid concentrations. Nutritional supplements contain either a natural or synthetic form of α-tocopherol.

Studies examining the effects of vitamin E supplementation on oxidative stress and lipid peroxidation during exercise are numerous. Compared to a placebo, supplementation of 800 mg/day α-tocopherol for 2 months [54] resulted in improvements in antioxidant potential 1.5 h after completing a triathlon. However, the large dose also appeared to cause significant increases in oxidative stress markers and did not improve performance time. Conversely, free radical production was reduced in basketball players following lower dose supplementation (1 month of 200 mg/day of α-tocopherol) [55]. Regarding performance, no difference in aerobic work capacity was observed following supplementation with a low (35 days of 268 mg/day of vitamin E [56]) or high dose (4 weeks of daily 1,200 IU of α-tocopherol [57]) of vitamin E. Additionally, supplementation with 400–1,000 IU of vitamin E does not appear to reduce biochemical indices of muscle damage following acute, strenuous exercise [58, 59]. Interestingly, data from a recent randomized controlled trial suggests that combined vitamin E and C supplementation (which often occurs together) may hamper beneficial cellular adaptations to exercise [60], with authors interpreting results to advocate caution when considering antioxidant supplementation combined with endurance exercise. Further research should be aimed at determining

specific recommendation regarding vitamin E supplementation on exercise performance, oxidative stress, and muscle damage.

5.2.2.4 Vitamin K

Two forms of vitamin K naturally exist: phylloquinones (vitamin K_1), produced by plants, and menaquinones (vitamin K_2), produced by bacteria in the large intestine. The predominant forms of intake in the diet are phylloquinones, from green leafy vegetables. Vitamin K functions as a critical cofactor of γ-carboxylase, an essential posttranslational modification required for the functional activity of coagulation proteins such as prothrombin. Deficiency of vitamin K leads to changes in blood clotting (increased prothrombin time) and a decrease in bone mineral density (increase in plasma under-γ-carboxylated osteocalcin) [61].

Although no studies on the effects of vitamin K supplementation and performance exist, supplementation benefits on bone mass have been studied. Vitamin K_1 (10 mg/day) supplementation in younger (20–30 years of age), female endurance athletes showed no effect on the rate of bone loss following 2 years of supplementation [62]. It was determined that females beginning endurance training at younger ages were at risk for higher amounts of bone loss than those that began their training at a later age; however, both groups had a relatively high rate of bone loss when compared to standards for females of the same age. In postmenopausal elite female athletes, 1 month of K_1 supplementation (10 mg/day) resulted in increased bone formation marker and decreased bone resorption marker production [63].

5.2.3 Vitamins and Exercise Summary

Because both fat- and water-soluble vitamins are essential to human physiological function, examining their effect on exercise, both on athletic performance and deficiency avoidance, is popular in sport nutrition research. In summary, the grouping of "B vitamins" has two major functions directly related to exercise. Thiamin, riboflavin, vitamin B_6, niacin, pantothenic acid, and biotin are involved in energy production during exercise, whereas folate and vitamin B_{12} are required for the production of red blood cells, protein synthesis, and tissue repair and maintenance. Vitamin C may play a role in improved immune function and may indirectly benefit athletic performance. Although it is thought that exercise may slightly increase the need for these vitamins, demands can usually be met by the increased energy intakes required for physically active persons to maintain energy balance. The two major functions of the fat-soluble vitamins include the antioxidant activity of vitamins A and E and bone formation of vitamins D and K.

In general, benefits of vitamin supplementation in regard to increased exercise needs or improved athletic performance are assumed inconclusive, unless stated otherwise. More research is needed before micronutrient supplementation above the DRI should be recommended to athletes, either as a requirement for increased needs during exercise or as an ergogenic aid.

Sidebar 5.1 Multivitamin and Mineral Supplementation: To Supplement or Not?

Current recommendations from the Academy of Nutrition and Dietetics suggest consuming a wide variety of foods to avoid chronic disease and micronutrient deficiency. Although it is ideal to consume nutrients through a balanced diet, over-the-counter multivitamin and mineral supplements may contribute to total nutrient intake, especially if dietary intake is inadequate. The percentage of US adults who used at least one multivitamin and mineral supplement increased from 30 % in 1988–1994 to 39 % in 2003–2006, with use more common among women than men [64]. Lun et al. [65] recently reported that multivitamin and mineral use in high-performance athletes is 16 %, with 87 % of taking ≥3 dietary supplements (e.g., com-

(continued)

Sidebar 5.1 (continued)

bination of multivitamin and mineral supplements, sports drinks, sports bars, protein powder, and meal-replacement products). In general, supplementation to an athlete on a well-balanced diet has not been shown to improve performance. Eight weeks of supplementation with a liquid multivitamin and mineral supplement in resistance-trained men did not appear to improve short-duration anaerobic exercise performance compared to a placebo [66]. In addition, no apparent difference in endurance performance was observed in athletes who regularly consume multivitamin and mineral supplements versus those who do not [67]. Research to evaluate whether supplementation with megadoses of multivitamin and mineral improves performance is necessary. However, because supplements are concentrated sources of nutrients and dietary supplements may be marketed without providing evidence of safety or efficacy, it is important for health-care professionals to monitor for excess nutrient intake in those choosing to consume a multivitamin and mineral supplement.

5.3 Mineral Introduction

Dietary minerals are chemical agents required by living organisms to maintain physical health. Like vitamins, minerals also regulate macronutrient use and are classified as either macrominerals or microminerals/trace elements, depending on the daily amount needed. Additionally, minerals play various roles involved in enzyme regulation, maintenance of acid-base balance, nerve and function, and cellular growth. Because many of these processes are heightened during exercise, the field of exercise nutrition has sought to explore the relationship between different mineral needs and physical activity. Such findings, along with the general function, effects of deficiency or over-supplementation, and recommended intake levels, are the focus of this section.

5.3.1 Macrominerals

Macrominerals are required in amounts greater than 100 mg/day and include calcium, phosphorus, magnesium, sulfur, potassium, sodium, and chloride. A comprehensive review of the above listed macrominerals and their role in physical performance can be found in Table 5.5.

5.3.1.1 Calcium

Calcium is the most abundant mineral in the body, totaling approximately 1–2 % of body weight. Ninety-nine percent of calcium in the body is found in the structure of the teeth and bones. The remaining 1 %, found in the blood, muscle, extracellular fluid, and other tissues, functions in different roles throughout the body, such as in vascular and muscle contractions, blood coagulation, and nerve transmission [68]. At low calcium concentration, absorption depends on the activation of vitamin D; however, passive diffusion becomes more common at higher concentrations [68]. In addition to vitamin D, calcitonin and parathyroid hormone (PTH) are two hormones that regulate serum calcium concentrations. Calcitonin and PTH increase when blood calcium concentrations drop, causing calcium to be released from bone, reabsorbed in the kidneys, and absorbed in the intestines. A high-protein diet, as well as foods containing sodium, phytates, fiber, oxalic acid, and caffeine, may decrease the bioavailability and absorption of dietary calcium.

The two main calcium compounds found in supplements are calcium citrate and calcium carbonate. Calcium carbonate supplements typically contain 40 % calcium, while calcium citrate supplements contain 21 % calcium; therefore, more calcium citrate must be taken to equal a similar amount of calcium available in calcium carbonate [69]. Amounts less than 500 mg/day of calcium generally are recommended because absorption decreases as the amount of calcium in the supplement increases. Calcium citrate supplements are typically better absorbed in individuals with decreased stomach acid [69], usually a result of taking the supplement with food. When adolescent females were supplemented with 670 mg/day of a calcium citrate malate

Table 5.5 Summary of minerals

Nutrient	Function	Adult (nonpregnant) recommended intake	Food sources	Comments for the athlete
Calcium	Structure of the teeth and bone, vascular and muscle contractions, blood coagulation, nerve transmission	• UL: 2,500 g/day in adults ≤50 years 2,000 g/day in adults >50 years • Deficiency: improper bone mineralization, tetany, muscle pain and spasms	Dairy products, pinto and black beans, spinach, fortified cereal, orange juice	Possible effects of calcium supplementation on body weight and sweat losses during exercise; however, current recommendation is DRI
Phosphorus	Essential for strong bones and teeth and energy metabolism	• UL: 4 g/day in adults ≤70 years 3 g/day in adults >70 years • Deficiency: anorexia, muscle weakness, bone pain, rickets, confusion	Milk, carbonated cola drinks, eggs, whole wheat bread, almonds, lentils, some fish	Phosphate loading may increase exercise performance; however, supplementation is potentially harmful
Magnesium	Energy metabolism, neuromuscular coordination, bone mineralization	• UL: 350 mg/day • Deficiency: hypocalcemia, tetany, tremors, muscular weakness, confusion	Wheat flour, artichokes, pumpkin seeds, almonds, tuna	Although exercise may increase needs, current recommendation is DRI
Sulfate	Protein synthesis and formation of disulfide bridges	• UL: N/A • Deficiency: stunted growth	Meat, poultry, fish, eggs, dried beans, broccoli, cauliflower	Although exercise may increase needs, current recommendation is DRI
Potassium	Water balance, acid-base balance, electrical potential gradients across membranes	• UL: N/A • Deficiency: muscle weakness, myalgia, increased risk of hyponatremia	Tomatoes, orange juice, beans, raisins, potatoes, grapefruit	Exercise does not appear to increase needs
Sodium	Maintain extracellular volume and plasma osmolality	• UL: 2.3 g/day • Deficiency: hyponatremia, muscle cramps, overhydration, hypotension	Processed and cured meats and cheeses, frozen meals	Ultra-endurance athletes and those with occupational physical activity and heat exposure may benefit from supplementation
Chloride	Same as sodium	• UL: 3.6 g/day • Deficiency: overhydration, hypotension, muscle cramps	Similar to sodium-containing foods	Similar to sodium
Iron	Transportation of oxygen in the body	• UL: 45 mg/day • Deficiency: fatigue, lack of stamina, breathlessness, headaches, insomnia	Lean red meats, seafood, beans, leafy green vegetables, molasses	May have beneficial effects on physical performance in those who are iron deficient
Zinc	Aids in wound healing and is a vital component of many enzymatic reactions	• UL: 40 mg/day • Deficiency: altered taste, hair loss, diarrhea, fatigue, delayed wound healing	Oysters, wheat germ, ground beef, liver, ricotta cheese	Evidence supporting zinc supplementation in athletes has been equivocal

(continued)

Table 5.5 (continued)

Nutrient	Function	Adult (nonpregnant) recommended intake	Food sources	Comments for the athlete
Chromium	Involved in carbohydrate, protein, and lipid metabolism and facilitates the action of insulin	• UL: N/A • Deficiency: weight loss, peripheral neuropathy, impaired glucose utilization, and increased insulin requirements	Eggs, liver, oysters, wheat germ, spinach, broccoli, apples, bananas	Studies suggest that chromium supplementation benefits may only occur in individuals with impaired chromium concentrations
Boron	Function unknown—proposed functions include metabolism of vitamin D, macromineral metabolism, and immune function	• UL: 20 mg/day • Deficiency: proposed effects include decreased bone density, mineral metabolism, and cognitive function	Grapes, leafy vegetables, nuts, grains, apples, raisins	Boron supplementation does not appear to effect physical performance
Copper	Enzyme catalyst, enhances iron absorption, antioxidant	• UL: 10,000 μg/day • Deficiency: leukopenia, fatigue, hair loss, anorexia, diarrhea	Shellfish, finfish, beef, table salt, coffee	No known benefits of supplementation on performance
Fluoride	Mineralized bones and teeth	• UL: 10 mg/day • Deficiency: dental caries weakened bone	Fluorinated water, tea, fish, legumes, potatoes	No known benefits of supplementation on performance; however, suboptimal intake may affect bone mineral density
Iodine	Essential in thyroid hormone function	• UL: 1,100 μg/day • Deficiency: goiter, reduced mental function, hypothyroidism	Iodized table salt, seafood, kelp, dairy	No known benefits of supplementation on performance; however, suboptimal thyroid hormone concentrations may affect performance
Manganese	Antioxidant, bone formation, metabolism of amino acids, lipids, and carbohydrates	• UL: 11 mg/day • Deficiency: decreased growth, impaired glucose tolerance, dermatitis	Nuts, leafy vegetables, whole grains, pineapple, teas	No known benefits of supplementation on performance
Molybdenum	Enzymatic cofactor	• UL: 2,000 μg/day • Deficiency: headache, night blindness, tachycardia, tachypnea	Carrots, cabbage, legumes, nuts	No known benefits of supplementation on performance
Selenium	Defends against oxidative stress	• UL: 400 μg/day • Deficiency: cardiomyopathy muscular weakness, pain	Brazil nuts, seafood, fish and shellfish, meats, garlic, eggs	No known benefits of supplementation on performance; however, may be beneficial due to antioxidant effects. Toxic if consumed in excess
Vanadium	Stimulates cell proliferation and differentiation, regulates phosphate-dependent enzymes, insulin-mimetic activity	• UL: 1.8 mg/day • Deficiency: heart and kidney disease, reproductive disorders	Black pepper, beer, wine, mushrooms, sweeteners, grains	No known benefits of supplementation on performance

supplement (mean daily intake approximately 1,500 mg/day) for 7 years, supplementation positively influenced gain of bone mass throughout the bone-modeling phase of the pubertal growth spurt, which is when requirements of calcium are determined to be the highest [70]. By the beginning of young adulthood, the only significant findings were seen in those of tall subjects, suggesting that calcium requirements vary with skeletal size. Positive effects of calcium supplementation were seen at all skeletal regions examined during the young adulthood assessment period.

In a large placebo-controlled trial of 1,000 mg calcium carbonate plus 400 IU vitamin D_3, examination of physical performance and self-reported exercise measures after 1, 2, and 4 years did not result in improvements in subjective or objective physical function [71]. However, the effects of calcium supplementation on physical performance are lacking. Possible effects of supplementation on body weight and sweat losses warrant review, especially since low calcium intake is well documented in athletes [72–74]. Martin et al. found that 400 mg/day of calcium carbonate supplementation can correct negative calcium balance attributable to low calcium dietary intake and additional dermal losses following a 1-h strenuous exercise session [75]. Elevated urinary calcium losses also are observed following high-impact and resistance training exercise program [76]. Thus, calcium supplementation may benefit those involved in high-intensity sports, as well as those with weight restrictions. Overall, current research does not support the need for calcium supplementation above the DRI; however, more research is required.

5.3.1.2 Phosphorus

Phosphorus is essential for all living cells as a component in phospholipid membranes, as well as in nucleic acids and nucleotides. Eighty-five percent of total body phosphorus is found in the bone, and the remaining 15 % is found in the soft tissues. The form of phosphorus most commonly found in nature is phosphate; however, while stored in the bone, the main form is hydroxyapatite crystals. Although extremely rare, because phosphorus is well dispersed throughout plant and animal foods, deficiency of serum phosphorus may lead to anorexia, muscle weakness, bone pain, rickets, confusion, and death. High intake of phosphorus may reduce serum calcium concentrations and reduce the formation of active vitamin D, leading to an increase of PTH. Elevated PTH is associated with increased bone loss to maintain serum calcium concentrations. Along with its adverse effects on the bone, overconsumption of phosphorus also may cause calcification of soft tissues, especially the kidney.

Athletes often consume excess phosphorus due to "phosphate loading." The aim of the supplementation is to improve tissue oxidation by increasing erythrocyte 2,3-diphosphoglycerate concentrations. Phosphate loading may result in improved athletic performance in endurance athletes by improving oxygen release in tissues. For ergogenic purposes, sodium phosphate typically is supplemented orally in capsule form, at a dose of 3–5 g/day for a period of between 3 and 6 days [77]. Numerous studies have shown positive effects of phosphate loading on peak power output, increased anaerobic threshold, and improved cardiovascular responses in trained athletes [78–80]. Before phosphorus supplementation is recommended among athletes; however, effects on performance and bone mineralization must be evaluated.

5.3.1.3 Magnesium

As a required cofactor for over 300 enzymatic reactions, magnesium plays an important role in aerobic and anaerobic energy generation. Other functions of magnesium include immune function, neuromuscular coordination, and bone mineralization. Magnesium is important in vitamin D absorption and metabolism. It also plays a structural role in the body. Fifty to sixty percent of body magnesium is stored in the bones, and the parathyroid hormone is dependent upon magnesium for regulation of calcium in the bone. Also, magnesium is required for regulating the outward movement of potassium from myocardial cells and the intracellular concentration of calcium during muscle contractions [68]. Serum magnesium depletion may lead to hypocalcemia, tetany, tremors, muscular weakness, and confusion.

Several studies report that athletes may be deficient in magnesium [74, 81, 82], and exercise is believed to increase magnesium requirements by as much has 10–20 % [83]. Because of its role in immune function, low magnesium status could contribute to the depressed immunological changes observed after strenuous exercise, which may be sufficient to lead to an infection, particularly upper respiratory tract infections [84]. Mooren et al. [85] observed that 2 months of magnesium supplementation was unable to prevent exhaustive exercise-induced alterations in immune cell function in athletes with balanced magnesium status. Marginal magnesium deficiency also resulted in increased peak oxygen uptake and peak heart rate following submaximal exercise compared to those with adequate magnesium intake [86]. Recently, Kass et al. found that supplementation with 300 mg of magnesium oxide resulted in reduced resting and recovery of systolic blood pressure following aerobic and resistance exercise, but did not have an effect on athletic performance [87]. Overall, studies do not support the need for supplementation of physically active individuals, with adequate magnesium status, to improve performance.

5.3.1.4 Sulfur

The mineral, sulfur, is a major constituent of three amino acids: cystine, cysteine, and methionine. Additionally, sulfur is involved in protein synthesis, as it is responsible for the formation of disulfide bridges, a necessary component of the tertiary structure of proteins. Dietary sources of sulfur include meat, poultry, fish, eggs, dried beans, broccoli, and cauliflower.

Current research studying the effect of sulfur on athletic performance is limited to amino acids containing the mineral. While a DRI is currently not available for sulfur, at present there is no literature to suggest that athletes need to consume higher amounts than the average person.

5.3.1.5 Potassium

As an electrolyte, potassium plays a major role in electrical and cellular body functions. Along with sodium and chloride, potassium is involved in maintaining water balance and distribution, osmotic equilibrium, acid-base balance, and electrical potential gradients across membranes [88]. Because nerve and muscle cells have the highest gradients of bodily cells, potassium plays a major role in nerve and muscle function.

Due to its role in muscle function, several studies have been conducted looking at the relationship between potassium and exercise performance. Prolonged exhaustive exercise has been shown to impair potassium transport processes in exercising muscle [89]. This impairment can lead to a rise in extracellular potassium concentration in the skeletal muscle, which is thought to play an important role in the development of fatigue during intense exercise [90].

Although few studies have been conducted looking at the effects of potassium supplementation on exercise performance, an interesting study suggests that potassium phosphate supplementation may mediate perceived and physiological exertion [91]. In a double-blind, placebo-controlled study, eight highly trained endurance runners were asked to provide a rating of perceived exertion (RPE) during maximal graded exercise tests. Results showed that overall RPE was lower with supplementation, thus encouraging prolonged activity; however, no group differences were observed in maximal physiological response. Additional studies are warranted before exercise-specific recommendations can be made.

5.3.1.6 Sodium and Chloride

The cation, sodium, and the anion, chloride, are normally found together in most foods as sodium chloride, also known as salt, with the highest concentrations found in prepared, cured, or pickled food products. In the body, sodium and chloride are required to maintain extracellular volume and plasma osmolality. Healthy adults should consume 1.5 g of sodium and 2.3 g of chloride each day, or 3.8 g of salt, to replace the amount lost in sweat [92]. Sweat is produced by our bodies as a by-product of thermoregulation. Should the capacity for sweat production be hindered, a rise in core temperature and resultant heat illness could result. For the athlete, conditions such as extreme heat or exercise intensity can significantly elevate sweat losses above what is

Table 5.6 Hydration guidelines for exercise

Pre-exercise	During exercise	Postexercise
• ~4 h before exercise, consume 5–7 mL/kg of a 20–50 mEq Na^+ solution • If urine is dark, drink another 3–5 mL/kg of a 20–50 mEq Na^+ solution ~2 h before exercise	• Consume 0.4–0.8 L/h • If prolonged, solution should contain: – 5–10 % carbohydrate solution – 20–30 mEq/L Na^+ – 2–5 mEq/L K^+	• If time permits, consumption of normal meals and beverages will restore euhydration • If a more rapid recovery is required, consume ~1.5 L fluid per kg body weight lost

American College of Sports Medicine [93]

considered normal, and resultant dietary adjustments must be made.

Given the critical need to maintain fluid homeostasis, the American College of Sports Medicine has put forth guidelines for proper hydration [93] (see Table 5.6). Inclusion of sodium chloride in rehydration beverages has been shown to reduce urinary water loss, leading to a more rapid recovery of fluid balance, with some experts now recommending sodium concentrations of 20–50 mmol/L and an osmolality between 200 and 330 mOsm/kg water in glucose-electrolyte beverages consumed during physical activity [94, 95]. Fruits, vegetables, and other high-moisture foods also make an important contribution to total fluid intake. Evidence suggests that humans receive 20–25 % of their daily water intake from foods and that recovery from exercise and heat exposure is improved when food is ingested before consuming water after exercise [96].

Recently, there have been reports of hyponatremia among individuals who tend to over-ingest water during exercise lasting more than 4 h in length [97]. Additionally, lower plasma sodium and development of exercise-associated hyponatremia may be attributed to pituitary secretion of vasopressin, an impaired mobilization of osmotically inactive sodium stores, and/or an inappropriate inactivation of osmotically active sodium. For ultra-endurance athletes, inclusion of sodium chloride in the fluid replacement beverage is often suggested as a potential means of reducing risk of hyponatremia. Although hyponatremia is not likely to be a major risk factor for the general population, ultra-endurance athletes and people with occupational physical activity and heat exposure may benefit from these recommendations [98].

5.3.2 Microminerals/Trace Elements

Microminerals, or trace elements, include iron, zinc, copper, selenium, iodine, fluoride, chromium, manganese, molybdenum, boron, and vanadium. In general, these elements are required in amounts less than 100 mg/day. Although 14 trace minerals have been identified as essential for life, there is sufficient information on only four, as related to physical performance. The following section will provide detailed information on four of these trace elements, with Table 5.5 summarizing recommended dietary intake, food sources, and functional role in the body for all other microminerals.

5.3.2.1 Iron

Dietary iron is a constituent of hemoglobin, myoglobin, cytochromes, and iron-containing enzymes. As such, iron plays a fundamental role in the transport of oxygen in the body, and adequate stores are necessary for optimal athletic performance. Dietary iron can be obtained through quality food sources, as well as obtained from foods prepared in cast iron cookware. Furthermore, the bioavailability of iron in certain foods (particularly vegetables) can be increased by the addition of an acid (i.e., vitamin C) during preparation.

Iron deficiency is the most common nutritional disorder disease [99], with iron status negatively altered in many populations of chronically exercising individuals [100]. Despite claims of blood loss as a result of foot striking, gastritis, and menstruation, as well as the pseudo-anemia caused by an increase in plasma volume during exercise, the true cause of anemia in athletes often can be

attributed to a diet inadequate in iron [101]; thus, efforts should be placed on the improvement of dietary quality. If left untreated, an iron deficiency can cause anemia, a condition where hemoglobin cannot be formed. Iron deficiency without anemia is found in 29 % of female and 4 % of male recreationally active subjects [102] and, depending on the sport surveyed, can increase to a prevalence of 80 % in elite athletes [103]. In general, reductions in tissue oxidative capacity hinder endurance and energetic efficiency, which translates into impaired athletic performance. Numerous studies have shown the negative impact of iron deficiency anemia on work output and physical performance [104, 105], with supplementation in deficient individuals shown to improve athletic performance [106, 107].

Because some individuals carry a gene for increased iron absorption, or hemochromatosis, over-supplementation is not advised. Iron is a very powerful oxidant and is toxic at high concentrations; it is for this reason that iron supplementation should only be reserved for those individuals who are deficient. Moreover, even in individuals without hemochromatosis, iron supplementation can cause side effects, usually stomach upset such as nausea, vomiting, diarrhea, dark stools, or constipation. In general, female athletes, vegetarians, and endurance athletes are considered at greater risk for iron deficiency than the typical athlete; however, proper diagnosis of the condition by assessing ferritin levels in the blood by a medical provider is necessary before supplementation should be considered.

Sidebar 5.2 The Vegetarian Athlete

In a recent poll, 4 % of US adults were found to be vegetarian [108]. While this percentage may seem small, in actuality it translates to over nine million people! With the prevalence at only 1 % in 1997 [109], the trend of vegetarianism shows no sign of stopping.

(continued)

Sidebar 5.2 (continued)

According to the Vegetarian Resource Group, vegetarian diets can be classified into four major groups:

Vegans: Do not eat meat, fish, or poultry. Additionally, do not use other animal products and by-products such as eggs, dairy products, honey, leather, fur, silk, wool, cosmetics, and soaps derived from animal products.

Lacto-vegetarians: Do not eat meat, fish, poultry, or eggs; do consume dairy products.

Ovo-vegetarians: Do not eat meat, fish, poultry, or dairy; do consume egg products.

Lacto-ovo vegetarians: Do not eat meat, fish, or poultry; do consume dairy and eggs.

Additionally, some persons may self-describe themselves as vegetarians if they are occasional meat eaters who predominately practice a vegetarian diet.

In addition to the numerous health benefits associated with a vegetarian diet [110], the high-carbohydrate nature of a vegetarian diet can be beneficial for the athlete during heavy training when maximizing body glycogen stores is a must. Although the benefits to following a vegetarian diet are numerous, appropriate nutrition education and planning are necessary to ensure that dietary needs are being met. Certain nutrients are either not present or are not as easily absorbed in plant products as they are in animal products. Specifically, vegetarians need to be mindful of their intake of iron, calcium, vitamin B_{12}, and vitamin D, as good sources of these nutrients are mostly of animal origin. Listed below in Table 5.7 are vegetarian-friendly food sources of the nutrients that are most likely to be lacking in a vegetarian diet.

Table 5.7 Good food sources of specific micronutrients for the vegetarian

Nutrient	Good food choices
Iron	Legumes, leafy green and root vegetables, prune juice, tahini, and dried fruits
Zinc	Grains, legumes, and nuts
Calcium	Calcium-set tofu, fortified beverages (orange juice, soy milk), kale, collard, mustard greens, tahini, and blackstrap molasses
Vitamin D	Fortified foods (soy and rice milk). Sun exposure (~10–15 min 2–3 times per week)
Vitamin B_{12}	Fortified foods (cereal, soy, and dairy products) and meat analogues

Adapted from the Vegetarian Resource Group [111]

5.3.2.2 Zinc

The mineral zinc primarily serves a structural role in thousands of proteins. Additionally, zinc is also involved as a cofactor in many enzyme reactions and plays a vital role in tissue repair. As with many other nutrients, it has been suggested that athletes generally consume less zinc than the RDA [112, 113]. In athletes, zinc deficiency can lead to anorexia, significant loss in body weight, latent fatigue with decreased endurance, and a risk of osteoporosis [114]. Zinc depletion can reduce total work capacity of the skeletal muscle [115]; however, exercise has not been shown to cause significant losses in the athlete when dietary zinc intake is sufficient [116].

To date, evidence supporting zinc supplementation in athletes has been equivocal. Two recent studies showed that zinc supplementation in athletes resulted in higher antioxidant [117] and greater inflammatory responses [118] than in non-supplemented athletes. Kilic et al. reported that 4 weeks of zinc supplementation positively affected hematological parameters in athletes [119]; yet Lukaski et al. found that neither zinc supplementation nor a restricted zinc intake was found to have any effect of maximal oxygen uptake over a 4-month period [120].

Although the ergogenic potential for zinc supplementation is debatable, the effects of oversupplementation are not. In the body, an intake of zinc greater than 50 mg/day has been shown to inhibit copper bioavailability [121]. Additionally, zinc intake ten times greater than the RDA has been shown to decrease immune function, reduce HDL cholesterol, and increase LDL cholesterol [122]. For these reasons, zinc supplements exceeding 15 mg/day are not recommended.

5.3.2.3 Chromium

The two most common forms of chromium are chromium III and chromium VI, with chromium III being the form most often found in foods because of its greater stability. Chromium VI is recognized as carcinogenic if inhaled or ingested, whereas chromium III is important in carbohydrate, lipid, and protein metabolism. Chromium helps facilitate the action of insulin, ultimately increasing insulin sensitivity and decreasing the need for insulin. Chromium is well dispersed throughout many food sources. Side effects associated with chromium deficiency include weight loss, peripheral neuropathy, impaired glucose utilization, and increased insulin requirements. Although nephritis, hepatic dysfunction, carcinogens, and rhabdomyolysis (extreme skeletal muscle damage) are possible effects of high chromium intake, at present, no upper limit for chromium has been set.

Because of chromium's role in energy metabolism, numerous studies examining the effects of chromium supplementation and exercise have been performed. Volek et al. determined that 11 μmol chromium III supplementation had no effects on glycogen synthesis during recovery from high-intensity cycle ergometry in overweight adult males on a high-carbohydrate diet [123]. Likewise, no differences in strength gains in older adults during twice-weekly resistance training for 12 weeks were observed with 924 μg chromium/d as chromium III versus a placebo [124]. Multiple studies have hypothesized that benefits of supplementation may only occur in individuals with impaired chromium concentrations [125, 126]. Further, chromium supplementation has been suggested to dispose an individual to iron deficiency, depending on the dose and duration of chromium supplementation [125].

5.3.2.4 Boron

The physiological role of boron in the body is not clearly understood. Proposed functions include metabolism of vitamin D, macromineral metabolism, and immune function. Due to a lack of evidence surrounding boron, no DRI has been established.

Some data suggest that boron may play an ergogenic role in athletic performance by increasing the concentration of plasma steroid hormones [127]. Additionally, Meacham et al. have conducted two studies to determine if supplementing 3 mg/day of boron versus a placebo in athletic versus sedentary participants has an effect on minerals, namely, phosphorus, magnesium, and calcium, affecting bone mineral density (BMD). The first study found that athletes supplemented with boron had lower serum magnesium concentrations than the sedentary subjects, but no differences were seen among activity groups receiving the placebo [128]. Plasma calcium did not differ between any groups, and serum phosphorus concentrations were significantly lower than baseline values among all groups. The second study not only looked at blood mineral concentrations, but also BMD using a dual-photon absorptiometer [129]. Boron supplementation did not appear to influence BMD; however, serum calcium and magnesium increased and phosphorus decreased over time in all subjects. Serum phosphorus concentrations were significantly lower in boron-supplemented subjects, with sedentary levels lower than active individuals. Athletic subjects supplemented with boron had lower serum magnesium levels than sedentary individuals. Due to varied findings on serum mineral concentrations with boron supplementation, more research should be conducted to determine effects on BMD.

5.3.2.5 Other Minerals

Little research exists on exercise and the following minerals: copper, fluoride, iodine, manganese, molybdenum, selenium, and vanadium. Functions, DRIs, known effects of exercise, and food sources of each nutrient may be found in Table 5.5. Exercise does not appear to increase needs above the DRIs, nor is there conclusive evidence recommending the use of supplementation for increased athletic performance.

5.3.3 Minerals and Exercise Summary

Athletes should consume a balanced diet in an attempt to obtain adequate amounts of minerals necessary for optimal performance. Mineral supplementation may be recommended in those who do not consume a balanced diet. Research has consistently found iron and calcium to be consumed in low amounts by athletes. During strenuous activity or exercise in a hot environment, elevated sweat losses may result in increased dietary requirements of sodium and chloride. Mineral deficiencies, especially iron and chromium, may lead to performance impairment, while deficiencies in calcium, magnesium, and phosphorus may decrease bone health. Overall, when well-nourished athletes are supplemented with minerals, including calcium, magnesium, iron, zinc, copper, and selenium, no improvements in athletic performance have been found. Phosphorus is the lone mineral in which multiple studies have shown that supplementation may improve performance in athletes without deficiency. However, due to adverse effects with over-supplementation and the need for further controlled research, current recommended intake remains the DRI.

5.4 Chapter Summary

In conclusion, the micronutrient needs of the athlete do not appear to differ from that of a healthy individual; that is, the athlete may refer to appropriate DRI tables to gauge nutrient needs. Generally, when dietary intake is adequate, supplementation is unnecessary. If dietary intake is inadequate (such as the case of strict vegans and intake of vitamin B_{12}), or increased losses through sweat occur, supplementation may be warranted; however, care should be taken not to exceed the upper limit of the specific micronutrients in question.

5.5 Practical Application

For the professional working with the athlete, proper assessment should be made of caloric intake and expenditure prior to dietary prescription recommendations. This involves evaluation of current dietary habits (i.e., analysis of a 4-day food record or 24-h dietary recall) and exercise status (i.e., type, frequency, duration, and intensity of exercise). Additionally, age and gender as well as environmental factors (i.e., temperature and terrain) should also be considered when making dietary recommendations. Professionals should emphasize consuming a well-balanced diet before recommending supplementation. Special attention should be given to female and vegetarian athletes who may present with low calcium and iron levels. Tables 5.3 through 5.5 serve as a quick reference for recommended intakes and good dietary sources of specific micronutrients, as well as the role each plays in physical performance.

References

1. American Dietetic Association, Dietitians of Canada, American College of Sports Medicine, Rodriguez NR, Di Marco NM, Langley S. American College of Sports Medicine position stand. Nutrition and athletic performance. Med Sci Sports Exerc. 2009;41(3):709–31.
2. Institute of Medicine's Food and Nutrition Board. Dietary reference intakes: recommended intakes for individuals. Washington, DC: National Academy Press; 2011. Available from http://www.iom.edu/Activities/Nutrition/SummaryDRIs/~/media/Files/Activity%20Files/Nutrition/DRIs/5_Summary%20Table%20Tables%201-4.pdf.
3. Manore MM. Effect of physical activity on thiamine, riboflavin, and vitamin B-6 requirements. Am J Clin Nutr. 2000;72(2 Suppl):598S–606.
4. Suzuki M, Itokawa Y. Effects of thiamine supplementation on exercise-induced fatigue. Metab Brain Dis. 1996;11(1):95–106.
5. Bautista-Hernandez VM, Lopez-Ascencio R, Del Toro-Equihua M, Vasquez C. Effect of thiamine pyrophosphate on levels of serum lactate, maximum oxygen consumption and heart rate in athletes performing aerobic activity. J Int Med Res. 2008;36(6):1220–6.
6. Webster MJ, Scheett TP, Doyle MR, Branz M. The effect of a thiamin derivative on exercise performance. Eur J Appl Physiol Occup Physiol. 1997;75(6):520–4.
7. Doyle MR, Webster MJ, Erdmann LD. Allithiamine ingestion does not enhance isokinetic parameters of muscle performance. Int J Sport Nutr. 1997;7(1):39–47.
8. Institute of Medicine's Food and Nutrition Board. Dietary reference intakes for thiamin, riboflavin, niacin, vitamin B6, folate, vitamin B12, pantothenic acid, biotin, and choline. Washington, DC: National Academy Press; 1998.
9. Marquart LF, Cohen EA, Short SH. Nutrition knowledge of athletes and their coaches and surveys of dietary intake. In: Wolinsky I, editor. Nutrition in exercise and sport. Boca Raton, FL: CRC; 1998.
10. Wierniuk A, Wlodarek D. Estimation of energy and nutritional intake of young men practicing aerobic sports. Roczniki Panstwowego Zakladu Higieny. 2013;64(2):143–8.
11. Sato A, Shimoyama Y, Ishikawa T, Murayama N. Dietary thiamin and riboflavin intake and blood thiamin and riboflavin concentrations in college swimmers undergoing intensive training. Int J Sport Nutr Exerc Metab. 2011;21(3):195–204.
12. Belko AZ. Vitamins and exercise—an update. Med Sci Sports Exerc. 1987;19(5 Suppl):S191–6.
13. Suboticanec K, Stavljenic A, Schalch W, Buzina R. Effects of pyridoxine and riboflavin supplementation on physical fitness in young adolescents. Int J Vitam Nutr Res. 1990;60(1):81–8.
14. Fogelholm M, Ruokonen I, Laakso JT, Vuorimaa T, Himberg JJ. Lack of association between indices of vitamin B1, B2, and B6 status and exercise-induced blood lactate in young adults. Int J Sport Nutr. 1993;3(2):165–76.
15. Ma Y, Chen H, He X, Nie H, Hong Y, Sheng C, et al. NAD+ metabolism and NAD(+)-dependent enzymes: promising therapeutic targets for neurological diseases. Curr Drug Targets. 2012;13(2):222–9.
16. Frankau IM. Acceleration of muscular effort by nicotinamide. Br Med J. 1943;2(4323):601–3.
17. Hilsendager D, Karpovich PV. Ergogenic effect of glycine and niacin separately and in combination. Res Q. 1964;35(Suppl):389–92.
18. Murray R, Bartoli WP, Eddy DE, Horn MK. Physiological and performance responses to nicotinic-acid ingestion during exercise. Med Sci Sports Exerc. 1995;27(7):1057–62.
19. Trost S, Wilcox A, Gillis D. The effect of substrate utilization, manipulated by nicotinic acid, on excess postexercise oxygen consumption. Int J Sports Med. 1997;18(2):83–8.
20. Heath EM, Wilcox AR, Quinn CM. Effects of nicotinic acid on respiratory exchange ratio and substrate levels during exercise. Med Sci Sports Exerc. 1993;25(9):1018–23.
21. Pernow B, Saltin B. Availability of substrates and capacity for prolonged heavy exercise in man. J Appl Physiol. 1971;31(3):416–22.

22. Shils ME, Shike M, Ross AC, Caballeo B, Cousins RJ, editors. Modern nutrition in health and disease. 10th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2006.
23. Webster MJ. Physiological and performance responses to supplementation with thiamin and pantothenic acid derivatives. Eur J Appl Physiol Occup Physiol. 1998;77(6):486–91.
24. Wall BT, Stephens FB, Marimuthu K, Constantin-Teodosiu D, Macdonald IA, Greenhaff PL. Acute pantothenic acid and cysteine supplementation does not affect muscle coenzyme A content, fuel selection, or exercise performance in healthy humans. J Appl Physiol (1985). 2012;112(2):272–8.
25. Manore MM. Vitamin B6 and exercise. Int J Sport Nutr. 1994;4(2):89–103.
26. Woolf K, Manore MM. B-vitamins and exercise: does exercise alter requirements? Int J Sport Nutr Exerc Metab. 2006;16(5):453–84.
27. Virk RS, Dunton NJ, Young JC, Leklem JE. Effect of vitamin B-6 supplementation on fuels, catecholamines, and amino acids during exercise in men. Med Sci Sports Exerc. 1999;31(3):400–8.
28. Linderman J, Kirk L, Musselman J, Dolinar B, Fahey TD. The effects of sodium bicarbonate and pyridoxine-alpha-ketoglutarate on short-term maximal exercise capacity. J Sports Sci. 1992;10(3):243–53.
29. Molina-Lopez J, Molina JM, Chirosa LJ, Florea DI, Saez L, Planells E. Effect of folic acid supplementation on homocysteine concentration and association with training in handball players. J Int Soc Sports Nutr. 2013;10(1):10.
30. Matter M, Stittfall T, Graves J, Myburgh K, Adams B, Jacobs P, et al. The effect of iron and folate therapy on maximal exercise performance in female marathon runners with iron and folate deficiency. Clin Sci. 1987;72(4):415–22.
31. Marti-Carvajal AJ, Sola I, Lathyris D, Karakitsiou DE, Simancas-Racines D. Homocysteine-lowering interventions for preventing cardiovascular events. Cochrane Database Syst Rev. 2013;1, CD006612.
32. Tin May T, Ma Win M, Khin Sann A, Mya-Tu M. The effect of vitamin B12 on physical performance capacity. Br J Nutr. 1978;40(2):269–73.
33. Montoye HJ, Spata PJ, Pinckney V, Barron L. Effects of vitamin B12 supplementation on physical fitness and growth of young boys. J Appl Physiol. 1955;7(6):589–92.
34. Braakhuis AJ. Effect of vitamin C supplements on physical performance. Curr Sports Med Rep. 2012;11(4):180–4.
35. Krinsky NI, Johnson EJ. Carotenoid actions and their relation to health and disease. Mol Aspects Med. 2005;26(6):459–516.
36. McLaren DS, Kraemer K. Retinoids and carotenoids in general medicine. World Rev Nutr Diet. 2012;103:137–47.
37. Lukaski HC. Vitamin and mineral status: effects on physical performance. Nutrition. 2004;20(7–8):632–44.
38. Jones G. Pharmacokinetics of vitamin D toxicity. Am J Clin Nutr. 2008;88(2):582S–6.
39. Close GL, Russell J, Cobley JN, Owens DJ, Wilson G, Gregson W, et al. Assessment of vitamin D concentration in non-supplemented professional athletes and healthy adults during the winter months in the UK: implications for skeletal muscle function. J Sports Sci. 2013;31(4):344–53.
40. Hamilton B, Grantham J, Racinais S, Chalabi H. Vitamin D deficiency is endemic in Middle Eastern sportsmen. Public Health Nutr. 2010;13(10):1528–34.
41. Constantini NW, Arieli R, Chodick G, Dubnov-Raz G. High prevalence of vitamin D insufficiency in athletes and dancers. Clin J Sport Med. 2010;20(5):368–71.
42. Ogan D, Pritchett K. Vitamin D and the athlete: risks, recommendations, and benefits. Nutrients. 2013;5(6):1856–68.
43. Willis KS, Smith DT, Broughton KS, Larson-Meyer DE. Vitamin D status and biomarkers of inflammation in runners. Open Access J Sports Med. 2012;3:35–42.
44. Razavi MZ, Nazarali P, Hanachi P. The effect of an exercise programme and consumption of vitamin D on performance and respiratory indicators in patients with asthma. Sport Sci Health. 2011;6:89–92.
45. Trivedi DP, Doll R, Khaw KT. Effect of four monthly oral vitamin D3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomised double blind controlled trial. BMJ. 2003;326(7387):469.
46. Lappe J, Cullen D, Haynatzki G, Recker R, Ahlf R, Thompson K. Calcium and vitamin d supplementation decreases incidence of stress fractures in female navy recruits. J Bone Miner Res. 2008;23(5):741–9.
47. Moreira-Pfrimer LD, Pedrosa MA, Teixeira L, Lazaretti-Castro M. Treatment of vitamin D deficiency increases lower limb muscle strength in institutionalized older people independently of regular physical activity: a randomized double-blind controlled trial. Ann Nutr Metab. 2009;54(4):291–300.
48. Sato Y, Iwamoto J, Kanoko T, Satoh K. Low-dose vitamin D prevents muscular atrophy and reduces falls and hip fractures in women after stroke: a randomized controlled trial. Cerebrovasc Dis. 2005;20(3):187–92.
49. Pfeifer M, Begerow B, Minne HW, Suppan K, Fahrleitner-Pammer A, Dobnig H. Effects of a long-term vitamin D and calcium supplementation on falls and parameters of muscle function in community-dwelling older individuals. Osteoporos Int. 2009;20(2):315–22.
50. Bunout D, Barrera G, Leiva L, Gattas V, de la Maza MP, Avendano M, et al. Effects of vitamin D supplementation and exercise training on physical performance in Chilean vitamin D deficient elderly subjects. Exp Gerontol. 2006;41(8):746–52.
51. Rejnmark L. Effects of vitamin d on muscle function and performance: a review of evidence from

randomized controlled trials. Ther Adv Chronic Dis. 2011;2(1):25–37.
52. Rigotti A. Absorption, transport, and tissue delivery of vitamin E. Mol Aspects Med. 2007;28(5-6):423–36.
53. Institute of Medicine's Food and Nutrition Board. Dietary reference intakes for vitamin c, vitamin E, selenium, and carotenoids. Washington, DC: National Academy Press; 2000.
54. McAnulty SR, McAnulty LS, Nieman DC, Morrow JD, Shooter LA, Holmes S, et al. Effect of alpha-tocopherol supplementation on plasma homocysteine and oxidative stress in highly trained athletes before and after exhaustive exercise. J Nutr Biochem. 2005;16(9):530–7.
55. Tsakiris S, Karikas GA, Parthimos T, Tsakiris T, Bakogiannis C, Schulpis KH. Alpha-tocopherol supplementation prevents the exercise-induced reduction of serum paraoxonase 1/arylesterase activities in healthy individuals. Eur J Clin Nutr. 2009;63(2):215–21.
56. Cobley JN, Marrin K. Vitamin E supplementation does not alter physiological performance at fixed blood lactate concentrations in trained runners. J Sports Med Phys Fitness. 2012;52(1):63–70.
57. Itoh H, Ohkuwa T, Yamazaki Y, Shimoda T, Wakayama A, Tamura S, et al. Vitamin E supplementation attenuates leakage of enzymes following 6 successive days of running training. Int J Sports Med. 2000;21(5):369–74.
58. Taghiyar M, Ghiasvand R, Askari G, Feizi A, Hariri M, Mashhadi NS, et al. The effect of vitamins C and e supplementation on muscle damage, performance, and body composition in athlete women: a clinical trial. Int J Prev Med. 2013;4 Suppl 1:S24–30.
59. Dawson B, Henry GJ, Goodman C, Gillam I, Beilby JR, Ching S, et al. Effect of vitamin C and E supplementation on biochemical and ultrastructural indices of muscle damage after a 21 km run. Int J Sports Med. 2002;23(1):10–5.
60. Paulsen G, Cumming KT, Holden G, Hallen J, Ronnestad BR, Sveen O, et al. Vitamin C and E supplementation hampers cellular adaptation to endurance training in humans: a double-blind randomized controlled trial. J Physiol. 2014;592(Pt 8):1887–901.
61. Institute of Medicine's Food and Nutrition Board. Dietary reference intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. Washington, DC: National Academy Press; 2001.
62. Braam LA, Knapen MH, Geusens P, Brouns F, Vermeer C. Factors affecting bone loss in female endurance athletes: a two-year follow-up study. Am J Sports Med. 2003;31(6):889–95.
63. Craciun AM, Wolf J, Knapen MH, Brouns F, Vermeer C. Improved bone metabolism in female elite athletes after vitamin K supplementation. Int J Sports Med. 1998;19(7):479–84.
64. Gahche J, Bailey R, Burt V, Hughes J, Yetley E, Dwyer J, et al. Dietary supplement use among U.S. adults has increased since NHANES III (1988–1994). NCHS Data Brief. 2011;61.
65. Lun V, Erdman KA, Fung TS, Reimer RA. Dietary supplementation practices in Canadian high-performance athletes. Int J Sport Nutr Exerc Metab. 2012;22(1):31–7.
66. Fry AC, Bloomer RJ, Falvo MJ, Moore CA, Schilling BK, Weiss LW. Effect of a liquid multivitamin/mineral supplement on anaerobic exercise performance. Res Sports Med. 2006;14(1):53–64.
67. Knechtle B, Knechtle P, Schulze I, Kohler G. Vitamins, minerals and race performance in ultra-endurance runners—Deutschlandlauf 2006. Asia Pac J Clin Nutr. 2008;17(2):194–8.
68. Institute of Medicine's Food and Nutrition Board. Dietary reference intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride. Washington, DC: National Academy Press; 1997.
69. National Institutes of Health's Office of Dietary Supplements. Calcium: Dietary supplement fact sheet 2013 [updated November 21, 2013]. Available from http://ods.od.nih.gov/factsheets/Calcium-HealthProfessional/
70. Matkovic V, Goel PK, Badenhop-Stevens NE, Landoll JD, Li B, Ilich JZ, et al. Calcium supplementation and bone mineral density in females from childhood to young adulthood: a randomized controlled trial. Am J Clin Nutr. 2005;81(1):175–88.
71. Brunner RL, Cochrane B, Jackson RD, Larson J, Lewis C, Limacher M, et al. Calcium, vitamin D supplementation, and physical function in the Women's Health Initiative. J Am Diet Assoc. 2008;108(9):1472–9.
72. Paschoal VC, Amancio OM. Nutritional status of Brazilian elite swimmers. Int J Sport Nutr Exerc Metab. 2004;14(1):81–94.
73. Rico-Sanz J, Frontera WR, Mole PA, Rivera MA, Rivera-Brown A, Meredith CN. Dietary and performance assessment of elite soccer players during a period of intense training. Int J Sport Nutr. 1998;8(3):230–40.
74. Papadopoulou SK, Papadopoulou SD, Gallos GK. Macro- and micro-nutrient intake of adolescent Greek female volleyball players. Int J Sport Nutr Exerc Metab. 2002;12(1):73–80.
75. Martin BR, Davis S, Campbell WW, Weaver CM. Exercise and calcium supplementation: effects on calcium homeostasis in sportswomen. Med Sci Sports Exerc. 2007;39(9):1481–6.
76. Nemoseck T, Kern M. The effects of high-impact and resistance exercise on urinary calcium excretion. Int J Sport Nutr Exerc Metab. 2009;19(2):162–71.
77. Buck CL, Wallman KE, Dawson B, Guelfi KJ. Sodium phosphate as an ergogenic aid. Sports Med. 2013;43(6):425–35.
78. Folland JP, Stern R, Brickley G. Sodium phosphate loading improves laboratory cycling time-trial

performance in trained cyclists. J Sci Med Sport. 2008;11(5):464–8.
79. Brewer CP, Dawson B, Wallman KE, Guelfi KJ. Effect of repeated sodium phosphate loading on cycling time-trial performance and VO2peak. Int J Sport Nutr Exerc Metab. 2013;23(2):187–94.
80. Kreider RB, Miller GW, Schenck D, Cortes CW, Miriel V, Somma CT, et al. Effects of phosphate loading on metabolic and myocardial responses to maximal and endurance exercise. Int J Sport Nutr. 1992;2(1):20–47.
81. Rankinen T, Lyytikainen S, Vanninen E, Penttila I, Rauramaa R, Uusitupa M. Nutritional status of the Finnish elite ski jumpers. Med Sci Sports Exerc. 1998;30(11):1592–7.
82. Beals KA. Eating behaviors, nutritional status, and menstrual function in elite female adolescent volleyball players. J Am Diet Assoc. 2002;102(9):1293–6.
83. Nielsen FH, Lukaski HC. Update on the relationship between magnesium and exercise. Magnes Res. 2006;19(3):180–9.
84. Laires MJ, Monteiro C. Exercise, magnesium and immune function. Magnes Res. 2008;21(2):92–6.
85. Mooren FC, Golf SW, Volker K. Effect of magnesium on granulocyte function and on the exercise induced inflammatory response. Magnes Res. 2003;16(1):49–58.
86. Lukaski HC, Nielsen FH. Dietary magnesium depletion affects metabolic responses during submaximal exercise in postmenopausal women. J Nutr. 2002;132(5):930–5.
87. Kass LS, Skinner P, Poeira F. A pilot study on the effects of magnesium supplementation with high and low habitual dietary magnesium intake on resting and recovery from aerobic and resistance exercise and systolic blood pressure. J Sports Sci Med. 2013;12(1):144–50.
88. Mahan LK, Escott-Stump S, editors. Krause's food and nutrition therapy. Philadelphia, PA: Saunders; 2007.
89. Juel C. Changes in interstitial K+ and pH during exercise: implications for blood flow regulation. Appl Physiol Nutr Metab. 2007;32(5):846–51.
90. Vissing J, Haller RG. Mechanisms of exertional fatigue in muscle glycogenoses. Neuromuscul Disord. 2012;22 Suppl 3:S168–71.
91. Goss F, Robertson R, Riechman S, Zoeller R, Dabayebeh ID, Moyna N, et al. Effect of potassium phosphate supplementation on perceptual and physiological responses to maximal graded exercise. Int J Sport Nutr Exerc Metab. 2001;11(1):53–62.
92. Institute of Medicine's Food and Nutrition Board. Dietary reference intakes: water, potassium, sodium, chloride, and sulfate. Washington, DC: National Academy Press; 2004.
93. Sawka MN, Burke LM, Eichner ER, Maughan RJ, Montain SJ, et al. American College of Sports Medicine position stand. Exercise and fluid replacement. Med Sci Sports Exerc. 2007;39(2):377–90.
94. Sharp RL. Role of sodium in fluid homeostasis with exercise. J Am Coll Nutr. 2006;25(3 Suppl):231S–9.
95. European Food Safety Authority Panel on Dietetic Products Nutrition and Allergies. Scientific Opinion on the substantiation of health claims related to carbohydrate-electrolyte solutions and reduction in rated perceived exertion/effort during exercise, enhancement of water absorption during exercise, and maintenance of endurance performance pursuant to Article 13(1) of Regulation (EC) No 1924/20061. EFSA J. 2011;9(6):29.
96. Sharp RL. Role of whole foods in promoting hydration after exercise in humans. J Am Coll Nutr. 2007;26(5 Suppl):592S–6.
97. Rosner MH. Exercise-associated hyponatremia. Semin Nephrol. 2009;29(3):271–81.
98. Jeukendrup AE. Nutrition for endurance sports: marathon, triathlon, and road cycling. J Sports Sci. 2011;29 Suppl 1:S91–9.
99. Centers for Disease Control and Prevention. Iron deficiency—United States, 1999–2000. Morb Mortal Wkly Rep. 2002;51:897–9.
100. Suedekum NA, Dimeff RJ. Iron and the athlete. Curr Sports Med Rep. 2005;4(4):199–202.
101. Weight LM, Noakes TD, Labadarios D, Graves J, Jacobs P, Berman PA. Vitamin and mineral status of trained athletes including the effects of supplementation. Am J Clin Nutr. 1988;47(2):186–91.
102. Sinclair LM, Hinton PS. Prevalence of iron deficiency with and without anemia in recreationally active men and women. J Am Diet Assoc. 2005;105(6):975–8.
103. Hinton PS, Giordano C, Brownlie T, Haas JD. Iron supplementation improves endurance after training in iron-depleted, nonanemic women. J Appl Physiol (1985). 2000;88(3):1103–11.
104. DellaValle DM, Haas JD. Impact of iron depletion without anemia on performance in trained endurance athletes at the beginning of a training season: a study of female collegiate rowers. Int J Sport Nutr Exerc Metab. 2011;21(6):501–6.
105. Dellavalle DM, Haas JD. Iron status is associated with endurance performance and training in female rowers. Med Sci Sports Exerc. 2012;44(8):1552–9.
106. DellaValle DM. Iron supplementation for female athletes: effects on iron status and performance outcomes. Curr Sports Med Rep. 2013;12(4):234–9.
107. Hinton PS, Sinclair LM. Iron supplementation maintains ventilatory threshold and improves energetic efficiency in iron-deficient nonanemic athletes. Eur J Clin Nutr. 2007;61(1):30–9.
108. Stahler C. How often do Americans Eat vegetarian meals? And how many adults in the U.S. are vegetarian?: The Vegetarian Resource Group; 2012 [cited 2014 March 20, 2014]. Available from Four percent of U.S. adults were found to be vegetarian—see more at http://www.vrg.org/blog/2012/05/18/how-often-do-americans-eat-vegetarian-meals-and-how-many-adults-in-the-u-s-are-vegetarian/#sthash.EeuVDYey.dpuf
109. How many vegetarians are there? Vegetarian J. 1997;XVI(5).

110. McEvoy CT, Temple N, Woodside JV. Vegetarian diets, low-meat diets and health: a review. Public Health Nutr. 2012;15(12):2287–94.
111. Veganism in a Nutshell: The Vegetarian Resource Group; 2014 [cited 2014 March 20, 2014]. Available from http://www.vrg.org/nutshell/vegan.htm
112. Giolo De Carvalho F, Rosa FT, Marques Miguel Suen V, Freitas EC, Padovan GJ, Marchini JS. Evidence of zinc deficiency in competitive swimmers. Nutrition. 2012;28(11-12):1127–31.
113. Daneshvar P, Hariri M, Ghiasvand R, Askari G, Darvishi L, Iraj B, et al. Dietary behaviors and nutritional assessment of young male isfahani wrestlers. Int J Prev Med. 2013;4 Suppl 1:S48–52.
114. Micheletti A, Rossi R, Rufini S. Zinc status in athletes: relation to diet and exercise. Sports Med. 2001;31(8):577–82.
115. Van Loan MD, Sutherland B, Lowe NM, Turnlund JR, King JC. The effects of zinc depletion on peak force and total work of knee and shoulder extensor and flexor muscles. Int J Sport Nutr. 1999;9(2):125–35.
116. Lukaski HC. Effects of exercise training on human copper and zinc nutriture. Adv Exp Med Biol. 1989;258:163–70.
117. Kara E, Gunay M, Cicioglu I, Ozal M, Kilic M, Mogulkoc R, et al. Effect of zinc supplementation on antioxidant activity in young wrestlers. Biol Trace Elem Res. 2010;134(1):55–63.
118. Kara E, Ozal M, Gunay M, Kilic M, Baltaci AK, Mogulkoc R. Effects of exercise and zinc supplementation on cytokine release in young wrestlers. Biol Trace Elem Res. 2011;143(3):1435–40.
119. Kilic M, Baltaci AK, Gunay M. Effect of zinc supplementation on hematological parameters in athletes. Biol Trace Elem Res. 2004;100(1):31–8.
120. Lukaski HC, Bolonchuk WW, Klevay LM, Milne DB, Sandstead HH. Changes in plasma zinc content after exercise in men fed a low-zinc diet. Am J Physiol. 1984;247(1 Pt 1):E88–93.
121. Fischer PW, Giroux A, L'Abbe MR. Effect of zinc supplementation on copper status in adult man. Am J Clin Nutr. 1984;40(4):743–6.
122. Chandra RK. Excessive intake of zinc impairs immune responses. JAMA. 1984;252(11):1443–6.
123. Volek JS, Silvestre R, Kirwan JP, Sharman MJ, Judelson DA, Spiering BA, et al. Effects of chromium supplementation on glycogen synthesis after high-intensity exercise. Med Sci Sports Exerc. 2006;38(12):2102–9.
124. Campbell WW, Joseph LJ, Ostlund Jr RE, Anderson RA, Farrell PA, Evans WJ. Resistive training and chromium picolinate: effects on inositols and liver and kidney functions in older adults. Int J Sport Nutr Exerc Metab. 2004;14(4):430–42.
125. Lukaski HC, Bolonchuk WW, Siders WA, Milne DB. Chromium supplementation and resistance training: effects on body composition, strength, and trace element status of men. Am J Clin Nutr. 1996;63(6):954–65.
126. Volpe SL, Huang HW, Larpadisorn K, Lesser II. Effect of chromium supplementation and exercise on body composition, resting metabolic rate and selected biochemical parameters in moderately obese women following an exercise program. J Am Coll Nutr. 2001;20(4):293–306.
127. Naghii MR. The significance of dietary boron, with particular reference to athletes. Nutr Health. 1999;13(1):31–7.
128. Meacham SL, Taper LJ, Volpe SL. Effect of boron supplementation on blood and urinary calcium, magnesium, and phosphorus, and urinary boron in athletic and sedentary women. Am J Clin Nutr. 1995;61(2):341–5.
129. Meacham SL, Taper LJ, Volpe SL. Effects of boron supplementation on bone mineral density and dietary, blood, and urinary calcium, phosphorus, magnesium, and boron in female athletes. Environ Health Perspect. 1994;102 Suppl 7:79–82.

Fluid Balance and Hydration for Human Performance

6

Neil M. Johannsen and Conrad P. Earnest

Abstract

This chapter examines fluid balance for human performance. Topics reviewed in this chapter include the nature and function of water in human physiology as it pertains to maintaining daily fluid balance; the relationship of fluid balance to human performance when administered before, during, and after exercise; and the efficacy of carbohydrate and specially formulated drinks to promote improved fluid balance. While dehydration is rarely observed during lower-intensity exercise associated with physical activity while indoors and under controlled environmental conditions, increased preventive strategies are required at higher-intensity, longer exercise bouts and under more extreme conditions. The chapter concludes with recommendations to optimize fluid balance in recreational activities and sports.

Keywords

Hydration • Fluid balance • Water • Exercise

6.1 Nature of Water in the Human Body

Water is considered the most essential macronutrient, as death can occur in as few as 3–7 days in the absence of adequate fluid intake. Water accounts for approximately 60 % of total body weight although the actual percentage varies greatly depending on several factors including age, sex, health status, and body composition. Specifically, body water percent is higher in individuals with a greater lean muscle mass (~65–75 %) and, consequently, lower in obese

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individuals (~50 %). Given this relationship between lean mass and body water percent, men and younger individuals tend to have higher body water content.

6.2 Function of Water in the Human Body

Water is the main solvent in the body and, as such, serves many physiological functions. The primary functions of water include transport of gasses and nutrient/waste, lubrication and protection, structure from intercellular and vascular pressures, and body temperature regulation. As to the last function, water helps the body maintain temperature equilibrium by absorbing considerable heat with only small changes in temperature and, combined with its high heat of vaporization (energy required to change 1 g of liquid into the gaseous state at the boiling point), maintains a relatively stable body temperature during environmental heat stress and the increased internal heat load generated by exercise [1].

Water is found in two main compartments inside the body: intracellular fluid (ICF), which represents the fluid inside the cells, and extracellular fluid (ECF), which includes the fluid that flows interstitially (found between cells) and intravascularly (fluid inside the vessels). The ECF accounts for about one-third of the total body water and provides cell structure in the human body. The ECF also acts as a reactive medium between various tissues, including lymph, saliva, the vitreous humor (fluid inside the eyes), fluid secreted by glands and the digestive tract, cerebrospinal fluid (CSF), and sweat and urine. Blood plasma accounts for approximately 20 % of the ECF fluid (3–4 L) and provides a solvent used in the transport of gasses and nutrients/wastes, as well as for sweat and the maintenance of acid/base balance. Of the total body water, it is commonly taught that ~62 % (26 L of the body's 42 L of water for an average 80-kg man) is intracellular, with the other third (~38 %) being ECF [1].

The precise volumes of fluids in the specified compartments represent average volumes because water in the body is in constant exchange between the compartments depending on the hydrostatic (blood pressure) and oncotic (colloid osmotic) pressure differences [2]. Chronic exercise training (in particular resistance training) can increase the amount of water in the ICF components because of associated increases in lean mass. Conversely, chronic aerobic exercise increases intravascular fluid volumes. During an acute bout of exercise, fluid from blood plasma is forced into the interstitial and intracellular spaces because of the increased hydrostatic pressure of fluid in the circulatory system.

6.3 Fluid Balance

Fluid balance is the difference between the amount of fluid entering the body and the amount that leaves the body. Considering the many factors that affect fluid balance, body water levels remain fairly stable over long periods of time. In this section, the fluid intake and losses will be discussed in detail beginning with fluid intake. Fluid intake comes from two sources, foods and liquids. In addition, water is created during the breakdown of fuel, termed metabolic water. Of the fluid ingested in foods and liquids, roughly 60 % comes from liquids ingested into the body (Table 6.1). These liquids not only include water but also juices, milk, sports drinks, and even caffeinated beverages such as sodas and coffee.

Table 6.1 Dietary reference intake values for total water (L/day)

Children		*Females*	
1–3 years	1.3	9–13 years	2.1
4–8 years	1.7	14–18 years	2.3
		19–70+ years	2.7
Males			
9–13 years	2.4	*Pregnancy*	3
14–18 years	3.3	Lactation	3.8
19–70+ years	3.7		

Adapted and modified from: Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids (2002/2005) and Dietary reference intakes for water, potassium, sodium, chloride, and sulfate (2005, www.nap.edu)

On any given day, the average adult consumes around 1,200 mL or 40 oz. of liquids per day [3].

Another 30 % of fluid intake comes from foods (e.g., fruits, vegetables). Fruits and vegetables can contain significant water (~90 %). In contrast, foods such as butter, oil, dried meats, chocolate, cookies, and cakes have comparatively low water content (<20 %). Peanut butter and shelled peanuts contain only traces of water, whereas walnuts contain 4 % water and dried coconuts and pecans around 7 %. This percentage increases for foods such as molasses (25 %), whole wheat bread (35 %), beef hamburger (54 %), and whole milk (87 %). The following foods contain at least 90 % water by weight: lettuce, raw strawberries, cucumbers, watercress, Swiss chard, boiled squash, green peppers, bean sprouts, boiled collards, watermelon, cantaloupe, canned pumpkin, celery, and raw peaches [4].

Metabolic water accounts for the remaining ~10 % of water that adds to fluid balance. In a sedentary person, metabolic water contributes approximately 14 % of the daily water requirement. The breakdown of the major macronutrients (carbohydrates, fats, protein) results in the formation of heat, carbon dioxide, and water. The breakdown of 100 g of carbohydrate releases 55 g of metabolic water, while water occurring from protein (41.3 g water/100 g protein) and fat (110 g water/100 g fat) is roughly equivalent [5]. In addition, each gram of glycogen is associated with ~2.7 g of water in storage which is liberated when glycogen is broken down during its catabolism for energy [6]. It should be noted, however, that metabolic water production alone has minimal affect at maintaining plasma volume levels during exercise [7].

The human body loses water via four mechanisms: through the skin (evaporation), in air leaving the lungs (expired air, water vapor), and in urine and feces. Under resting conditions, water lost in the urine constitutes the main route for water loss. Water loss through seepage from the skin during rest, called insensible perspiration, can account for ~250–350 mL of water per day. Additional water loss from the skin comes in the form of perspiration via sweat glands. Under normal environmental conditions, sweat losses can amount to between 500 and 700 mL/day, depending on body size. However, sweat losses can greatly exceed resting levels during exercise, especially under significant thermal stress (high ambient temperature and humidity). For example, someone exercising in a hot environment can produce up to 12 L of sweat (equivalent of 12 kg) at a rate of 1 L/h during prolonged exercise. These levels of sweat losses can exceed 3 L/h in well-acclimated athletes [2, 8]. Insensible water losses also occur when relatively dry air is brought into the lungs and moistened before reaching the alveoli. Typical water losses in the expired air amount to 250–350 mL daily but can be much higher in physically active individuals [1]. For physically active persons, the respiratory passages release 2–5 mL of water each minute during vigorous exercise, depending on climatic conditions of the environment. Ventilatory water loss is less in hot, humid climates than in cold temperatures (cold air contains little moisture) and at high altitudes. At high altitude, water losses, from insensible sources, are greater because water evaporates more quickly under lower air pressures and ventilation rates are higher resulting in more air requiring humidification as it enters the lungs [9].

The volume of urine excreted daily by the kidneys ranges from 1,000 to 1,500 mL, or about 1.5 quarts. This water loss is termed obligatory water losses because it is necessary to rid the body of metabolic by-products like urea, the end product of protein metabolism. Total daily urine output can be upregulated to match fluid intake in order to prevent excessive water accumulation in the body and the associated electrolyte disturbances. Urine output may also increase depending on the macronutrients (carbohydrate, fats, protein) in the diet. For example, eating large amounts of protein can increase obligatory water losses as each gram of solute excreted by the kidneys requires 15 mL of water [1]. Intestinal water loss in the form of feces amounts to 100–200 mL/day. However, water losses can be much higher (1,500–5,000 mL/day) in cases where individuals have intestinal disturbances and/or vomiting. In addition to losing large quantities of water, electrolytes are lost resulting in fluid and

electrolyte imbalances that can be deadly if not corrected [1].

In healthy individuals, water lost through excessive sweating during exercise can quickly result in significant dehydration (≥2 % body weight loss) [10]. The intensity of the physical activity, environmental temperature, and relative humidity contribute to the amount of water lost through sweating. The mechanisms for sweat loss during exercise are covered in the next section. Overall, the equation to determine daily fluid balance can be found below where fluid balance is in L/day, body weight is in kg weighed approximately 24 h apart after voiding (urination and defecation), and insensible water loss is the sum of evaporative water loss from the lungs and skin:

$$\begin{aligned}\text{Fluid balance} = &\left(\text{food intake} + \text{fluid intake} + \text{metabolic water}\right)\\ &-\left(\text{Insensible water loss} + \text{sweat loss} + \text{urine volume} + \text{fecal loss}\right) \cong \text{BW}_{\text{day2}} - \text{BW}_{\text{dayl}}\end{aligned}$$

6.4 Exercise and Hydration Requirements

In order to discuss hydration requirements with exercise, heat balance must first be outlined. Heat balance or heat storage (HS) is the sum of heat gain and loss (see equation below). Heat balance during exercise occurs through four main processes: evaporation (sweat and respiratory; *E*), conduction (contact with a solid surface; Cd), convection (contact with a fluid; Cv), and radiation (electromagnetic waves; *R*). Exercise increases metabolic heat production (*M*):

$$\text{Heat Storage}\left(\text{HS}\right) = M \pm \text{Cd} \pm \text{Cv} \pm R - E$$

While all four mechanisms are important at rest, evaporation is the primary mechanism for heat loss during exercise. Not accounting for changes in the environment, heat loss through evaporation must make up for the increase in metabolic heat production. This is apparent in the equation below as an increase in metabolic heat production increases heat storage (+) and evaporation reduces heat storage (−). The increase in metabolic heat production during exercise occurs because the body is ~25 % efficient at converting stored fuels (fat and carbohydrates) into usable energy for muscle contraction and movement. The remaining ~75 % of the energy released in metabolism accumulates in the body as heat and raises the body's core temperature. Consequently, higher metabolic demands on the body, or an increase in exercise intensity, will result in greater body heat accumulation and accelerated core temperature. In order to stabilize the rise in body heat, or core temperature, sweat volume increases with an increase in exercise intensity, or metabolic heat production.

Environmental factors affect all the mechanisms responsible for heat storage shown in the above equation. A hot environment can increase the stored body heat by increasing, or reducing the cooling effect of, conduction, convection, and radiation. However, a hot environment can increase the amount of sweat produced and, therefore, the potential for heat loss through evaporation. Relative humidity, or the amount of water in the air relative to the total amount the air can hold, impacts the effectiveness of sweat to maintain core body temperature by directly affecting the rate of evaporation of sweat from the skin. Under extreme environmental conditions, high ambient temperature, and relative humidity, sweat beads on the skin and rolls off before it has the chance to evaporate. In dry or less humid environments, ambient air can hold substantially more moisture, and fluid evaporates from the skin into the surrounding air and, with it, carries substantial heat from the remaining water on the skin. The overall effect is cooler water on the skin and overall heat loss from the body.

Dehydration results from loss of significant amounts of body water during exercise that exceeds 1-h duration depending on the intensity and type of exercise and resultant sweat rate. Larger amounts of water are lost as the result of

exercise at greater intensity especially when coupled with hot and humid environments as shown previously. However, even when exercise is conducted in milder environmental conditions, sweat is still produced. Sweat rate is also influenced by the level of acclimation to a hot/humid environment. Acclimatized individuals can achieve sweat rates of around 3 L/h during a bout of intense exercise and may reach a total volume of 12 L in a single day.

The level of dehydration will determine the level of physiologic and performance changes that occur. Dehydration approaching 2 % negatively affects body temperature regulation and cardiovascular functioning. For example, in one study, body fluid deficits of only 1 % body weight increased the core temperature when compared with that seen during equivalent exercise and a normal hydrated state; and for each liter of fluid lost, the heart rate increased approximately 8 beats per minute and there was a 1.0 L/min decline in cardiac output [11]. As dehydration worsens, the plasma volume and peripheral blood flow decline, and thus, the sweat rate declines in the exercising individual, further complicating the body's ability to maintain a safe core temperature. Specifically, dehydration prior to exercise or competition equal to approximately 5 % of body weight can result in an increase in heart rate and core temperature and a reduction in the sweating rate, VO_2max, and exercise capacity compared to a normal euhydrated state [12]. In a dehydrated state, this is explained by the reduction in blood volume that results in less ventricular filling pressure, which ultimately causes an increased heart rate and an approximately 25–30 % reduction in stroke volume. The consequences are reduced cardiac output and arterial blood pressure, leading to reduced aerobic performance [13]. In one study, physical work capacity and physiological function were shown to decline with fluid loss of around 4–5 % body weight [14]. Dehydration equal to 4.3 % of the body mass reduced walking endurance by 48 % along with a 22 % decrease in VO_2max in this study [14]. The rise in core body temperature is directly related to reduced peripheral blood flow and sweat rate. This becomes most pronounced in hot humid environments in which ambient air is, for the most part, completely saturated.

Many sports and athletic events have the potential to cause large fluid deficits if adequate fluid intake is not encouraged. Triathletes and other elite endurance athletes can lose approximately ≥5 L of fluid (~6–10 % of body mass) during competition. For athletes of lower caliber, fluid loss does not usually exceed 500 mL/h, whereas even in temperate climates of 10 °C (50 °F), soccer players can lose an average of 2 L during a 90-min game [15]. Substantial water loss occurs outside typical exercise-related events too. For example, athletes concerned with "making weight" (e.g., boxers, wrestlers, weightlifters) seek out rapid weight loss methods such as saunas, steam rooms, or severe dietary alterations including restricting fluids, diuretics, and purging. These techniques accelerate weight loss but also increase an athlete's susceptibility to heat-related illness (e.g., muscle cramps, heat exhaustion, heat stroke) [16, 17].

6.5 Fluid Balance and Exercise

As mentioned in Sect. 6.3, fluid balance is the sum of fluid intake and fluid loss. In addition, we discussed the effect of water losses, particularly through evaporation, during exercise and the requirements for fluid intake according to environmental conditions and the types of activities in Sect. 6.4. Much research has been conducted on optimal hydration strategies to improve fluid balance during exercise. While additional research is needed to optimize and individualize these strategies, solid recommendations for the pre-exercise, during exercise, and post-exercise time frames have been made. In each section, the recommendations from the American College of Sports Medicine position stand on fluid replacement will be outlined first, followed by supporting evidence. Note that many of the strategies attempt to optimize not only fluid balance but also sodium balance recognizing that sodium, the primary extracellular and intravascular cation, has important implications in reducing water lost in urine.

6.5.1 Before Exercise

The American College of Sports Medicine recommends that individuals try to achieve at least a euhydrated, adequately hydrated state before starting exercise. Depending on previous exercise, environmental exposure, and age, among other modifying factors, more aggressive approaches than recommended may be necessary to achieve a euhydrated state. Hydration strategies should start at least 4 h before exercise and consist of ingesting 5–7 mL of fluid per kg body weight. Additional fluids should be ingested about 2 h before exercise if the urine color is still dark. In order to reduce the amount of ingested fluids before exercise, foods or snacks containing sodium are recommended. The evidence to support these recommendations is strong, in particular, core temperature and cardiovascular function (heart rate and cardiac output) are better maintained during exercise when the individual is properly hydrated at the onset. At the time the position stand was written, research into sodium-containing beverages before exercise was scarce. However, recent research in which participants ingested 350 mL of chicken noodle soup as a pre-exercise beverage showed an increase in ad libitum water intake during long-duration exercise and a potential alteration in kidney function to reduce urine output during exercise in both temperate and hot/dry environments [18, 19]. Other methods of pre-exercise hyperhydration aimed at expanding intravascular volumes, including glycerol (discussed in Sect. 6.8), have not been very successful.

6.5.2 During Exercise

Prior to exercise, additional fluid intake (hyperhydration) can provide some initial prevention against dehydration and other heat-related problems affecting performance. This is especially true during exercise in which there is no fluid intake. The pre-exercise ritual helps facilitate increases in sweating during exercise with a much less pronounced increase in body temperature. A sensible method for increasing pre-exercise hydration is to ingest around 500 mL of water the night before competition, another 500 mL first thing in the morning, and another 400–600 mL (13–20 oz.) of cool water approximately 20 min before exercise [8, 20]. In a study involving elite soccer players, a regimented intake of fluid of roughly 4.5 L/day a week (even though greater urine output) before competition helped facilitate better temperature regulation during a warm weather competition creating a 1.1 L greater total body fluid volume when compared to the athletes' typical daily intake of fluid [21].

Pre-exercise water/fluid intake benefits:

1. Delays dehydration
2. Increases sweating during exercise
3. Diminishes the rise in core temperature

The goal for fluid intake during exercise is to prevent fluid balance changes greater than 2 % body weight. As mentioned earlier, this level of dehydration is associated with reduced physical and cognitive performance as well as altered cardiovascular function and heat tolerance. Many factors play into the absolute amounts of water lost during exercise including environmental conditions, age, health status, heat acclimatization, and genetics among others. In planning the amounts of fluid replacement required during exercise, typical body weight losses, as determined by the difference between pre- and post-body weight accounting for fluid intake, can be used to estimate sweat rates and, therefore, fluid needs. For example, an 80-kg man who exercises for 1 h and weighs 79.5 kg after exercise and drinks 1 L of fluid has an approximate sweat rate, and fluid requirement, of 1.5 L/h to maintain euhydration assuming 1 L of fluid is equal to 1 kg. Thirst is not a good indicator of fluid losses during exercise, and in the absence of forced fluid intake, individuals will progressively become more dehydrated, termed voluntary dehydration. Ad libitum fluid intake during exercise, however, can be influenced by beverage temperature, flavor, and composition with cool, flavored beverages containing carbohydrates and sodium resulting in greater amounts of fluid ingested. Last, the likelihood of making an error in the

amount of fluid needed to maintain euhydration is greater in events lasting several hours. In longer bouts of exercise, minor miscalculations in sweat rates can lead to significant dehydration or dilutional hyponatremia, a serious condition whereby plasma sodium is diluted by the ingested beverage [22].

6.5.3 After Exercise

As previously noted, pre-exercise fluid ingestion does not negate the responsibility of fluid replacement during the bout of exercise itself. If an athlete does not ingest fluids during an event such as a marathon, the benefits of hyperhydration before competition are soon negated, especially in a hot, humid climate, because it is not possible to match fluid loss (~2,000 mL/h) with fluid intake due to the slower gastric emptying rate (~1,000 mL/h) of the stomach. Thus, pre-exercise hyperhydration becomes imperative prior to competition, especially long-endurance events.

The main goal after exercise is to completely replace fluid and electrolytes lost during exercise. Under normal time constraints to achieve euhydration, normal meals and fluid intake is adequate. However, if a shorter time period exists until the next exercise bout, larger volumes of water and electrolyte (sodium) intakes will be necessary. The additional sodium intakes can be achieved through sports beverages and salty snacks or by adding extra salt to your food. Depending on how short the duration between exercise bouts, individuals will need to ingest more than the level of dehydration at the end of the exercise (i.e., 150 % of the dehydration level) to account for future fluid losses in urine. Less fluid will be needed if greater amounts of sodium in the beverages or foods are ingested. In addition to reducing urinary water losses, the additional sodium intake will encourage fluid intake further improving the likelihood of achieving euhydration before the next exercise bout begins.

Perception of thirst is not a good indicator of overall fluid balance. Additional methods must be used to ensure adequate hydration. As noted earlier, body weight prior to and immediately after exercise can help assess water or fluid loss resulting from physical activity and/or exercise. Monitoring urine output is another method by which the hydration level can be visually monitored, as a dark amber/yellow output with subsequent odor is a sign of dehydration whereas a normal euhydrated individual excretes lighter, clearer urine with little or no odor. Coaches and athletic trainers should encourage periodic water breaks during activity to prevent severe dehydration and subsequent loss of performance.

6.6 Electrolyte Replacement

It is generally accepted that a small increase in the amount of salt added to the food in the diet is adequate to replace any sodium lost through sweat. However, sodium balance can be disturbed by increased loses of large amounts of sweat or urine or ingesting large quantities of plain water in conjunction with a diet low in sodium. However, electrolytes and glucose found in sports drinks may hasten rehydration either through reducing urine losses or increasing fluid intake or both [23, 24]. Restoration of water and sodium balance in recovery occurs more rapidly by adding moderate to high amounts of sodium (20–60 mmol/L) to the rehydration drink or combining solid food with appropriate sodium content. Adding a small amount of potassium (2–5 mmol/L) may enhance water retention in the intracellular space and replace lost potassium during exercise [8, 20]. The American College of Sports Medicine (ACSM) also recommends that sports drinks contain 0.5–0.7 g of sodium per liter of fluid consumed during exercise lasting more than 1 h [20].

Restoring fluid balance in the body requires ingesting a fluid volume that exceeds the volume of fluid or water lost through sweat by approximately 25–50 % [25]. When a fluid is ingested, especially dilute beverages like water, the changes in blood plasma and gut distension cause the body to increase urine production and rapidly decrease the perception of thirst. Therefore, keeping a consistently higher plasma sodium concentration by adding sodium to ingested fluid

may sustain the thirst mechanism and promote retention of ingested fluids. Typical activity including exercise generally results in only minimal loss of potassium (partially due to the potassium-conserving mechanism in the kidneys), and at higher-intensity exercise levels, losses appear to have no consequences [26]. Even under extreme conditions, potassium needs can be met by ingesting foods that contain this mineral (e.g., bananas and potassium-rich citrus fruits).

6.7 Hyponatremia

Though hydration is important to exercise, excessive fluid consumption during longer events (i.e., marathons and longer triathlons) under certain conditions can result in the serious medical illness hyponatremia, sometimes referred to as "water intoxication" [22]. Hyponatremia occurs when low plasma sodium concentrations are created in the blood due to the over-ingestion of water. In essence, the blood becomes "dilute" of sodium, thus creating an imbalance in osmotic pressure across the blood–brain barrier that initiates rapid water influx to the brain resulting in edema of brain tissue. In addition, the following symptoms, from mild to severe, can also be caused by this condition: confusion, headache, malaise, nausea, cramping, seizures, coma, pulmonary edema, cardiac arrest, and death [22, 27, 28].

During exercise in hot, humid weather, the body produces a sweat rate of more than 1 L an hour, with a sweat sodium concentration ranging between 20 and 100 mEq L^{-1} [8]. In addition, repeatedly ingesting large volumes of plain water draws sodium from the extracellular fluid compartment into the unabsorbed intestinal water, further diluting serum sodium concentration [29, 30]. Exercise compounds the problem because urine production decreases during exercise due to a significantly reduced renal blood flow. This reduces the body's ability to excrete excess water [8, 20]. Although hyponatremia is usually associated with competitive athletes, recreational participants and occupational workers should be aware of the dangers of excessive hydration and should ensure that fluid intake does not exceed fluid loss [8, 20]. It has been recommended that the following steps be taken to prevent development of hyponatremia when planning on competing in prolonged endurance activities [8, 20]:

1. Drink 400–600 mL (14–22 oz.) of fluid 2–3 h before exercise.
2. Drink 150–300 mL (5–10 oz.) of fluid about 30 min before exercise.
3. Drink no more than 1,000 mL/h (32 oz.) of plain water spread over 15-min intervals during or after exercise.
4. Add a small amount of sodium (~ ¼–½ tsp. per 32 oz.) to the ingested fluid. Water, carbohydrate fuel, and electrolytes from manufactured sports drinks can also be helpful.
5. Do not restrict salt in the diet.

6.8 Glycerol

Glycerol is also known as glycerin and an alcohol compound that is more commonly found in the diet as a component of fat or triglycerides. It serves as a backbone onto which fatty acid molecules are attached and is marketed as an aid for "hyperhydrating" the body by increasing blood volume and helping delay dehydration. Thus, glycerol may aid endurance athletes training or competing in hot, humid environments by hydrating tissues, increasing blood volume, and ultimately delaying fatigue and exhaustion associated with dehydration. Glycerin dosages used in research are based on body weight or total body water and have been approximated to be 1 g/kg body weight, with each gram diluted in about 20–25 mL of water or similar fluid [31].

Numerous studies support the theory that glycerol added to fluids increase tissue hydration compared with drinking fluid without glycerol added. Following glycerol consumption, the heart rate and body core temperature are lower during exercise in the heat, suggesting an ergogenic effect. In endurance type of activities, a larger supply of stored water may lead to a delay in dehydration and exhaustion [32, 33]. More specifically, one study examined the effect of

glycerol (1 g/kg) supplementation on body temperature while exercising on a treadmill (60 % VO_2max) at 42 °C at 25 % relative humidity for 90 min 2.5 h after ingestion of the glycerol. Results showed that the urine volume decreased before exercise, the sweat rate increased, and the rectal temperature was lower during exercise [34]. These findings imply that glycerol ingestion was helpful in maintaining normal body temperature during exercise in the heat.

Another study reporting positive results gave 11 fit adults glycerol (1.2 g/kg in a 26 mL/kg body weight solution) or a placebo (26 mg/kg body weight aspartame-flavored solution) 1 h prior to cycle exercise to exhaustion at 60 % of maximum workload (temperature 23.5–24.5 °C, humidity 25–27 %). The heart rate for those taking glycerol was 2.8 bpm lower, and endurance time was 21 % longer [35]. In a follow-up study, these same researchers wanted to determine whether the same pre-exercise routine followed by a carbohydrate oral replacement solution during exercise had any further effect. Once again, they found that when glycerol had been taken, the endurance time was 25 % longer [35].

It is important to note that not all studies show an ergogenic effect and that the benefits—although noted for trained endurance athletes exercising in hot, humid environments—are not necessarily observed in athletes who are less well trained or are exercising in more temperate climates [33, 36]. These factors should be taken into account when considering glycerol supplements. Research is still unclear about its usefulness; and although it may have more value during exercise under extreme conditions of heat and humidity, the United States Olympic Committee (USOC) currently lists glycerol as a banned substance. It should also be noted that there are currently no tests for the use of supplemental glycerol.

6.9 Carbohydrate Drinks and Exercise Performance

As previously noted, water by itself may not be enough to replace the deficit created from excessive sweat rates during prolonged exercise. If fluid lost during exercise is to be completely restored, it cannot occur without replacing electrolytes, particularly sodium [37]. In addition to sodium, carbohydrate added to fluid replacement solutions can enhance the intestinal absorption of water. It also helps maintain the blood glucose concentration and so delays dependence on muscle glycogen stores, thereby delaying fatigue during bouts of exercise lasting more than 1 h [38]. Aerobic exercise of high intensity for 1 h or more decreases liver glycogen by about 55 %, and a 2-h strenuous workout almost completely depletes the glycogen content of the liver and active muscle fibers [1]. Activities such as football, soccer, hockey, and other similar sports that have repeated supramaximal exercise with intervals of rest can also result in substantial depletion of glycogen content of the liver and muscle [39]. Therefore, it seems prudent to include carbohydrate in drinks used to rehydrate because it is necessary to maintain blood glucose levels during exercise that lasts more than an hour. Repeated ingestion of water and other fluids containing carbohydrate and electrolytes can be an easy method by which to promote optimal performance in athletes.

A carbohydrate concentration of 4–8 % seems optimal in fluids ingested during exercise. It appears to help replace fluid lost through sweating, maintain blood glucose, and stave off fatigue. This percent solution also contributes to temperature regulation and fluid balance during extreme heat and humidity, as effective as plain water, and includes an extra 5 calories per minute for maintaining glucose and glycogen levels [40, 41]. When it comes to the type of carbohydrate used in the solution, no significant difference exists between glucose, sucrose, and starch. However, the simple sugar fructose or high-fructose corn syrup should not be used because it has the potential to cause gastrointestinal distress. In addition, because of fructose's low glycemic index, absorption by the gut is slower and promotes less fluid uptake than an equivalent amount of glucose [1].

As noted, carbohydrate ingestion during prolonged activity of an hour or more provides a readily available energy nutrient for active muscles during intense exercise. Studies have found

that consuming about 60 g of liquid or solid carbohydrates each hour during exercise benefits high-intensity, long-duration aerobic exercise and repetitive short bouts of near-maximal effort [42–44]. Additionally, supplemental carbohydrate during extended intermittent supramaximal exercise may also provide the same benefits. To improve performance, it has been recommended that athletes should take in 25–30 g of carbohydrate (100–200 kcal) every half hour through either food or fluids. However, it is advised that carbohydrate drinks should be consumed every 15 min due to gastric emptying concerns surrounding hydration and simultaneous carbohydrate ingestion [8].

Additionally, it has been found that flavored beverages with added salt improve voluntary rehydration in children and young and older adults [24]. In a study examining after exercise, dehydration, and heat exposure, boys voluntarily consumed one of three beverages: (1) plain water, (2) grape-flavored water, or (3) grape-flavored water containing 6 % carbohydrate (14 g/8 oz.) and 18 mmol L^{-1} NaCl (110 mg/8 oz.). The flavored carbohydrate–electrolyte drink elicited the largest total voluntary fluid intake (1,157 mL), followed by the flavored drink (1,112 mL), with the smallest volume recorded for plain water (610 mL) [45, 46]. The final result is improved endurance at higher intensities or during intense intermittent exercise as well as increased sprint capacity toward the end of prolonged physical activity such as a marathon in which sustained high energy output and final sprint contribute immensely to the overall and perhaps winning performance.

6.10 Caffeine

It has been a long-held belief that the consumption of caffeinated beverages will increase urine production and increase dehydration. Despite this widely held belief, there is no substantive research to support its recommendation. In 2000, Grandjean et al. examined the effects of caffeinated, non-caffeinated, and noncaloric beverages on hydration in 18 participants receiving four counterbalanced treatments: (1) carbonated cola, (2) caffeinated cola, (3) non-caffeinated cola, and (4) coffee. A small subset ($n = 10$) of participants water and carbonated, non-caffeinated, citrus soft drink during a fifth trial. Collectively, no significant differences in the effect of various combinations of beverages on hydration were noted [47].

Armstrong et al. [48] extended this body of work by examining three levels of controlled caffeine consumption to examine whether caffeine affected fluid–electrolyte balance and renal function differently in 60 men receiving a placebo, 3 mg/kg/day of caffeine, or 6 mg/kg/day of caffeine in capsular form. The results of this study showed no effect on body mass, urine osmolality, urine specific gravity, urine color, 24-h urine volume, 24-h Na+ and K+ excretion, 24-h creatinine, blood urea nitrogen, serum Na+ and K+, serum osmolality, hematocrit, and total plasma protein when measured at days 1, 3, 6, 9, and 11 of treatment [48]. Similar and consistent effects are noted for hydration indices when caffeine is co-ingested with carbohydrates and electrolytes in a warm climate (28.5 °C/83.3 °F) and under more practical conditions such as during a soccer match or when examining a cycling time trial [49–51]. In point of fact, caffeine ingestion not only did not adversely affect hydration status in soccer and cycling but improved performance indices concurrent to each investigation [50, 51].

6.11 Creatine

While it is well established that creatine is a safe and reliable ergogenic aid, anecdotal and opinion-driven descent regarding the use of the supplement still persists. One point of contention is the effects of creatine on hydration and heat tolerance. In the year 2000, the American College of Sports Medicine even issued an advice in a sports medicine roundtable that athletes "…subjected to strenuous exercise and/or hot environments" avoid creatine [8, 20].

In brief, the underlying hypothesis surrounding the hydration/heat tolerance risk was posited as follows. Associated with creatine intake is an increase in skeletal muscle creatine concentration

[52, 53]. In turn, this leads to an increased intracellular water concentration of fluid volume. During dehydration, plasma volume decreases, and if creatine were to hinder hydration, it would be due to creatine's potential to hold fluid within the cell, thus leading to an increased regulatory burden and risk of heat-related illnesses. Research has evolved, however, to show that creatine may indeed decrease thermoregulatory strain, subsequently decreasing the risk of heat illness by releasing intracellular water from inside the cells to maintain hydration status [54–60].

Shortly after the release of the ACSM statement, Volek et al. [57] examined the use of creatine administered at 0.3 g/kg during 35 min of exercise at 60–70 % of VO2max, followed by three 10-s sprints in the heat (37 °C/99 °F, 80 % relative humidity) following 7 days of creatine supplementation. The authors reported no differences in rectal temperature response in either group and no significant changes in sodium, potassium, and creatinine excretion rates obtained from 24-h and exercise urine collections. The creatine group did show a modest increase in aldosterone (263 % vs. 224 %). At the end of the trial, peak power was greater in the creatine group for all three 10-s sprints, and no adverse symptoms, including muscle cramping during supplementation or exercise, were observed. Similar findings using a slightly different protocol have also been reported [60].

Kilduff et al. [54] reported similar findings by examining endurance-trained males who performed cycling tests to exhaustion at ~63 % of VO2max in the heat (~30 °C/86 °F before and after 7 days of creatine administered at 20 g/day in conjunction with 140 g/day of a glucose polymer). The results of their study showed that creatine increased intracellular water yet reduced work-related heart rate, rectal temperature, and sweat rates. While no changes were noted for time to exhaustion for all creatine-supplemented participants, a subset deemed to be "responders" did show a significant (~4 min) improvement [54]. Mendel et al. [55] extended these findings showing a similar overall response to individuals doing a 40-min exercise at 55 % VO2max at 39 °C/102 °F supplementing with and without 20 g/day coupled with the ingestion of a commercial sports drink. Collectively, these effects appear to be due to an undisturbed distribution of total body water without corresponding disturbances between intra- and extracellular water components [56]. In a more intriguing research study, Watson et al. [58] examined the effects of creatine supplementation in dehydrated men [58].

Using a double-blind, randomized, crossover design, Watson and colleagues had 12 men supplemented with ~21 g of creatine for 7 days compared to a placebo treatment. Unique to this study is that the investigators had participants lose 2 % of their body mass by exercising in 33.5 °C/92 °F and then complete an 80-min heat tolerance test by having participants perform four 20-min sequences of 4-min rest followed by 3-min walk and 1-min high-intensity run three times and walking for 4 min. Their results showed no differences between the creatine and placebo conditions for rectal temperature, thermoregulation, heart rate, mean arterial pressure, thirst perception, perceived thermal sensation, perceived exertion, urine osmolality, urine specific gravity, urine gravity, or symptomatology associated with Environmental Symptoms Questionnaire [58]. Collectively, it appears that creatine has no adverse effect on hydration or exercise performance during strenuous exercise conditions at high ambient temperatures.

6.12 Coconut Water

Though little data exists, recent research has sought new ingredients that aid hydration. One such example is coconut water. Early research on coconut water stems from medical reports in remote parts of the world where saline may be a premium and physicians may need alternative means for providing intravenous solutions for hydration needs [61, 62]. However, the current literature related to exercise is sparse. One study by Kalman et al. [63] examined the ingestion of (1) pure coconut water, (2) coconut water from concentrate, (3) a carbohydrate–electrolyte sports drink, or (4) bottled water after 60 min of treadmill exercise. Overall, no differences were

noted between coconut water and a traditional carbohydrate–electrolyte sports drink for body mass loss or time to exhaustion. While participants in both treatment groups reported more bloated and experienced greater stomach upset versus the water group, no differences between treatment groups were otherwise noted [63].

6.13 Practical Applications

Along with the many aforementioned studies investigating fluid regulation and human performance, the ACSM has made the following recommendations concerning fluid intake before, during, and after exercise [20, 64]:

1. It is recommended that individuals consume a nutritionally balanced diet and drink adequate fluids during the 24-h period before an event—especially during the period that includes the meal prior to exercise—to promote proper hydration before exercise or competition.
2. It is recommended that individuals drink about 500 mL (about 17 oz.) of fluid around 2 h before exercise to promote adequate hydration and allow time for excretion of excess ingested water.
3. During exercise, athletes should start drinking early and at regular intervals in an attempt to consume fluids at a rate sufficient to replace all the water lost through sweating (i.e., body weight loss) or consume the maximum amount that can be tolerated.
4. It is recommended that the ingested fluids should be cooler than ambient temperature—15–22 °C (59–72 °F)—and flavored to enhance palatability and promote fluid replacement. Fluids should be readily available and served in containers that allow adequate volumes to be ingested with minimum interruption of exercise.
5. Addition of proper amounts of carbohydrates and/or electrolytes to a fluid replacement solution is recommended for exercise events lasting longer than 1 h because it does not significantly impair water delivery to the body and may enhance performance. During exercise lasting less than 1 h, there is little evidence of physiological or physical performance differences after consuming a carbohydrate–electrolyte drink or plain water.
6. During intense exercise lasting longer than 1 h, it is recommended that carbohydrates be ingested at a rate of 30–60 g/h to maintain oxidation of carbohydrates and delay fatigue. This rate of carbohydrate intake can be achieved without compromising fluid delivery by drinking solutions containing 4–8 % carbohydrate (grams per 100 mL) at a rate of 600–1,200 mL/h. The carbohydrates can be sugars (glucose or sucrose) or starch (e.g., maltodextrin).
7. Including sodium (0.5–0.7 g/L of water) in the rehydration solution ingested during exercise lasting longer than 1 h is recommended because it may enhance palatability, promote fluid retention, and possibly prevent hyponatremia (less than normal concentrations of sodium in the blood) in individuals who drink excessive quantities of fluid [39]. There is little physiological basis for the presence of sodium in an oral rehydration solution for enhancing intestinal water absorption so long as sodium is sufficiently available from the previous meal.

6.14 ACSM Guidelines for Maintaining Fluid Levels During Practice and Competition

1. Weigh in without your clothes before and after exercise, especially during hot weather. For each pound of body weight lost during exercise, drink two cups of fluid.
2. Drink a rehydration beverage containing sodium to replenish lost body fluids quickly. The beverage should also contain 6–8 % glucose or sucrose.
3. Drink 17–20 fluid oz. of water or sports drink 2–3 h before practice or competition.
4. Drink 7–10 fluid oz. of water or sports drink 10–20 min before the event.

5. Drink 7–10 fluid oz. of water or sports drink every 10–20 min during training and competition.
6. Do not restrict fluids before or during the event [8, 65].

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References

1. McArdle WD, Katch FI, Katch VL. Exercise physiology: energy, nutrition, and human performance. 7th ed. Philadelphia: Lippincott Williams & Wilkins; 2007.
2. Sawka MN, Coyle EF. Influence of body water and blood volume on thermoregulation and exercise performance in the heat. Exerc Sport Sci Rev. 1999;27:167–218.
3. Volpe SL. Serving on the Institute of Medicine's Dietary Reference Intake Panel for Electrolytes and Water. J Am Diet Assoc. 2004;104(12):1885–7.
4. Pennington JAT. Bowes & Church's food values of portions commonly used. 19th ed. Philadelphia: Wolters Kluwer/Lippincott, Williams & Wilkins; 2010.
5. Mellanby K. Metabolic water and desiccation. Nature. 1942;150:21.
6. Sherman WM, Plyley MJ, Sharp RL, Van Handel PJ, McAllister RM, Fink WJ, et al. Muscle glycogen storage and its relationship with water. Int J Sports Med. 1982;3(1):22–4.
7. Pivarnik JM, Leeds EM, Wilkerson JE. Effects of endurance exercise on metabolic water production and plasma volume. J Appl Physiol. 1984;56(3):613–8.
8. American College of Sports Medicine, Sawka MN, Burke LM, Eichner ER, Maughan RJ, Montain SJ, et al. American College of Sports Medicine position stand. Exercise and fluid replacement. Med Sci Sports Exerc. 2007;39(2):377–90.
9. Richardson A, Watt P, Maxwell N. Hydration and the physiological responses to acute normobaric hypoxia. Wilderness Environ Med. 2009;20(3):212–20.
10. Cheuvront SN, Carter 3rd R, Sawka MN. Fluid balance and endurance exercise performance. Curr Sports Med Rep. 2003;2(4):202–8.
11. Coyle EF, Montain SJ. Benefits of fluid replacement with carbohydrate during exercise. Med Sci Sports Exerc. 1992;24(9 Suppl):S324–30.
12. Shibasaki M, Kondo N, Crandall CG. Nonthermoregulatory modulation of sweating in humans. Exerc Sport Sci Rev. 2003;31(1):34–9.
13. Gonzalez-Alonso J, Mora-Rodriguez R, Below PR, Coyle EF. Dehydration reduces cardiac output and increases systemic and cutaneous vascular resistance during exercise. J Appl Physiol. 1995;79(5):1487–96.
14. Burge CM, Carey MF, Payne WR. Rowing performance, fluid balance, and metabolic function following dehydration and rehydration. Med Sci Sports Exerc. 1993;25(12):1358–64.
15. Maughan RJ, Leiper JB. Fluid replacement requirements in soccer. J Sports Sci. 1994;12 Spec No:S29–34.
16. Montain SJ, Smith SA, Mattot RP, Zientara GP, Jolesz FA, Sawka MN. Hypohydration effects on skeletal muscle performance and metabolism: a 31P-MRS study. J Appl Physiol. 1998;84(6):1889–94.
17. Sawka MN, Latzka WA, Matott RP, Montain SJ. Hydration effects on temperature regulation. Int J Sports Med. 1998;19 Suppl 2:S108–10.
18. Johannsen NM, Lind E, King DS, Sharp RL. Effect of preexercise electrolyte ingestion on fluid balance in men and women. Med Sci Sports Exerc. 2009;41(11):2017–25.
19. Johannsen NM, Sullivan ZM, Warnke NR, Smiley-Oyen AL, King DS, Sharp RL. Effect of preexercise soup ingestion on water intake and fluid balance during exercise in the heat. Int J Sport Nutr Exerc Metab. 2013;23(3):287–96.
20. Casa DJ, Clarkson PM, Roberts WO. American College of Sports Medicine roundtable on hydration and physical activity: consensus statements. Curr Sports Med Rep. 2005;4(3):115–27.
21. Costill DL, Cote R, Miller E, Miller T, Wynder S. Water and electrolyte replacement during repeated days of work in the heat. Aviat Space Environ Med. 1975;46(6):795–800.
22. Noakes T. Hyponatremia in distance runners: fluid and sodium balance during exercise. Curr Sports Med Rep. 2002;1(4):197–207.
23. Shi X, Summers RW, Schedl HP, Flanagan SW, Chang R, Gisolfi CV. Effects of carbohydrate type and concentration and solution osmolality on water absorption. Med Sci Sports Exerc. 1995;27(12):1607–15.
24. Wilk B, Bar-Or O. Effect of drink flavor and NaCL on voluntary drinking and hydration in boys exercising in the heat. J Appl Physiol. 1996;80(4):1112–7.
25. Sharp RL. Role of sodium in fluid homeostasis with exercise. J Am Coll Nutr. 2006;25(3 Suppl):231S–9.
26. Wapnir RA, Sia MC, Fisher SE. Enhancement of intestinal water absorption and sodium transport by glycerol in rats. J Appl Physiol. 1996;81(6):2523–7.
27. Noakes TD. The hyponatremia of exercise. Int J Sport Nutr. 1992;2(3):205–28.
28. Noakes TD. Hyponatremia during endurance running: a physiological and clinical interpretation. Med Sci Sports Exerc. 1992;24(4):403–5.
29. Speedy DB, Noakes TD, Schneider C. Exercise-associated hyponatremia: a review. Emerg Med. 2001;13(1):17–27.
30. Speedy DB, Rogers IR, Noakes TD, Wright S, Thompson JM, Campbell R, et al. Exercise-induced

hyponatremia in ultradistance triathletes is caused by inappropriate fluid retention. Clin J Sport Med. 2000;10(4):272–8.
31. Williams MH. The ergogenic edge. Champaign, IL: Human Kinetics; 1998.
32. Jimenez C, Melin B, Koulmann N, Allevard AM, Launay JC, Savourey G. Plasma volume changes during and after acute variations of body hydration level in humans. Eur J Appl Physiol Occup Physiol. 1999; 80(1):1–8.
33. Wagner DR. Hyperhydrating with glycerol: implications for athletic performance. J Am Diet Assoc. 1999;99(2):207–12.
34. Lyons TP, Riedesel ML, Meuli LE, Chick TW. Effects of glycerol-induced hyperhydration prior to exercise in the heat on sweating and core temperature. Med Sci Sports Exerc. 1990;22(4):477–83.
35. Montner P, Stark DM, Riedesel ML, Murata G, Robergs R, Timms M, et al. Pre-exercise glycerol hydration improves cycling endurance time. Int J Sports Med. 1996;17(1):27–33.
36. Arnall DA, Goforth Jr HW. Failure to reduce body water loss in cold-water immersion by glycerol ingestion. Undersea Hyperb Med. 1993;20(4):309–20.
37. Coggan AR, Coyle EF. Carbohydrate ingestion during prolonged exercise: effects on metabolism and performance. Exerc Sport Sci Rev. 1991;19:1–40.
38. Duchman SM, Ryan AJ, Schedl HP, Summers RW, Bleiler TL, Gisolfi CV. Upper limit for intestinal absorption of a dilute glucose solution in men at rest. Med Sci Sports Exerc. 1997;29(4):482–8.
39. Brooks GA, Fahey TD, Baldwin KM. Exercise physiology: human bioenergetics and its applications. New York: McGraw Hill; 2005.
40. Coyle EF, Coggan AR, Hemmert MK, Ivy JL. Muscle glycogen utilization during prolonged strenuous exercise when fed carbohydrate. J Appl Physiol. 1986;61(1):165–72.
41. Shi X, Gisolfi CV. Fluid and carbohydrate replacement during intermittent exercise. Sports Med. 1998;25(3):157–72.
42. Jeukendrup A, Brouns F, Wagenmakers AJ, Saris WH. Carbohydrate-electrolyte feedings improve 1 h time trial cycling performance. Int J Sports Med. 1997;18(2):125–9.
43. McConell G, Kloot K, Hargreaves M. Effect of timing of carbohydrate ingestion on endurance exercise performance. Med Sci Sports Exerc. 1996;28(10): 1300–4.
44. Mitchell JB, Costill DL, Houmard JA, Flynn MG, Fink WJ, Beltz JD. Effects of carbohydrate ingestion on gastric emptying and exercise performance. Med Sci Sports Exerc. 1988;20(2):110–5.
45. Wong SH, Sun FH. Effect of beverage flavor on body hydration in Hong Kong Chinese children exercising in a hot environment. Pediatr Exerc Sci. 2014;26(2): 177–86.
46. Johannsen NM, Buyckx M, Cocreham S, Earnest CP, Kramer K, Lupo M, et al. Fluid balance and performance are improved with Ad Libitum carbohydrate-electrolyte beverage intake in the heat. Med Sci Sports. 2014;46(5 Suppl 1):483–4.
47. Grandjean AC, Reimers KJ, Bannick KE, Haven MC. The effect of caffeinated, non-caffeinated, caloric and non-caloric beverages on hydration. J Am Coll Nutr. 2000;19(5):591–600.
48. Armstrong LE, Pumerantz AC, Roti MW, Judelson DA, Watson G, Dias JC, et al. Fluid, electrolyte, and renal indices of hydration during 11 days of controlled caffeine consumption. Int J Sport Nutr Exerc Metab. 2005;15(3):252–65.
49. Millard-Stafford ML, Cureton KJ, Wingo JE, Trilk J, Warren GL, Buyckx M. Hydration during exercise in warm, humid conditions: effect of a caffeinated sports drink. Int J Sport Nutr Exerc Metab. 2007;17(2): 163–77.
50. Kingsley M, Penas-Ruiz C, Terry C, Russell M. Effects of carbohydrate-hydration strategies on glucose metabolism, sprint performance and hydration during a soccer match simulation in recreational players. J Sci Med Sport. 2014;17(2):239–43.
51. Hodgson AB, Randell RK, Jeukendrup AE. The metabolic and performance effects of caffeine compared to coffee during endurance exercise. PLoS One. 2013; 8(4), e59561.
52. Greenhaff PL, Casey A, Short AH, Harris R, Soderlund K, Hultman E. Influence of oral creatine supplementation of muscle torque during repeated bouts of maximal voluntary exercise in man. Clin Sci. 1993;84(5):565–71.
53. Harris RC, Soderlund K, Hultman E. Elevation of creatine in resting and exercised muscle of normal subjects by creatine supplementation. Clin Sci. 1992;83(3):367–74.
54. Kilduff LP, Georgiades E, James N, Minnion RH, Mitchell M, Kingsmore D, et al. The effects of creatine supplementation on cardiovascular, metabolic, and thermoregulatory responses during exercise in the heat in endurance-trained humans. Int J Sport Nutr Exerc Metab. 2004;14(4):443–60.
55. Mendel RW, Blegen M, Cheatham C, Antonio J, Ziegenfuss T. Effects of creatine on thermoregulatory responses while exercising in the heat. Nutrition. 2005;21(3):301–7.
56. Powers ME, Arnold BL, Weltman AL, Perrin DH, Mistry D, Kahler DM, et al. Creatine supplementation increases total body water without altering fluid distribution. J Athl Train. 2003;38(1):44–50.
57. Volek JS, Mazzetti SA, Farquhar WB, Barnes BR, Gomez AL, Kraemer WJ. Physiological responses to short-term exercise in the heat after creatine loading. Med Sci Sports Exerc. 2001;33(7):1101–8.
58. Watson G, Casa DJ, Fiala KA, Hile A, Roti MW, Healey JC, et al. Creatine use and exercise heat tolerance in dehydrated men. J Athl Train. 2006;41(1): 18–29.
59. Weiss BA, Powers ME. Creatine supplementation does not impair the thermoregulatory response during a bout of exercise in the heat. J Sports Med Phys Fitness. 2006;46(4):555–63.

60. Wright GA, Grandjean PW, Pascoe DD. The effects of creatine loading on thermoregulation and intermittent sprint exercise performance in a hot humid environment. J Strength Cond Res. 2007;21(3):655–60.
61. Campbell-Falck D, Thomas T, Falck TM, Tutuo N, Clem K. The intravenous use of coconut water. Am J Emerg Med. 2000;18(1):108–11.
62. Pummer S, Heil P, Maleck W, Petroianu G. Influence of coconut water on hemostasis. Am J Emerg Med. 2001;19(4):287–9.
63. Kalman DS, Feldman S, Krieger DR, Bloomer RJ. Comparison of coconut water and a carbohydrate-electrolyte sport drink on measures of hydration and physical performance in exercise-trained men. J Int Soc Sports Nutr. 2012;9(1):1.
64. Rehrer NJ. The maintenance of fluid balance during exercise. Int J Sports Med. 1994;15(3):122–5.
65. Casa DJ, Armstrong LE, Hillman SK, Montain SJ, Reiff RV, Rich BS, et al. National athletic trainers' association position statement: fluid replacement for athletes. J Athl Train. 2000;35(2):212–24.

Part III

Specialized Nutritional Strategies & Supplements

Building Muscle Mass: Physiology, Nutrition, and Supplementation

7

Kyle Levers and Kelley Vargo

Abstract

One of the most common-sought after goals in athletic performance is attaining and maintaining muscle mass. From protein to creatine, arginine to human growth hormone, how is one to determine what really works, what is legitimate, and what is merely another gimmick in the supplement industry? Coupling the array of supplements with the unique performance needs of an athlete creates an infinite amount of possible combinations. How do you know what is the right combination for successfully building the desired amount of muscle mass, maintaining an "optimal" body composition, and (during periods when additional body mass is desired) ensuring lean mass is gained over fat mass? It is with great time, research, and a foundation laid for us by our predecessors in the field of sports nutrition that we write this chapter on muscle building and optimizing lean body mass. By the end of this chapter you should be able to:

- Describe the muscle building process
- Define and determine net protein balance
- Describe how genetics play a role in muscle growth
- Know the recommended amounts of protein for gaining muscle
- Know the suggested protein: carbohydrate ratio for optimal muscle hypertrophy
- Define nutrient timing and its role in muscle hypertrophy
- Explain the difference between whey, casein, egg, soy, and vegan protein supplements

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- Explain why and when supplementing with BCAAs are important to muscle growth
- Explain the major hormones that play a role in muscle growth
- Explain the potential benefits and drawbacks of anabolic steroids
- Define the role of IGF in muscle growth
- Describe the creatine-phosphate system and why creatine is used for muscle hypertrophy
- Explain why supplements that promote the production of nitric oxide are used by athletes
- Explain how resistance training stimulates muscle hypertrophy

Keywords

Sports nutrition • Lean body mass • Muscle hypertrophy • Creatine • Protein supplements • Net protein balance • Nutrient timing • Anabolic • Anti-catabolic

7.1 Introduction

Before any food, supplement, or substance is ingested for the sake of gaining muscle, a clear understanding of how a particular substance will influence the growth of muscle mass is important. The entire process of breaking down protein, transport of compounds, and utilization of amino acids is important for understanding why certain proteins are better than others at given times, why creatine is beneficial for a speed power or strength athlete, and why nitric oxide doesn't necessarily mean bigger muscles despite the creative marketing campaigns from the supplement industry. This is the basic foundation of how the building blocks of muscle are processed in the body. In conjunction with amino acid utilization, there are internal and external physiological factors, which affect the production of muscle. A few of the most important ones are:

- Net protein balance
- Genetics
- Diet: composition and timing
- Hormones
- Supplements
- Cellular level activity
- Resistance training

This chapter will provide evidence as well as reasoning to if, when, and why a nutritional supplement should be consumed. Specifically, this chapter will focus on the use of nutrition and supplementation for muscle hypertrophy. In other words, although other substances are considered ergogenic aids, the ones discussed in this chapter are those related to muscle growth.

7.2 Importance of Net Protein Balance

An increase in lean mass, more commonly referred to as muscle hypertrophy, is the foundation upon which athletes and bodybuilders train to solidify gains in strength. The importance of gains in or maintenance of lean muscle mass cannot be overstated in the athletic population; therefore, the metabolic basis for fluctuations in muscle mass or *net protein balance* must be considered. Over the course of a 24 h period, all bodily proteins are cycling though periods of synthesis and degradation. Particularly referring to exercise and sports performance, continuous changes in muscle mass are a result of a balance between synthesis and breakdown of muscle myofibrillar proteins [1]. Both actin and myosin serve as the primary myofibrillar proteins and the

main functional components of skeletal muscle contraction. Of the two proteins, myosin typically demonstrates the largest increases in size and therefore attracts the majority of attention when referencing changes in skeletal muscle mass at the cellular level. As a general principle, periods of positive net protein balance are highlighted by accrual of muscle protein, whereas periods of negative net protein balance are defined by muscle protein losses [1]. As a result, the optimal cellular environment for skeletal muscle hypertrophy occurs when an athlete spends more time in positive net protein balance. From an exercise and sports performance perspective, it is important to understand that both nutritional intake and resistance training have a significant influence on shifts in net protein balance. Without proper nutrition and exercise stimulus, net protein balance is negative and thus offsets significant skeletal muscle hypertrophy [2–5].

Nutritionally, daily changes in net protein balance are a result of alternations of fasting and feeding periods throughout the day. Protein balance is negative in the postabsorptive state, but feeding results in a shift to positive net protein balance, hence the importance of meal consumption in athletes. Not only does the magnitude and duration of these positive and negative protein balance periods affect changes in skeletal muscle mass, particular macronutrient composition of these meals can also affect muscle protein synthesis [1]. Greater amino acid availability and specific combinations of amino acids, as addressed later in this chapter, promotes positive protein balance through stimulation of muscle protein synthesis [1, 6]. In the absence of nutrient intake and proper exercise stimulus, net protein balance will continue to remain negative, which adversely affects muscle mass development [2–5].

Resistance training, acting as the most effective exercise stimulus for lean mass accrual, contributes to an increase in skeletal muscle mass growth in combination with proper nutrient intake to reduce instances of negative net protein balance in the basal and postabsorptive states. Resistance training coupled with nutrient intake increases the magnitude and duration of positive net protein balance periods following feeding; however, resistance exercise alone will not promote an anabolic environment [1]. Resistance exercise also acts to reduce losses of amino acids during periods of fasting. Furthermore, when meals contain adequate protein, particularly whey isolates and hydrolysate protein, as sources of essential amino acids (EAAs) to maximally stimulate insulin secretion, muscle protein synthesis is increased with simultaneous decreases in muscle protein breakdown to promote a significant boost in positive protein balance and muscle protein growth [1]. Other specific nutrients and supplements discussed later in this chapter in conjunction with resistance training also contribute to shifting net protein balance in the positive direction.

7.2.1 Application

As an athlete, gaining and maintaining lean muscle mass is important for strength and performance. To achieve an anabolic state, a positive net protein balance must be achieved through a combination of sound nutrition and resistance training. Therefore, the two most important steps an individual can take to elicit muscle gains are engaging in a consistent resistance training program and consuming a diet promoting a positive net energy and protein balance.

7.3 Role of Genes in Skeletal Muscle Hypertrophy

The previous section highlighted the importance of proper nutrition and supplementation in conjunction with resistance exercise and described their effects on the two primary components of net protein balance: synthesis and breakdown. Providing an optimal physiological environment with a positive net protein balance requires an understanding of nutrient and supplement effects on the biochemical processes of muscle hypertrophy.

The functional unit of all bodily processes, including the growth of skeletal muscle, can be found at the level of genes. The expression of skeletal muscle proteins, specifically those of the

contractile unit, actin and myosin, is accomplished through associated genes to initiate muscular growth. The original mechanism of action is the activation of muscle-specific genes that are then incorporated into messenger RNA (mRNA) with specific relation to proteins in muscle cells. The mRNA carrying the gene-specific information about a certain protein is transcribed from the DNA of muscle-related gene and then translated into the formation of actual proteins. As previously stated, myosin is the myofibrillar protein that demonstrates the greatest increase in size during the process of training-induced muscle hypertrophy, but this growth process must be first initiated with the activation of the myosin gene. The activation of the myosin gene initiates the formation and copying of genetic information to myosin mRNA which is responsible for the incorporation of individual amino acids into polypeptides. Upon formation of multiple polypeptides under the direction of the information coded on myosin mRNA, a new functional myosin protein is folded into the existing sarcomere matrix. This functional incorporation of the newly activated myosin protein defines the "expression" of the originally transcribed myosin gene.

A brief review of the biochemical transcription and translation process as it relates to formation of new protein is necessary because any nutritional supplement that claims to help increase muscle mass must influence the aforementioned process in some capacity. For example, many muscle-building supplements claim to increase growth hormone. Increases in growth hormone have been linked to increases in insulin-like growth factor 1 (IGF-1), which influences greater activity of muscle-related cell-signaling pathways and ultimately higher rates of myosin gene transcription and eventual expression. As an example, Hulmi et al. [7] examined the effects of high-quality whey protein intake, a common supplement used by individuals who perform resistance training, before and after resistance training workouts for 21 weeks. The researchers found increased cyclin-dependent kinase 2 (cdk2) gene expression in conjunction with attenuation of the normative exercise-induced decrease in myostatin and myogenin mRNA expression [7]. This lower myostatin signaling in muscle fibers coupled with an increase in cdk2 gene expression demonstrated greater muscle cell activation response with whey protein supplementation, ultimately providing a greater stimulus for muscle hypertrophy [7]. Other sports nutrition supplements affect the aforementioned biochemical process posttranscription as they claim to increase muscle mass by increasing the rate of amino acid incorporation into formal muscle protein under the guidance of mRNA. Still other supplements do not affect the transcription and translation processes at all, but rather claim to expedite nutrient delivery to working skeletal muscle. This expedited delivery of essential muscle fuel theoretically results in a more favorable environment of lean body mass development. The remainder of this chapter discusses the contributions of various sports nutrition supplements to skeletal muscle hypertrophy through the mechanisms described above.

7.3.1 Application

Further understanding the biological mechanism of muscle hypertrophy from a genetic level provides a rationale for sound nutrition and supplementation as it pertains to influencing skeletal muscle DNA. By knowing the mechanism and physiological processes involved in muscle hypertrophy, one can discern the physiology behind supplement and nutrient claims. Couple this understanding with supportive research and much guesswork can be eliminated from the often inflated supplement industry.

7.4 Protein Supplements

Under fasting or limited energy and/or protein ingestion conditions, net protein balance will continue to remain negative. This is due to an increase in muscle protein breakdown as a result of the intense exercise bout despite a simultaneous stimulation of muscle protein synthesis [2, 8–10]. In order to build lean body mass, it is necessary to incorporate high-quality protein as a part of dietary consumption in addition to a

proper resistance training program. A quality protein source is necessary to optimize cellular and tissue repair. Protein is also used as a substrate for numerous hormonal and metabolic activities during the recovery process. To maintain positive nitrogen (or protein) balance and an optimal environment for muscle hypertrophy, protein, as the only macronutrient containing nitrogen, should be ingested at every major meal as a part of a nutritionally sound whole-food diet. When protein is discussed as a supplement in addition to the normative dietary consumption, two primary questions arise: [1] What is the quantity of protein necessary for an individual who regularly resistance trains as part of their exercise program? [2] What are the varieties of protein supplements available and which are the best sources of quality amino acids and proteins?

7.4.1 Protein Requirements

Unlike many nutritional recommendations for the general public, the protein needs of athletes are unique. One of the most debated sports nutrition topics is the protein requirement for athletes. It was initially recommended that athletes need not consume more than the 0.8–1.0 g/kg/day recommended daily allowance (RDA) for children, adolescents, and sedentary to lightly active adults [11, 12]. Countless clinical trials have indicated that individuals who are physically active or exercise regularly require protein intake above the RDA value of 0.8 g/kg/day irrespective of the exercise mode (e.g., interval, resistance, endurance) [13–17] or level of fitness (e.g., recreational, moderately, or well trained) [18–20]. The debate surrounding this recommendation is torn by the safety and efficacy of this quantity as it is based on individual differences in protein metabolic capacity, the biological value of protein as a macronutrient, and nitrogen excretion. A vast amount of relatively recent research has conclusively determined that athletes engaging in intense training regimens must consume approximately double the RDA of protein or approximately 1.2–2.2 g/kg/day to maintain sufficient nitrogen balance [19–24]. More specifically, strength and power athletes working to gain lean muscle mass require high-quality protein intake quantities ranging from 1.5 to 2.0 g/kg/day, with special classes of high-level athletes sometimes benefiting from daily protein intakes slightly exceeding 2.0 g/kg/day. While these daily guidelines are easy to follow for many athletes and have been supported by professionals in the field, there has been a recent trend toward allotting protein intake on a meal-based system to ensure a more balanced approach throughout the day. This balanced meal-based approach may be advantageous for athletes who have a variable practice and competition schedule as, theoretically, it provides better nitrogen/protein balance throughout the day. As previously discussed, if an athlete does not obtain enough dietary protein as part of their daily caloric intake, they will remain in a state of negative energy and protein balance which will increase protein catabolism, hinder recovery, and negatively affect performance [12, 24, 25].

A meal-based recommendation of approximately 20–25 g of high-quality protein per meal is a good starting point for most athletes to maximize skeletal muscle recovery and growth following a resistance exercise session [26]. Recent research analyzing postexercise muscle and albumin protein synthesis more specifically suggests that this type of protein synthesis is maximized after ingestion of 20 g high-quality protein. Further ingestion beyond 20 g of protein, significantly increases the stimulation of whole-body leucine oxidation, thus defining an upper limit of amino acid incorporation into muscle and albumin protein [27]. While the 20–25 g of protein per meal is a good starting point, athletes and others desiring to stimulate muscle growth would not benefit beyond consumption of approximately 20 g of high-quality protein 5–6 times per day. Exceeding this maximal stimulus of muscle protein synthesis with excessive protein intake will lead to amino acid loss via oxidation and potentially risk dampening the synthesis stimulus toward lower levels of protein intake [27]. An individual needs analysis and assessment of performance goals for each athlete is vital when determining the quantity and frequency of protein

ingestion in order to facilitate an increase in lean body mass.

Other factors regarding protein supplementation must be considered as not all proteins are the same. The needs and goals of the athlete with respect to the accretion of lean mass are important when determining protein needs as they differ according to source, quality, amino acid profile, methods employed to process or isolate the protein, rate of digestion and/or absorption, and metabolic activity [12]. Additional considerations that are indirectly linked to athlete protein intake, performance, and lean mass gains are the total energy intake, carbohydrate intake, hydration status, phase of training program periodization associated with the volume and intensity of resistance training, and timing of the protein source. A final consideration is the use of other "ergogenic" substances that may affect overall energy efficiency, such as anabolic steroids, thermogenic agents, beta agonists, etc., to increase lean mass and performance. In conjunction with proper muscular facilitation during a resistance training program, high-quality protein intakes matching the recommended ranges will aid in the maintenance of a positive nitrogen balance environment, optimizing muscle hypertrophy.

7.4.2 Types of Protein Supplements

Power and resistance-trained athletes should plan to acquire the majority of daily protein requirements from high-quality whole-food sources; however, supplementation with protein products (e.g., protein powders, post-workout supplements, protein/energy bars, and meal replacement drinks) can be a safe and effective addition to attain daily protein intakes [12]. Food processing techniques and technology have allowed the industry to grow significantly with more refined high-quality amino acid and protein isolation from plant and animal sources. Protein supplementation in the diet for resistance-trained individuals provides other benefits such as simplicity, convenience, longer shelf life, and more economical option compared to whole-food sources of high-quality protein.

Table 7.1 Classification of amino acids

Essential amino acids	Conditionally essential amino acids	Nonessential amino acids
Isoleucine	Arginine	Alanine
Leucine[a]	Cysteine (cystine)	Asparagine
Lysine	Glutamine	Aspartic acid
Methionine	Histidine	Citrulline
Phenylalanine	Proline	Glutamic acid
Threonine	Taurine	Glycine
Tryptophan	Tyrosine	Serine
Valine[a]		

[a]Branched-chain amino acids

The emphasis thus far has been on the quantity of daily protein intake (1.2–2.2 g/kg/day), but not all proteins are created equal as many differ in quality, source, composition (i.e., amino acid profile), and method of isolation or processing. The differences exhibited between various protein supplements influence the pharmacokinetics, pharmacodynamics, and metabolic activity of the protein in addition to the bioavailability of peptides and amino acids [12, 28]. There are 22 amino acids that can be used as building blocks in the body to fuel or drive protein synthesis (see Table 7.1). Eight of these twenty-two amino acids are classified as "essential" (or indispensable) because they must be obtained from food, as the body cannot synthesize them. An additional seven of these amino acids are considered "conditionally essential" as the body has difficulty synthesizing, which creates a dietary dependence for these amino acids as well. The remaining seven amino acids can be readily synthesized by the body, thus are classified as "nonessential."

As previously mentioned, many protein supplements differ in amino acid quantity and composition. Sources of protein are classified based on the adequacy of their essential amino acid profile as *complete* or *incomplete* proteins. The source of the protein is also critical as differences exist between animal and plant sources. Animal protein sources contain all essential amino acids and are considered complete, whereas plant proteins fail to contain all eight of the essential amino acids, leaving them as an incomplete protein resource. Evaluating the quality of the pro-

tein, or the quantity of essential amino acids present, is a vital criterion when selecting the proper protein supplement. The most common high-quality and complete proteins found in many protein supplements are whey, casein, soy, and egg (ovalbumin). Recently, vegetarian and vegan protein supplements have been introduced to the supplement market. Details concerning each protein type will be discussed in the following sections.

7.4.2.1 Whey Protein

Out of the four most well-known high-quality and complete proteins in the sports nutrition market, whey protein has become the industry and athlete favorite as it can be found in most muscle mass gainer and post-workout supplements. Derived from milk protein, whey protein comprises approximately 20 % of the total protein content in commercial bovine milk, which is significantly less than the 50–90 % (depending on stage of lactation) whey fraction of total protein found in human milk [8, 29–31]. The high fraction of whey protein in human milk is a key nutritional component to child growth and development. Whey protein is commercially categorized and available as whey protein concentrate (70–80 % PRO), whey protein isolate (90 % PRO), or whey protein hydrolysate (90 % PRO). Differences between these three forms of whey protein are exhibited by the processing technique. The various methods of processing affect the concentration of whey protein subtypes and peptides, which have been determined to help counteract various health-related issues beyond enhancement of muscle hypertrophy. Other differences among the forms of whey exist between fat and lactose content (remaining protein nutrient composition), their ability to preserve glutamine residues, and their amino acid profiles [8, 24]. Elliot et al. demonstrated that the greater fat composition within the protein profile may slightly facilitate a postexercise positive net protein balance and amino acid utilization [8, 32]. The most common form of whey protein used in sports nutrition supplements is whey protein concentrate (70 % and 80 % composition) due to its lower raw material pricing and postulated better flavor profile characteristics compared to the other whey forms [8, 33].

Whey tends to be digested quicker due to its sustained solubility and rapid emptying in the stomach, has better mixing characteristics, and is commonly considered a higher-quality protein compared other complete proteins [24, 34, 35]. The digestibility of whey contributes to its more rapid onset of amino acid appearance in the blood compared to casein, resulting in a greater stimulation of muscle protein synthesis [24, 36, 37]. The higher quality of whey protein can be partly attributed to its dominance in branched-chain amino acid composition, particularly leucine [38]. A study conducted by Tipton and colleagues demonstrated peaks in arterial leucine concentration occurred sooner and with greater magnitude following postexercise whey supplementation compared to casein [34]. Additional research has demonstrated that the essential amino acid composition of whey alone, compared to whey protein as a whole, resulted in greater muscle protein balance among the latter at rest [8, 39]. This finding suggests a possible synergistic effect within the protein composition that feeds muscular hypertrophy. Despite research finding that a higher leucine content is essential to muscle protein synthesis stimulation with resistance training in older adults [40], the addition of leucine to whole proteins, such as whey, after bouts of resistance exercise had little to no effect on protein synthesis and net nitrogen balance [8, 41, 42]. Similar to the frequent meal-based protein ingestion concept, consuming whey protein throughout the day is effective for increasing protein synthesis compared to less frequent or erratic intakes of other protein types [43]. In conjunction with resistance training, supplementation with whey protein is beneficial due to its rapid absorption, high branched-chain amino acid content, and health benefits when attempting lean muscle mass accretion.

7.4.2.2 Casein Protein

Casein, a second type of milk protein, is separated from whey protein within skim milk through resolubilizing and drying. Like whey, casein protein is found in commercial sports

nutrition supplements in several variations, such as potassium caseinate, sodium caseinate, calcium caseinate, and casein hydrolysate [24]. Compared to whey, casein is a slower digesting protein. This fact is attributed to its coagulation within the stomach, which significantly reduces rate of elimination and increases transit time through the stomach [34, 44]. Tipton et al. compared the acute rate of arterial leucine appearance after post-resistance exercise protein ingestion of whey or casein [24, 34]. The results indicated that casein protein peaked later and to a lesser extent than whey protein, but the release of amino acids into the blood was sustained over a longer period of time with casein intake. A recent 8-week training study conducted by Wilborn and colleagues also assessed post-resistance exercise consumption of either whey or casein protein and demonstrated an increase in total protein synthesis, but no significant difference was exhibited between the two groups [34, 45]. Not all studies have found this response. A post-resistance training study conducted by Cribb et al. found the whey supplementation group had significantly greater gains in strength and lean body mass compared to the casein supplementation group after a 10-week training period [46]. Despite the inconclusive findings in the literature, casein has been shown to improve protein synthesis when combined with resistance training, but unlike whey, casein also has been found to have anti-catabolic properties [47]. Casein is also a moderately inexpensive form of protein, thus the reason why it is commonly found in many protein-based nutritional supplements. Due to the variation in casein formulation, a result of the specific resolubilizing processing technique affecting the amino acid profile, casein proteins are available in different grades based on protein quality (amino acid content), taste, and mixing characteristics [24, 28]. Perhaps the primary disadvantage to casein protein incorporation into a particular nutritional supplement is that it typically does not mix well in liquid, leaving clumps in suspension.

In summarizing the aforementioned protein research findings, whey was found to maximally stimulate protein synthesis, while casein was discovered to have anti-catabolic properties. Currently, most post-workout and lean mass gain supplements contain both proteins as part of their formulation. The rationale for this protein combination was confirmed by a 10-week resistance training study performed by Kerksick et al. in which three different supplement formulations were compared. The combination of both whey and casein protein supplementation groups proved to be the most effective as they demonstrated the most significant gains in lean muscle mass [48]. An interesting practical application of this study is to simply mix whey protein in bovine milk (which is ~80 % casein).

7.4.2.3 Soy Protein

Soy protein is the only plant-based protein source that is considered high quality due to its high concentration of all essential amino acids except methionine. Soy protein is made from legume and soybeans through a water- or water-ethanol-based extraction method [49]. Variations in this extraction method produce a soy protein concentrate or isolate. When compared to the consumption of milk proteins, soy protein was able to induce significant changes in muscle protein synthesis; however, greater net protein balance, fractional synthesis rate (of mixed muscle proteins), and protein synthesis in skeletal muscle were found with milk protein ingestion postexercise [38, 50, 51]. There are currently several studies that have attempted to explain the difference in muscle protein synthesis response between milk and soy proteins. In general, they have concluded that milk protein tends to support peripheral (e.g., skeletal muscle) protein synthesis, while soy protein tends to support greater splanchnic protein synthesis [38, 52, 53].

In addition to promoting muscle protein synthesis, soy protein sources, such as soy milk, contain the omega-3 fat alpha linolenic acid (ALA) and isoflavone phytoestrogens. Soy milk also has less saturated fat and cholesterol and tends to have a lower glycemic index than most bovine milk products [24]. Isoflavone phytoestrogens have been reported to stimulate estrogen receptors and promote nonhormonal estrogen-like properties that could benefit (pre- and post-) menopausal women [24, 54, 55]. More specifically, soy

protein isolate contains a myriad of antioxidant compounds such as isoflavones, saponins, and copper, a primary component of many antioxidant enzymes [51]. Recent research has attributed soy isoflavones to improving markers of bone (i.e., protection against osteoporosis), lipid, and thyroid function while decreasing the risk of heart disease and promoting a chemo-protective effect against breast and prostate cancer [24, 56]. Despite the purported beneficial health effects of soy protein with no long-term side effects, there are several studies that question the long-term impact of diets containing high levels of phytoestrogens. Additional research needs to be conducted on several soy-related questions, such as whether soy protein ingestion effects hormone levels or semen quality in men, as it could potentially have a large impact on athletic performance [24].

The variable effects that soy protein supplementation can have on different genders leads to a difference in supplementation recommendation values. With the nonhormonal estrogen-like properties, soy protein can be an excellent source of high-quality protein for both pre- and postmenopausal female athletes. For male athletes, the lower muscle protein fractional synthesis rate of soy protein compared to whey may be less advantageous, but for female athletes, the lower saturated fat and cholesterol content may help to promote more nutrient-dense caloric intake when used as a supplement. Finally, due to the lower glycemic index of soy protein and its moderate rate of digestion between casein and whey, supplementation may be beneficial in isolated situations or in conjunction with the primary milk proteins.

7.4.2.4 Egg Protein

Egg protein has been a staple protein source in many nutritional supplements as it historically was considered the best source of protein due to its wide consumer acceptance as a high-quality protein. When processed for incorporation into a nutritional supplement, egg protein is extracted from chicken egg whites (ovalbumin) or whole eggs using a range of different techniques [24, 49]. Unlike casein protein, egg protein is highly miscible and able to form a homogeneous mixture when incorporated in liquids. Despite their decrease in popularity and regular incorporation into newer nutritional supplements due to its higher cost compared to other protein forms, egg white protein is labeled as the reference standard for comparing protein quality [24, 57]. Due to higher cost and poor taste of egg protein supplements, most athletes choose other sources of complete protein. Several studies compared post-resistance training effects of egg protein supplementation to casein and whey sources and concluded that there is no difference between the three forms of complete protein when assessing promotion of nitrogen retention. Due to its effectiveness and place as a reference standard, egg protein or ovalbumin is still incorporated in some meal replacement and protein power supplements on a minor scale [49].

7.4.2.5 Vegetarian and Vegan Protein Sources

Evidence from the Academy of Nutrition and Dietetics (AND) and other associated research confirms the nutritional needs of athletes can be met through consumption of a vegetarian or vegan diet. Despite this, doubt continues to linger among many nutrition professionals who counsel athletes. There are a growing number of athletes, especially endurance athletes, who have adopted a vegetarian- or vegan-based diet to help control body weight and meet increased carbohydrate needs [58, 59]. In comparison to omnivorous diets, vegetarian and vegan diets contain significantly higher quantities of complex carbohydrates, fiber, antioxidants, and phytochemicals. The high ratio of carbohydrates can help many athletes, particularly endurance or strength-endurance athletes, maintain adequate levels of glycogen storage in the muscle and liver as required fuel for muscular contraction [60]. Maintenance of adequate glycogen stores sustains a physiological state of higher energy availability, directly correlated to an environment primed for muscle mass development. Secondly, the inclusion of various antioxidants (e.g., vitamin C/ascorbic acid, vitamin E/tocopherol, and β-carotene) and phytochemicals from plant sources may positively affect athletic perfor-

mance, recovery, and lean mass accretion by mitigating exercise-induced oxidative stress [59]. The potential to optimize glycogen stores from increased carbohydrate intake has been shown to have negative effects on the bioavailability of key nutrients such as iron, zinc, and other trace minerals among the general active population. The impaired nutrient bioavailability, particularly suboptimal iron levels, has been speculated in the vegetarian/vegan athletic population, but no connection to impaired muscle mass growth has been demonstrated [60, 61].

All essential and nonessential amino acids can be obtained from a diet strictly fueled from plant sources if enough calories are consumed to match the activity level of the individual and if a variety of sources are used to obtain those calories [59, 60, 62, 63]. Vegetarians (lacto-ovo-vegetarians) are more likely to meet the necessary protein macronutrient requirements due to their consumption of dairy products, eggs, and complementary mixtures of high-quality plant proteins (e.g., soy protein) resulting in approximately 12–14 % of their calories coming from protein [59]. Quality protein consumption can be a large concern for vegans (those who avoid consumption of all animal proteins) because plant-based proteins, making up only 10–12 % of caloric consumption, can be limiting in quantity of lysine, threonine, tryptophan, and/or sulfur-containing amino acids (methionine, cysteine, homocysteine, and taurine) as seen in Table 7.2 [59, 61]. Vegetarian athletes now have a wide variety of high-quality protein food and beverage sources (egg, dairy, and soy) containing all of the essential amino acids necessary to drive protein synthesis. However, vegan athletes may need to consider specific meal planning strategies that focus on plant sources rich in protein such as legumes, nuts and seeds, rice, and other whole-grain products in order to achieve proper nitrogen balance during periods of muscular growth [59, 62]. Additionally, well-planned vegan diets for competitive athletes may meet or exceed the RDA for protein in general, but may be deficient in lysine as most plant protein sources do not provide sufficient quantities [61]. As previously mentioned, recent protein and amino acid research demonstrates that leucine is the primary driving force behind the positive effects of branched-chain amino acids in the development of new muscle. In order to provide sufficient quantities of leucine in the diet of vegan athletes, a focus must be directed toward overall higher protein quantity of which a greater percentage should be provided by beans and legumes [61].

Compared to omnivores, vegetarians and vegans typically have a lower creatine pool, measured by significant decreases in total and free creatine concentration in addition to muscle creatine content [60, 61]. This decreased creatine pool demonstrates that the diminished dietary creatine intake from meat sources is not completely offset by increases in endogenous creatine production within vegetarian and vegan athletes [60, 64]. Creatine supplementation has been shown to have large ergogenic effects in active and athletic populations, but with diminished endogenous creatine

Table 7.2 Essential amino acid content comparison of dietary protein sources

	Lysine	Threonine	Tryptophan	Methionine/cysteine[a]
Protein source	EAA (mg/g protein)			
Beef	83	44	11	37
Egg	70	49	16	56
Wheat	28	30	13	39
Brown rice	38	37	13	35
Almonds	29	32	15	25
Chickpeas	67	37	10	28
Soybeans	63	41	14	28

Table adapted from Barr et al. [61]
EAA essential amino acid
[a]Sulfur-containing amino acids incorporated into proteins (excludes homocysteine and taurine)

stores, vegetarian and vegan athletes experience greater metabolic, performance, and body composition changes through increases in lean mass when supplementing with creatine [59]. Refer to Sect. 6 of this chapter for additional information concerning creatine supplementation.

7.4.3 Application

High-quality protein through whole foods and supplements, in adequate quantities addressing the intensity, volume, and duration of exercise, is the foundation for muscle hypertrophy. All four sources of high-quality protein, whey, casein, soy, and egg, are viable options for inducing lean muscle mass gains in strength-power athletes. While soy and egg proteins are less common protein sources found in today's muscle-building supplements, they are great options for lactose-intolerant athletes. In order to maximize the benefits of protein ingestion on lean muscle gains, both quantity and quality have to be considered in addition to proper protein nutrient timing.

7.5 Dietary Considerations and Nutrient Timing

It has been well established that protein ingestion is necessary for muscle hypertrophy. To optimize muscle hypertrophy, carbohydrate-protein combinations and nutrient timing strategies can be used. In the absence of nutrient intake pre- and postexercise, the body will remain in a negative net protein balance state, therefore stimulating muscle catabolism [2, 4, 65]. This section will explain the importance of the carbohydrate-protein combination for muscle hypertrophy, nutrient timing optimization, as well as what happens when nutrition is neglected.

7.5.1 The Absence of Nutrition

As stated previously, the net protein balance determines whether muscle protein synthesis or muscle protein breakdown will occur. To achieve (net) muscle protein synthesis, a positive protein balance must occur in conjunction with a stimulus for muscle growth. Although resistance training stimulates muscle protein synthesis, that alone is not enough to supersede muscle protein breakdown [66].

To highlight this concept, a study was conducted evaluating rates of protein synthesis and breakdown at rest and 3 h following a weight training session among fasted individuals [2]. The individuals in the exercise group had a 108 % increase in protein synthesis and 51 % increase in muscle protein breakdown. Despite this increase in synthesis, it was not enough to result in an anabolic response. Similar studies have demonstrated the same results: increase muscle protein breakdown and synthesis rates but no net anabolic response [3, 4]. This research exemplifies the importance of nutrition for anabolic responses to occur.

7.5.2 Insulin, Amino Acids, and Protein Synthesis

As mentioned previously, weight training exercise provides a stimulus for muscle growth through muscle-specific genes. In conjunction with these genes being transcribed into the mRNA, other factors must be in place in order to convert this mRNA into skeletal muscle protein. Insulin and amino acids are fundamental compounds for protein synthesis. Bolster and colleagues [67] stated, "Without question, investigating the singular role of amino acids or insulin in promoting changes in skeletal muscle protein synthesis with resistance exercise is crucial to elucidating mechanisms regulating muscle hypertrophy."

Insulin plays an important role in muscle protein synthesis, specifically following a resistance training bout [68, 69]. Following exercise, insulin is instrumental for amino acid incorporation into skeletal muscle [70–72] as well as minimizing the breakdown of muscle protein [71, 73–75]. Much of the early carbohydrate and protein research on the effects of insulin secretion demonstrated that the ingestion of carbohydrates

surrounding an exercise session will increase plasma insulin levels, but an increase will also be seen in response to the infusion of free amino acids [76–78]. More recent literature has shown a significant insulin response to the ingestion of a carbohydrate, whole protein, and free amino acid (e.g., leucine and phenylalanine) mixture when compared to only carbohydrate at rest and postexercise in trained athletes [78–80]. As a safety disclaimer, insulin levels should be altered through diet, as insulin injections can lead to adverse effects. Simply consuming carbohydrates to elevate insulin levels will not result in an anabolic response, as amino acids must be present in the blood stream for muscle protein synthesis to occur [81]. This concept supports the importance of nutrient timing and combinations of protein and carbohydrate supplementation surrounding an exercise bout, which are discussed in detail below.

As stated previously, amino acids are the fundamental building blocks for muscle tissue. Thus, the availability of essential amino acids (EAAs) following a workout is a determining factor in creating a positive net protein balance for muscle protein synthesis. While some researchers have demonstrated that amino acid ingestion following a workout shifts net protein balance from negative to positive [9], consuming *only* amino acids may not provide the optimal nutrition for maximal gains in lean mass. Therefore, a combination of essential amino acids or high-quality protein and carbohydrates may be necessary to initiate maximal muscle protein synthesis following resistance exercise and is further investigated below.

7.5.3 Importance of Combined Carbohydrate-Protein Supplements

By consuming both carbohydrate and protein before and after a resistance training bout, muscle protein breakdown is attenuated and muscle protein synthesis is stimulated [65, 82, 83]. The complimentary roles these two macronutrients play on protein kinetics may help optimize muscle hypertrophy. The primary role of carbohydrate is to replenish glycogen stores, prevent muscle protein breakdown, and increase insulin levels [84–86]. One study provided subjects an amino acid-carbohydrate drink or a placebo after a resistance training bout and found there was an anabolic response at 1 and 3 h postexercise as measured by increased muscle protein synthesis and arterial phenylalanine and insulin concentrations among the treatment group [87].

Studies that have shown anywhere from 20 to 40 g of protein postexercise optimally stimulate muscle protein synthesis, the latter being more beneficial for older adults [86, 88, 89]. According to the International Society of Sports Nutrition, the recommended 0.15–0.25 g/kg/day addition of protein during all instances of carbohydrate intake helps to maximize muscle protein synthesis and glycogen restoration [12]. The addition of a carbohydrate source when supplementing with protein post-workout may be particularly necessary following sessions highlighting goals associated with endurance or muscular strength-endurance training where expedited glycogen restoration is critical. The most success with carbohydrate-protein combination supplementation in terms of maximizing muscle protein synthesis is the addition of carbohydrates to a source of EAAs [87]. However, more recent nutrient timing research with respect to carbohydrate dosage in the early recovery period following a bout of resistance training has found that the addition of carbohydrates post-workout may not be necessary to further increase whole-body protein balance when proper protein supplementation is provided to strength or hypertrophy athletes [90]. These latest findings highlight that the minimum requirements for sustaining gains in muscle mass as a result of resistance training are to supplement with high-quality protein pre- and postexercise along with ensuring that overall daily macronutrient needs are addressed throughout the course of a training day, particularly carbohydrates. Specific training goals, necessary energy systems for performance, and recovery timelines should be considered when determining the proper supplementation combination of carbohydrates and protein to optimize lean mass accrual.

7.5.4 Nutrient Timing

The central premise of nutrient timing is to time the ingestion of protein and carbohydrate to facilitate the greatest muscle protein synthesis. Despite muscle's ability to ingest protein during the 24 h following a resistance training session [91], the ability to maximize muscle protein synthesis and minimize muscle protein breakdown may rely on the timing of nutrition. As science continues to evolve, The International Society of Sports Nutrition acknowledges the difficulty in specific recommendations, as the research regarding nutrient timing is inconsistent and varies between individuals [84]. This section explores the current literature relating to nutrient timing.

7.5.4.1 Before a Workout

Research suggests that ingesting protein before and after exercise can increase muscle protein synthesis [32, 92–96]. One study compared carbohydrate-amino acid (EAA) consumption before versus after a workout and found that consuming before a workout resulted in greater muscle protein synthesis among the pre-workout group [97]. Tipton and colleagues were interested in comparing net protein balance when ingesting whey protein before or after a workout. They discovered that amino acid availability increased equally pre- and post-workout, unlike a previous study that found a significant increase in muscle protein synthesis with pre-workout carbohydrate-EAA supplementation [98]. More research is needed in this area; however, the current evidence reflects positive outcomes from pre-workout nutrition.

7.5.4.2 After a Workout

The anabolic window, the immediate time period after a resistance training bout, has been thought to be a critical period for preventing protein breakdown, optimizing protein synthesis and muscle hypertrophy, and replenishing glycogen stores via proper nutrition. This section aims to explore the validity of these claims.

By consuming a meal after a workout, muscle protein breakdown is slowed down due to the rise in insulin levels [6, 84, 99]. The combination of both carbohydrate and protein has the potential to elevate insulin greater than just carbohydrates [84, 100], but as mentioned previously, strength and hypertrophy athletes with goals to maximize muscle gain should shift their carbohydrate focus away from a specific post-workout timeline and more toward meeting an overall daily macronutrient need for carbohydrates [90]. However, although theoretically sound, this idea has yet to be demonstrated in practice. Research has demonstrated that the influence of elevated insulin on net protein balance reaches a plateau between 15 and 30 mU/L, approximately three to four times the normal levels [101, 102]. A study conducted by Power and colleagues [103] demonstrated lasting peak insulin concentration, needed for muscle protein balance, for up to 2 h after consuming 45 g of whey protein isolate. Therefore, consuming food immediately postexercise might not be as critical as once thought, unless a pre-workout meal is absent.

Previously, for maximal muscle protein synthesis, it was crucial to include free amino acids (e.g., EAAs or BCAAs) and/or whole protein sources immediately post-workout [9, 82, 84]. To further emphasize the importance of post-workout nutrition, a study demonstrated the effects of consuming 10 g of protein, 8 g of carbohydrate, and 3 g of fat immediately after exercise compared to consumption of the same macronutrient composition 3 h after exercise. There was a 12 % increase in protein synthesis for the group that consumed the meal immediately following the workout [104]. However, studies have also demonstrated there are no timing effects with respect to the anabolic window. Rasmussen and colleagues [87] provided 6 g of essential amino acids with 35 g of carbohydrates to two groups: 1 h vs. 3 h postexercise. The results of the study concluded that there was no significant difference between net leg amino acid concentrations. Similarly, a study conducted by Tipton and colleagues [97] demonstrated that consumption of an essential amino acid-carbohydrate supplement pre-exercise demonstrated greater muscle protein synthesis when compared to postexercise consumption of the same supplement, although there have been disputes on the validity of this study design [99].

Tipton also looked at the physiological response when consuming whey versus casein protein following a weight training session and found that both types of protein led to increases in muscle protein balance and synthesis [34]. The main difference found between the two types of protein was the amino acid response in the blood: a sustained response was elicited by casein, whereas a quick, initial response was elicited by whey. When considering the implications of supplementing whey versus casein protein post-workout, ideally both types of protein should be provided together to optimize muscle protein balance over the course of the extended recovery period to help maximize muscle recovery, synthesis, and regeneration. However, the training program and goals in addition to the training experience should be considered when choosing the optimal type of protein supplementation.

There is conflicting evidence in the literature regarding the effects of nutrient timing post-workout on muscle hypertrophy. A number of studies have been conducted: some demonstrating muscular hypertrophy, whereas others have shown no changes. For a more detailed description on the studies discussed above, please reference Table 7.3 and/or the following text by Alan Argon and Brad Schoenfeld: *Nutrient Timing revisited: is there a post-exercise anabolic window?*

7.5.5 Application

The value of nutrient timing plays an important role when addressing muscle protein synthesis. Despite numerous studies in this area of research, there is no exact science to maximizing the effects of nutrient timing; rather, an individual approach may work best to promote optimal muscle hypertrophy. To optimize overall muscle mass gains, high-quality protein supplementation pre- and postexercise is critical along with ensuring that overall daily macronutrient needs are addressed throughout the course of a training day, particularly carbohydrates. Therefore, a general recommendation for nutrient timing around a workout is 0.4–0.5 g/kg of quality protein per lean body mass at both pre- and post-workout [27, 89, 105]. Ideally, no more than 3–4 h should pass between pre- and post-workout meals, unless a larger meal is consumed, in which 5–6 h is okay [84]. Realistically, nutrient timing and training timing will depend on the individual. In respect to carbohydrates around a workout, the verdict is still unclear as to if carbohydrates post-workout is necessary for optimizing muscle hypertrophy; rather the individual should emphasize daily carbohydrate needs [84].

7.6 Creatine

Creatine is one of the most extensively researched and popular nutrition supplements. Over the last two decades, creatine has been examined in over 500 research studies that have assessed its viability on muscle physiology, body composition, and/or exercise performance in trained, healthy, and various diseased populations. The vast quantity of research conducted supports the claim that creatine supplementation during training, particularly high-intensity exercise, results in promotion of significant strength, fat-free mass, and performance improvements. The majority of scientific evidence available in the literature demonstrates that creatine monohydrate supplementation in athletic, active, and clinical populations is a generally effective nutritional ergogenic aid when paired with various forms of exercise [106]. The laundry list of proven benefits as a result of creatine supplementation coupled with solidified safety, when the recommended dosages are consumed, cements the reason why creatine is considered the gold standard of nutritional supplements.

7.6.1 Supplementation Protocols

Most of the research investigating the effects of creatine supplementation has utilized creatine monohydrate and employed a dosage pattern involving an initial loading phase followed by a maintenance phase. Incorporation of this loading phase, typically 0.3 g/kg/day (15–25 g/day) ingestion of creatine monohydrate for 5–7 days, is the most common method for increasing

Table 7.3 Current literature: effects of postexercise supplementation on muscle hypertrophy

Study	Subjects	Supplementation	Matched control group?	Instrument of measurement	Training protocol	Results
Esmark et al.	13 untrained elderly males	10 g milk/soy protein combo consumed either immediately or 2 h postexercise	Yes	MRI and muscle biopsy	Progressive resistance training consisting of multiple sets of lat pulldown, leg press, and knee extension performed 3 days/week for 12 weeks	↑↑ muscle CSA w/ immediate vs. delayed supplementation
Cribb and Hayes	23 young recreational male bodybuilders	1 g/kg of a supplement containing 40 g whey isolate, 43 g glucose, and 7 g creatine monohydrate consumed either immediately pre- and postexercise or in the early morning and late evening	Yes	DEXA and muscle biopsy	Progressive resistance training consisting of exercise for the major muscle groups performed 3 days/week for 10 weeks	↑↑ lean body mass ↑↑ muscle CSA of type II fibers both w/ immediate vs. delayed supplementation
Willoughby et al.	19 untrained young males	20 g protein or 20 g dextrose consumed 1 h pre- and postexercise	No	Hydrostatic weighing, muscle biopsy, surface measurements	Progressive resistance training consisting of 3 sets of 6–8 reps for all the major muscle groups performed 4 days/week for 10 weeks	↑↑ total body mass ↑↑ fat-free mass ↑↑ thigh mass all w/protein vs. carb supplementation
Hulmi et al.	31 untrained young males	15 g whey isolate or placebo consumed immediately pre- and postexercise	No	MRI and muscle biopsy	Progressive, periodized total body resistance training program consisting of 2–5 sets of 5–20 reps performed 2 days/week for 21 weeks	↑↑ vastus lateralis CSA ↔ other 3 quad muscles CSA both w/ protein vs. placebo
Verdijk et al.	28 untrained elderly males	10 g casein hydrolysate or placebo consumed immediately pre- and postexercise	No	DEXA, CT, and muscle biopsy	Progressive resistance training consisting of multiple sets of lat pulldown, leg press, and knee extension performed 3 days/week for 12 weeks	↔ muscle CSA no significant difference between groups
Hoffman et al.	33 well-trained young males	Supplement containing 42 g protein (milk/collagen blend) and 2 g carbohydrate consumed either immediately pre- and postexercise or in the early morning and late evening	Yes	DEXA	Progressive resistance training program consisting of 3–4 sets of 6–10 reps of multiple exercises for the entire body performed 4 days/week for 10 weeks	↔ total body mass ↔lean body mass no significant differences between groups
Erskine et al.	33 untrained young males	20 g high-quality protein or placebo consumed immediately pre- and postexercise	No	MRI	4–6 sets of elbow flexion performed 3 days/week for 12 weeks	↔ muscle CSA no significant difference between groups

Table adapted from Aragon and Schoenfeld [84]
MRI magnetic resonance imaging, *DEXA* dual-energy X-ray absorptiometry, *CT* computed tomography, *Reps* repetitions, *CSA* cross-sectional area

muscle creatine stores [24, 107]. Loading has also been described as consuming 5 g creatine monohydrate four times per day (20 g total) over the course of a 5–7-day period, an approach that increases muscle creatine and phosphocreatine levels by 10–40 % [24, 107, 108]. Recent studies demonstrate that the loading period may only need to last 2–3 days if taken in combination with carbohydrate and/or protein to maximize creatine stores [24, 109–111]. Many post-workout recovery supplements on the market utilize a combination of creatine monohydrate, protein (whey, soy, and/or casein), and carbohydrate to help maximize muscle growth and development. Beyond the 2–7-day creatine loading/muscle creatine saturation period, the maintenance phase consists of a 3–5 g daily dose (or 0.03 g/kg) of creatine monohydrate for several weeks to a few months, matching the periodization pattern of the training program [107]. One of the alternative creatine loading methods, if the immediate maximization of creatine stores is not an important consideration, is to ingest 3 g/day of creatine monohydrate for at least 28 days resulting in a linear muscle creatine increase. This progressive method has been proven to achieve similar intramuscular creatine and phosphocreatine levels as the aforementioned loading methods [24, 112].

Rather than basing the quantity of creatine supplementation on total body mass or a specific quantity, Burke et al. [113] found successful promotion of muscle growth and performance by basing creatine dosage on the subjects' lean body mass, more specifically, ingesting creatine monohydrate based on a dose of 0.1 g/kg of lean body mass per day. Other training studies observing the effects of creatine supplementation on performance and changes in lean mass determined that both a high-dose protocol (15–25 g/day or 0.3 g/kg/day, equivalent to a loading phase protocol) and a low-dose protocol (3–6 g/day) during training increased intramuscular creatine levels [24]. The dosing protocol should match the goals of the training program, the anaerobic nature of the sport or event, and/or the anabolic needs for lean mass development. Alternatively, during training, a cyclic loading protocol for creatine may be the most appropriate for athletes as it takes 4–6 weeks for elevated intramuscular creatine stores to return to baseline. This cyclic loading involves supplementation of 0.3 g/kg/day (15–25 g/day) creatine monohydrate for 3–4 weeks and then cycling off for 4–6 weeks to most effectively escalate and maintain elevated creatine stores over time [24, 114].

7.6.2 Effects on Lean Body Mass

In addition to gains in performance, particularly strength, power, and anaerobic capacity, increases in body weight in the form of lean mass have been demonstrated in numerous studies when subjects supplement with creatine. During a typical creatine loading period (first 5–7 days), the literature indicates that individuals will experience approximately 0.6–2.0 kg gains in lean body mass [24, 106, 109, 115, 116]. Research suggests that short-term creatine supplementation, perhaps during a single training cycle, has proven to increase total body mass by approximately 0.7–1.6 kg (~1.5–3.5 lb.) [117]. Specifically, a 28-day creatine supplementation (20 g/day) and resistance training study conducted by Earnest et al. [116] found a 1.7 kg increase in total body mass of which 1.5 kg was fat-free mass [115]. Creatine supplementation over the course of a long-term resistance training program (approximately 6–8 weeks) has revealed 2.8–3.2 kg (~7 lb.) increases in lean body mass [116, 118, 119]. Additional research indicates that 4–8 weeks of resistance training plus supplementation with creatine in combination with glucose, taurine, and electrolytes may promote greater gains in lean mass (~1.03–3.83 kg) when compared to creatine supplementation alone [115, 120]. Similar gains in lean muscle mass with resistance training and creatine supplementation have been reported in women. A 10-week study conducted with females assessed resistance training and creatine supplementation [121]. The females who ingested creatine based on the aforementioned loading and maintenance protocol (20 g/day for 4 days followed by 5 g/day for 65 days) reported a 2.6 kg (~5.7 lb.) increase in lean mass [121]. An increase in lean mass (60 % greater than the placebo in the

previous study) is a typical ergogenic benefit seen by women with creatine supplementation; however, gains in overall body mass and lean mass are generally slower than men [24]. The acute (initial 5–7 days) increase in lean mass following creatine monohydrate supplementation coupled with a resistance training program was found to be lower in women (500–700 g) compared to men (1.0–1.5 kg) in a study conducted by Mihic et al. [122].

7.6.3 Physiological Mechanisms for Increasing Lean Body Mass

Some research has addressed the potential physiological mechanisms responsible for the promotion of lean body mass as result of creatine supplementation, but no definitive conclusions have been agreed upon. The initial studies investigated creatine supplementation and associated gains in lean mass, concluding that the primary reason for increased body mass was due to additional water retention in the muscle. Recent research suggests that creatine supplementation increases body mass through greater myofibrillar protein synthesis and overall lean mass accretion [115, 123]. A 12-week resistance training study by Volek et al. [124] demonstrated that resistance-trained males ingesting a creatine supplement accrued significantly greater lean mass compared with those ingesting a placebo. More specifically, significant differences in fiber cross-sectional area were observed in all three muscle fiber types between the creatine supplementation and placebo groups: type I (35 % vs. 11 %), type IIA (36 % vs. 15 %), and type IIX (35 % vs. 6 %). The muscle fiber cross-sectional area growth in the creatine group, for all muscle fiber types, was more than twice the increases observed in the placebo group, with the largest difference found in the most anaerobic fiber type (type IIX) [117, 124].

The physiological mechanisms connecting increases in lean body mass as a result of creatine supplementation were further analyzed by Willoughby and Rosene in a series of two studies examining the effects of oral creatine supplementation on contractile filament gene expression and myosin heavy-chain protein expression [125, 126]. The first of the two studies recruited and divided untrained male subjects into two supplement groups: creatine (6 g/day) or placebo. Both groups participated in a 12-week resistance training program. Similar to previously mentioned studies, the creatine supplementation group had significantly greater gains in lean mass compared to the placebo (~7 lb vs. ~1 lb). Despite similar results in lean mass, this initial study also noted some interesting differences between groups at the cellular level of skeletal muscle. The marker for quantity of intracellular protein content, or myofibrillar protein content, demonstrated significantly greater elevations in the creatine supplementation group compared to the placebo when both groups participated in the same resistance training program. This difference between supplementation groups was associated with the significant increases found in the two isoforms of myosin heavy-chain protein (fundamental units of contractile skeletal muscle) in the creatine group compared to the placebo [125].

The second study conducted by Willoughby and Rosene expanded upon the results of their first study by analyzing the effects of creatine supplementation in conjunction with a similar 12-week resistance training program on changes in myogenic regulatory factor gene expression. Myogenic regulatory factors (e.g., Myo-D, myogenin, MRF-4, andMyf-5) are vital proteins that drive the regulation of gene expression through their function as transcription activators. These myogenic regulatory factors work to regulate gene expression by binding to DNA and subsequently activating muscle-specific gene transcription for important muscular components such as myosin light chain, myosin heavy chain, troponin I, α-actinin, and creatine kinase [127]. At the conclusion of the 12-week resistance training program, subjects supplementing with creatine demonstrated significantly greater myogenin and MRF-4 mRNA expression compared with subjects ingesting the control during the resistance training program [126]. These studies conducted by Willoughby and Rosene demonstrate greater mechanistic insight into the development of lean body mass when supplementing

with creatine in conjunction with a resistance training program. Furthermore, these studies indicate that increases in lean body mass from creatine supplementation are not solely attributed to greater water retention in the muscle, but rather demonstrated that creatine supplementation may induce skeletal muscle hypertrophy at the level of gene expression within the muscle environment.

7.6.4 Satellite Cell Activity

In conjunction with all of the aforementioned benefits of creatine supplementation for increasing lean body mass, the literature also demonstrates that creatine ingestion may enhance the increase in skeletal muscle satellite cell numbers, normally attributed to strength training alone. The activation of muscle-specific satellite cells is speculated to be the primary factor associated with amplifying skeletal muscle hypertrophy beyond muscle-specific transcription and translation. Load-induced muscle hypertrophy, as a result of strength training, is a stimulus for a growth process defined by satellite cell proliferation, differentiation, and fusion with existing myofibers or muscle cells [128]. The *myonuclear domain theory* defines the involvement of satellite cells in the process of skeletal muscle hypertrophy, suggesting that the myonucleus defines the production of mRNA and proteins through transcription and translation for a specific volume of cytoplasm. Hypertrophy of the muscle through increases in fiber size must include a proportional increase in myonuclei, which are typically contributed to the myofibers via fusion of satellite cell populations [129]. If satellite cells are the primary contributor of myonuclei in a growing muscle, then the myonuclear domain theory, if correct, indirectly states that anything promoting increases in satellite cell activity will ultimately lay the foundation for greater changes in skeletal muscle hypertrophy.

The influence of creatine supplementation on satellite cell activity, based on the myonuclear domain theory, was explored by Olsen et al. [130]. These researchers studied changes in satellite cell frequency and the number of myonuclei in human skeletal muscle over a 16-week resistance training program in conjunction with creatine supplementation, protein ingestion, or a placebo cohort. At the end of the 16-week resistance training regimen, all groups demonstrated an increase in satellite cell proportion. Despite increases in satellite cell proliferation across the board, creatine was the only supplement that demonstrated significantly different increases in the myonuclear density of the muscle fiber. As a result, Olsen et al. determined that resistance training in conjunction with creatine supplementation intensifies the strength training-induced increase in both satellite cell number and concentration of myonuclei in human skeletal muscle. Skeletal muscle fiber hypertrophy is amplified when creatine supplementation is combined with the proper resistance training program [130].

7.6.5 Application

Regarded as one of the most highly researched nutritional ergogenic aids from clinical to athletic applications, creatine has proven to be the most effective and safest supplement to increase lean body mass, strength, and performance. Concerns about the safety and potential side effects of creatine supplementation have been put to rest by long-term safety and pharmacokinetic studies that revealed no apparent side effects with supplementation. As a consumer of supplements containing creatine or creatine supplements, it is important to note the type, quality, and/or source of the creatine, as not all forms are equal. Despite numerous attempts by various nutritional companies to develop the latest and most effective form of creatine, creatine monohydrate remains as the gold standard for supplementation. Additionally, it is highly recommended that creatine supplementation be closely aligned with the periodization pattern and goals of the athlete's training program in order to maximize performance and lean body mass gains.

7.7 Anabolic Hormone Enhancers

Serving as key messengers in the body, hormones play an essential role to building and maintaining muscles. Food, stress, and activity all heavily influence the concentration of hormone levels in the body. Although there are hundreds of hormones in the body, the ones discussed in this chapter are specifically related to muscle building. The first set of hormones reviewed is anabolic hormones, better known as the hormones that directly stimulate muscle growth. The next set of hormones is concerned with preventing catabolism of muscle (Sect. 9). Understanding the role of hormones in the muscular growth process is important for optimizing body composition as well as realizing the positive and negative effects of supplementation. The key anabolic hormones found in the body are testosterone, human growth hormone, insulin, and insulin-like growth factor 1 (IGF-1).

7.7.1 Testosterone

Testosterone is a lipid-soluble hormone that is produced in both males and females. Its role in muscle hypertrophy is to promote protein synthesis, prevent catabolism [131], and promote the release of growth hormone. Testosterone and its synthetic derivatives, known as anabolic-androgenic steroids (AAS), have been used in medicine and recreation to induce muscle hypertrophy and/or reduce muscle atrophy due to disuse and aging. It is a banned substance by the NCAA, the International Olympic Committee, and by all major North American Professional Leagues [132]. It is currently legal to administer testosterone and AAS in a medical setting, but it is also used in sport and competition, despite being illegal.

Many supplements claim to increase testosterone; however it is thought that only bioavailable or free testosterone promotes an anabolic response in muscle tissue. When assessing supplement claims for increasing testosterone levels, one should note changes in total testosterone, free testosterone, estradiol, as well as sex hormone-binding globulin. Of these hormones, only free testosterone can bind to androgen receptors and promote anabolism. A few supplements that claim to increase testosterone are ZMA, tribulus terrestris, and aromatase inhibitors. ZMA and tribulus terrestris are discussed in the sections below, while aromatase inhibitors are further referenced in Sect. 8.

7.7.1.1 ZMA

ZMA is a supplement typically comprised of zinc monomethionine aspartate, magnesium aspartate, and vitamin B_6. Physiologically, zinc is a component of many enzymes that maintain balanced hormone levels [132]. Magnesium is involved in over 300 enzymatic reactions and plays a pivotal role in immunity, hormone structure and development, and heart function [133, 134]. Vitamin B_6 is a key vitamin for energy production. Studies have shown that physically active individuals may have zinc and magnesium deficiencies compounded by the loss of these vitamins and minerals through sweat and urine following exercise [133, 135–138]. Many ZMA products claim to elevate testosterone levels in the body; however, the literature has demonstrated conflicting evidence.

One study demonstrating the positive effects of ZMA supplementation on testosterone levels was conducted with collegiate football players [139]. During 8 weeks of spring practice, they were provided ZMA supplementation (30 mg zinc monomethionine aspartate, 450 mg magnesium aspartate, and 10.5 mg of vitamin B_6). At the conclusion of the study, both total and free testosterone levels were significantly higher than the control group. An important factor to consider when evaluating this study outcome was the observed deficiencies in zinc and magnesium in the placebo group throughout the study. Thus, the assumed increase in testosterone levels among the supplement group may have been due to the nutritional deficiency found in the placebo group.

A double-blind control-treatment study conducted by Koehler colleagues assessed the effects

of ZMA supplementation on testosterone levels after 56 days in healthy. The study participants were healthy, active men who consumed sufficient zinc levels prior to the study. Following the study, serum testosterone levels were measured for both the placebo and control group, in which no significant differences between groups were found. Therefore, among individuals consuming sufficient zinc, there appears to be no elevated serum testosterone level from ZMA supplementation [140]. Another study assessed the effects of ZMA supplementation on training adaptations among 42 resistance-trained male athletes. After 8-week supplementation, no significant differences in anabolic hormone levels, catabolic hormone levels, and body composition were observed between the groups [141].

From the literature, it appears that maintaining optimum levels of ZMA through proper whole-food nutrition can determine the impact of ZMA supplementation on testosterone levels. In those athletes who are not deficient in magnesium and zinc, no benefit of ZMA supplementation should be expected.

7.7.1.2 Tribulus Terrestris

Tribulus terrestris (TT) is an herbal plant whose extracts have been used for diuretic, tonic, and aphrodisiac properties [142]. Marketing claims for TT include increasing testosterone levels, thereby making it a popular supplement among athletes and bodybuilders [142]. Currently, there is limited research on the effects of TT on human testosterone levels. One study showed no effect on testosterone levels after a 4-week supplementation with TT [143]. Another study assessed TT supplementation during a 5-week preseason training program in rugby players [144]. A double-blind matched-paired design was used to assess the effects of TT compared to a placebo on strength, body composition, and urinary testosterone/epitestosterone ratio. At the end of 5 weeks, there were no significant differences between groups in any of the aforementioned physiological or hormonal measurements [144]. In conclusion, the existing research on TT supplementation demonstrates no evidence of increasing testosterone levels, and therefore it is not recommended.

7.7.2 Human Growth Hormone

Human growth hormone (GH) is produced in the anterior pituitary gland and is known (under certain conditions) to increase lipolysis and lean body mass and plays an important role in collagen synthesis [145]. GH has been attributed to gains in lean mass while decreasing fat mass among diseased populations [146–150]. Due to the known physiological benefits of GH, it is a popular performance-enhancing hormone used among weight lifters [151]. Despite the physiological benefits of GH, there are negative implications from long-term supplement use such as acromegaly, diabetes, decreased respiratory function, as well as certain type of cancers [151]. Many sports supplements claim to enhance GH levels, but what most fail to report is that studies demonstrating this effect were conducted intravenously or in subjects who were clinically deficient.

Perhaps the most well-known supplement that claims to increase GH secretion is arginine [147, 152, 153]. The proposed mechanism of elevated GH attributed to arginine is through endogenous somatostatin depression [147]. Arginine supplementation of 12–30 g has been shown to elevate GH levels [147, 149]. Arginine supplementation in conjunction with other amino acids has been shown to be effective for increasing GH. Two amino acids coupled with arginine supplementation are ornithine and lysine. Zajac and colleagues found increases in both GH and IGF-1 after supplementation with 12 g arginine and 3 g ornithine during a 3-week training period [153]. Isidori and colleagues found that increases in GH levels were 8 times higher 90 min after ingesting 1.2 g of arginine with 1.2 g of lysine [154].

Another commonly used compound coupled with arginine to stimulate GH release is aspartate. One study assessed the effects of a 7-day arginine-aspartate supplementation regiment on GH levels [155]. Results concluded that peak sleeping GH levels were 60 % higher among the supplement group in comparison to the control group. Another study observed the effects of arginine-aspartate supplementation among endurance athletes [156]. The athletes were given 7.5 g of the supplement two times daily (morning

and evening), 14 days prior to competing in a marathon. Greater hormone levels were present in the supplement group (8 % higher) compared to the control group.

Not all studies have elicited an elevated GH response with arginine supplementation. Alvares et al. assessed the effects of a 4-week supplementation with 6 g of arginine in comparison to a placebo and found no significant difference in GH levels [157]. Other studies, such as the research conducted by Walberg-Rankin, provided resistance-trained males 8 g of arginine for 10 days and found no significant elevation in GH levels [158]. Despite these studies concluding that no relationship exists between arginine supplementation and GH levels, one must consider the dose of arginine prescribed. As mentioned above, the recommended dose of arginine supplementation in order to have an effect on GH levels is between 12 and 30 g per day.

A study assessed the influence of L-arginine on growth hormone levels by providing trained runners 6 g of L-arginine or a placebo [159]. Serum blood GH was tested in each of the runners before exercise, immediately following the two bouts of a 5 k timed run and 20 min postexercise. There was no difference in GH hormone levels between study groups, indicating that L-arginine did not appear to enhance GH hormone levels.

Forbes and colleagues assessed the combined effect of exercise and oral L-arginine supplementation on growth hormone levels among strength-trained males [160]. Fourteen males were divided into two groups, a placebo group and an L-ARGININE-SUPPLEMENTED group (0.075 g/kg body mass). Subjects performed resistance exercises, and blood samples were collected before and at 15 min intervals following the bout, up to 1 h postexercise. The study concluded that plasma L-arginine levels in the supplement group were elevated, but GH levels were attenuated as a result of supplementation.

Another L-arginine study evaluated supplementation among trained cyclists [161]. Fifteen males were assigned to either a placebo or L-ARGININE supplement (0.075 g/kg body mass) before a submaximal exercise. The study found no differences in growth hormone levels between groups.

A long-term study assessed the influence of a 4-week L-arginine supplementation protocol on hormonal responses among trained runners [157]. Following supplementation, blood samples were collected before a 5 km timed trial, following the trial, following a second 5 km timed trial, and 20 min after recovery. The study concluded there were no significant differences in hormonal responses, including GH, between the placebo and the L-arginine-supplemented group. Hormonal changes recorded over time occurred similarly in both groups and thus were attributed to the exercise stimulus.

Research has also implicated that supplementation with melatonin in combination with exercise may result in elevated GH levels [162]. Nassar and colleagues randomly assigned 30 males and 30 females, all physically active, to various levels of supplementation: 0.5 mg melatonin, 5.0 mg melatonin, or 1.0 mg dextrose placebo. Blood samples were taken prior to the resistance training bout and were collected up to 120 min postexercise at 15 min increments. The study concluded that the combination of exercise and melatonin supplementation positively influenced GH levels when compared to the dextrose placebo. Similarly, Meeking et al. studying the effects of 5 mg of melatonin supplementation on exercise induced changes in growth hormone levels [163]. This double-blind randomized control trial contained 7 healthy male subjects who received both the placebo and melatonin supplement at separate times prior to completing a graded cycle ergometer exercise protocol; there was a 3-week washout period between trials. Following analysis of the blood samples collected before and during 15 min intervals until the study was complete, the researchers observed greater GH levels when the subjects completed the melatonin-exercise scenario.

Another study assessed the influence of oral melatonin supplementation in combination with resistance training [164]. In a randomized, double-blind, crossover study, 10 healthy males received a placebo or 6 mg of melatonin on two separate occasions. Supplements were ingested 60 min before exercise, while blood samples were taken in the morning, pre-resistance workout,

during resistance training, and at 15 min intervals for 60 min postexercise. This study concluded that melatonin ingestion during the daytime in conjunction with intense resistance training may lower GH concentrations.

Based on the literature, there is no definitive link between these amino acids and muscle hypertrophy, despite some research demonstrating increases in GH levels. More research needs to be completed on the effects of melatonin and exercise on GH levels to have a clearer understanding of its effects. Overall, a consistent aspect throughout these studies for elevating GH levels is exercise.

7.7.3 Insulin-Like Growth Factor 1

IGF-1 "is the mediator of the anabolic and mitogenic activity of GH" [165]. The majority of IGF-1 is produced in the liver and functions as an endocrine hormone in the body [149, 166]. IGF-1 plays a role in all three muscle protein hypertrophy mechanisms: gene transcription, protein translation, and satellite cell activity [167]. Therefore, the presence of IGF-1 is associated with the potential for activation of muscle protein synthesis. Very few studies have shown any effective supplement mechanisms to increase endogenous IGF-1.

The two single most influential factors for increasing IGF-1 in the body are mechanical stimulation and the release of GH. There have been a few studies demonstrating that bovine colostrum supplementation among training athletes resulted in elevated IGF-1 levels [168, 169]. Despite the elevated IGF-1 levels, there was no reported information on body composition changes. Another study found no significant changes in strength and muscle protein balance after 2 weeks of bovine colostrum supplementation [168].

Creatine supplementation has been shown to increase intramuscular levels of IGF-1. Deldicque and colleagues conducted a double-blind crossover study assessing muscle biopsies from subjects who had taken creatine or a placebo for 5 days following a high-intensity resistance exercise bout. The researchers found greater levels of mRNA for IGF-1 among subjects in the creatine supplementation group [170]. Another study demonstrating the effects of creatine supplementation coupled with resistance training on IGF-1 was led by Burke et al. [171]. This randomized control study assessed the effects of creatine or placebo supplementation on muscle IGF-1 over 49 days of training in active, healthy adults. The study found that the creatine group had an increased IGF-1 intramuscular content 78 % above baseline, compared to a 54 % change from baseline in the control group, thus supporting the claim that creatine supplementation increases intramuscular IGF-1 concentration.

Recent research has also shown potential mechanisms with vitamin D_3 supplementation to increase serum IGF-1 levels in adults [172]. Ameri and colleagues provided study subjects vitamin D_3 orally (5,000 or 7,000 IUD) in comparison to a placebo group over a 12-week period and measured serum IGF-1 levels pre- and post-supplementation. The group that received 7,000 IUD of vitamin D_3 weekly saw significant increases in circulating IGF-1 levels. The results of this particular study may lead to a more effective clinical treatment in patients with GH deficiency, but further investigation is necessary to assess effectiveness of vitamin D_3 supplementation in the active and athletic populations before solidifying more formalized recommendations.

7.7.4 Application

There are supplements on the market that claim to increase anabolic hormone levels; however, not all of them have been proven to do so. Testosterone is a key anabolic hormone for the promotion of muscle hypertrophy. Two supplements that are proclaimed to increase testosterone levels are ZMA and tribulus terrestris. Based on the current literature, it appears that proper nutrition is superior to supplementation in this case and the best option for optimizing levels of zinc monomethionine aspartate, magnesium aspartate, and vitamin B_6. To date there is no evidence that tribulus terrestris increases testosterone levels. Another major anabolic hormone

responsible for muscle hypertrophy is human growth hormone. The amino acids arginine and arginine-aspartate have been shown to elevate GH levels in a few (but not all) studies; however, this has not been translated into lean mass gains. IGF-1 is another important factor for muscle protein synthesis, where recent research suggests that creatine and possibly vitamin D3 supplementation may increase IGF-1 levels.

7.8 Aromatase Inhibitors

Aromatase inhibitors (AIs) are pharmacological agents used to prevent or minimize the activity of the enzyme aromatase. Aromatase converts androgens to estrogens through aromatization, therefore decreasing the concentration of estrogen in the body [173]. Conventionally, AIs have been used in breast cancer treatment; however, their use has crossed over into the world of bodybuilding and training due to their reputation for increasing endogenous testosterone concentrations. To assess the influence of AI supplements on body composition and testosterone levels, Willoughby and colleagues had male participants consume 72 mg of an AI supplement over 8 weeks [95]. A 3-week washout phase followed the 8-week supplementation phase. Throughout the study, subjects were asked to maintain their normal exercise routines. At the end of the 8 weeks, changes in testosterone levels from baseline, both total and free, were significantly higher in the treatment group compared to the control, 283 and 625 %, respectively. At the end of the study, subjects in the AI supplement group had a 3.5 % decrease in fat mass. Following the post-supplementation washout period, testosterone levels returned to pre-intervention levels.

From the results of this study, it is evident that the specific AI supplement had a positive effect on testosterone levels. Keep in mind this was only one study. Thus, much more research is needed to confirm the efficacy as well as safety when using AI supplements. As a result, AI supplements cannot be recommended at the present time.

7.8.1 Application

The central purpose of aromatase inhibitors is to prevent aromatase from converting androgens to estrogens and increase endogenous testosterone production via a negative feedback mechanism. Evidence demonstrates positive effects resulting from AI supplementation on testosterone levels when introduced into a preexisting exercise program. However, the benefits of AI supplements on gains in lean mass or performance remain to be demonstrated.

7.9 Anti-catabolic Supplements

In order to optimize muscle hypertrophy and the development of lean mass, muscle protein synthesis must be greater than muscle protein breakdown. Therefore, there is a rather extensive supplement market promoting products that purport to decrease muscle catabolism (i.e., the breakdown of muscle tissue). Three of the most popular supplements used to prevent muscle protein breakdown are glutamine, β-hydroxyl-β-methylbutyrate (HMB), and α-ketoisocaproic acid (KIC). These three supplements are further discussed below. Insulin is also a compound that plays a permissive role in reducing muscle protein breakdown [71, 74, 174], hence the reason why consuming carbohydrate and protein following a workout is recommended.

7.9.1 Glutamine

Glutamine, a nonessential amino acid, is revered for its anti-catabolic properties and is often a supplement typically consumed after a resistance training workout. It is the most prevalent free amino acid in skeletal muscle and accounts for over fifty percent of amino acid concentration within muscle tissue [175]. Glutamine is one of the major sources of fuel for the gut and gastrointestinal tract and under certain circumstances can provide an alternative source of energy to skeletal muscle. Theoretically, supplementing with glutamine prevents skeletal muscle glutamine from

being metabolized by the gut, thus diminishing muscle protein breakdown.

Research assessing exercise and its effects on glutamine concentration has had mixed results at best. Some studies show that plasma glutamine concentration levels decline following eccentric resistance training [176], whereas others have shown no change in plasma glutamine levels [177]. Street and colleagues found that glutamine supplementation following an eccentric workout decreased the perception of muscle soreness and attenuated strength losses within 96 h following exercise [178]. A few studies in the literature have demonstrated potential anti-catabolic effects of glutamine supplementation among ill or recent surgery patients [179, 180]. Contrary to these findings, other studies have found no benefit of glutamine supplementation on lean mass or performance. Pellegrinotti et al. saw no changes in swimming performance between glutamine and cornstarch groups after 30 days of supplementation, a study conducted among 10 adolescent (10–18 years old) male endurance swimmers [181]. Another study conducted by Ramallo et al showed that glutamine supplementation did not have an effect on muscle damage profile following resistance training [182]. Untrained subjects were placed into one of two supplement groups: maltodextrin and maltodextrin plus glutamine. The results of this study demonstrated that the inclusion of glutamine did not have any influence on the level of muscle tissue damage incurred by these subjects.

7.9.2 β-Hydroxy-β-Methylbutyrate

Another supplement associated with preventing muscle protein breakdown is β-hydroxy-β-methylbutyrate (HMB), a metabolite of leucine. The first study demonstrating the anti-catabolic properties of HMB was led by Nissen and colleagues [183], who introduced HMB supplementation (3 g/day) to untrained individuals compared to a control group during a 3-week resistance training program. To measure muscle protein breakdown, urine analysis of 3-methyhistidine was conducted. The smallest amount of muscle protein breakdown was shown in the HMB supplementation group, as 50 % less 3-methylhistidine was present in their urine during week 1. However, by the end of week 3, there were no significant differences among groups [183]. The results of this initial study provide difficulty in forming a concrete conclusion concerning HMB supplementation as 3-methylhistidine is not the best marker to use in the evaluation of muscle protein breakdown. In a more recent study, a 2-week HMB supplementation protocol during a high-volume training regimen resulted in lower serum cortisol levels and decreased prevalence of creatine kinase as a marker of muscle damage [184]. Other studies have demonstrated similar findings resulting from HMB supplementation [185].

In some research, HMB supplementation demonstrates the ability to attenuate muscle protein breakdown as well as reduce blood markers of muscle degradation. The effects of HMB supplementation on body composition and gains in lean mass remain under contention. Nissen and colleagues extended the study mentioned above to 7 weeks of HMB supplementation (3 g/day) in comparison to a control group in conjunction with the aforementioned resistance training program. The study concluded that those who supplemented with HMB saw increases in lean mass throughout the intervention. However, the cumulative gains in lean mass at the end of the study were not significantly greater than the control [183]. Another study assessed the outcomes of supplementing with HMB-ATP on lean body mass over a 12-week period in trained subjects and found a 12.7 % increase in lean body mass [186].

Dunsmore and colleagues [187] assessed the effects of 3 g/day HMB free acid (FA) or a placebo over the course of a 12-week periodized resistance training study. Following the 12-week intervention, strength, power, and muscle hypertrophy improved among the HMB supplement group. To further demonstrate the positive effects of HMB supplementation, Lowery et al. conducted a three-phase double-blind study that provided subjects 3 g/day HMB free acid, 400 mg/day of Peak ATP, or a combination of the two

[188]. The greatest strength gains were achieved in the combination group followed by the HMB free acid group.

From the literature, there is evidence suggesting that HMB supplementation may prevent muscle protein breakdown. Second to only carbohydrate consumption, HMB supplementation is recommended for preventing muscle catabolism. The ISSN recommends consuming 1–2 g of HMB-FA 30–60 min prior to exercise, as well as consuming 3 g/day of HMB for 2 weeks prior to high-intensity training [90].

7.9.3 α- Ketoisocaproic Acid

Commonly referred to as KIC, α- ketoisocaproic acid is another supplement purported to have anti-catabolic effects in muscle. Structurally, KIC is the ketoacid of leucine, one of the branched-chain amino acids. Although supplement companies market KIC as an anti-catabolic supplement, there is minimal scientific research supporting these claims. One study assessed the influence of 0.3 g/day of KIC supplementation, in combination with 3 g/day of HMB, on creatine kinase, a biomarker representative of muscle damage [185]. The 14-day supplementation protocol yielded lower creatine kinase appearance in blood in comparison to the placebo group. This initial finding is interesting, but the effect of KIC on muscle protein breakdown has yet to be conclusively demonstrated.

7.9.4 Application

Reducing muscle catabolism is one mechanism for optimizing lean mass. Glutamine, β-hydroxy-β-methylbutyrate (HMB), and α- ketoisocaproic acid (KIC) are three supplements that are marketed to have anti-catabolic properties. Out of the three, HMB is the most promising to prevent muscle protein breakdown. It may be especially helpful during periods of overreaching (i.e., deliberate increases in intensity and duration of training).

7.10 Nitric Oxide Boosters

7.10.1 Nitric Oxide Physiology

One of the latest trends in the supplement industry is the promotion of supplements claiming to increase nitric oxide (NO) production. Physiologically, NO plays important roles in skeletal muscle physiology including regulating force production, glucose homeostasis, and blood flow [189]. NO also promotes smooth muscle relaxation and is produced by nitric oxide synthase within cells. It is commonly believed that NO influences metabolic responses during exercise including increased blood flow and oxygen distribution to cardiac and skeletal muscle as well as promoting glucose utilization to preserve sources of skeletal muscle energy [190].

7.10.2 Nitric Oxide-Boosting Supplements

The fundamental ingredient contained in "nitric oxide-enhancing" supplements is typically arginine, an amino acid and a precursor for NO synthesis [191]. Arginine dictates the body's production of NO as it is the only nitrogen-containing NO synthase substrate. One study assessed the effects of an arginine supplement on NO production over an 8-week resistance training program [192]. Although the intervention group demonstrated improved strength, there was no measure of NO production and no significant increases in lean body mass. Another study assessed the effects of a 7-day arginine-containing supplement regimen combined with resistance training on brachial artery blood flow, NO levels, arginine levels, and endothelial nitric oxide synthase (eNOS) levels in a randomized setting [193]. Blood samples were taken both pre- and post-resistance training bouts. Arginine was significantly higher in the supplement group prior to the exercise bout (84.7 %). There were elevated levels of NO, brachial artery flow, and eNOS in both groups postexercise and no significant differences between groups. Theoretically, arginine

supplementation may result in increased performance due to the physiological role it has in NO production. Scientifically, there is not enough research to support the claim that a nitric oxide-boosting supplement can influence muscle hypertrophy and lean body mass.

Alvares et al. [194] assessed the effect of L-arginine supplementation on nitric oxide indicators, nitrite and nitrate (NO_x). In this double-blind, randomized controlled study, 15 males were provided 6 g of L-arginine or a placebo. Pre-supplement blood samples were collected. 80 min following supplementation, the exercise protocol began. Blood samples were collected at 30 min intervals following supplementation, up to 120 min post-supplementation. The study concluded there was no significant difference in NO_x levels between groups.

Willoughby and colleagues studied the effects of a 7-day arginine-alpha-ketoglutarate (AAKG) supplement on various biomarkers, including nitric oxide metabolites and plasma L-arginine [195]. Twenty-four active males were prescribed 12 g/day of the AAKG supplement or a placebo for 7 days. A resistance training bout was performed, and blood samples were taken before, immediately postexercise, and 30 min postexercise. The AAKG supplement group increased plasma L-arginine levels, but there was no difference found in NO_x levels between groups. A study conducted by Forbes et al. [161] assessing the effects of L-arginine supplementation among trained cyclists was mentioned previously in the growth hormone section. This study also concluded that L-arginine supplementation did not have any influence on NO_x levels.

Another supplement thought to have an influence on nitric oxide levels is citrulline, which contributes to greater L-arginine levels in the blood [196]. Seventeen trained male cyclists were randomly assigned to a placebo or 6 g L-citrulline-malate-supplemented group. The design of the study called for the supplements to be consumed 2 h prior to exercise. Blood samples were collected before the 137 km cycling phase, 15 min post-cycling, and 3 h post-cycling. This study found that L-citrulline-malate significantly increased plasma nitrite levels, but no research literature has demonstrated a direct link between L-citrulline or L-citrulline-malate supplementation and changes in NO_x levels, particularly in relation to responses during exercise.

Schweldhelm and colleagues observed the influence of L-arginine and L-citrulline supplementation on nitric oxide at rest [197]. In a randomized, double-blind crossover study, 20 subjects received one of six different dosing combinations containing citrulline, arginine, or a placebo for a week (7 days) with a week washout period between treatments. On the seventh day, a biochemical analysis was run on blood samples collected pre- and post-supplementation to assess biomarkers and pharmacodynamics. The study found that L-citrulline supplementation increased plasma L-arginine as well as NO-dependent signaling.

L-citrulline supplementation may improve arterial stiffness, as demonstrated by a study conducted by Ochiai et al. [198]. L-citrulline is a byproduct of nitric oxide formation and contributes to the regulation of nitric oxide [199]. For this study, 15 males were recruited to partake in the double-blind randomized study in which subjects received either 5.6 g of L-citrulline or a placebo. After 7 days of treatment, brachial-ankle pulse waves (baPWVs) were measured. The authors concluded that L-citrulline supplementation had a positive influence on arterial stiffness, as baPWVs were lower in the supplement group.

A combined exercise and L-citrulline supplement study was conducted in mice to demonstrate the potential positive effects of L-citrulline on performance for athletes [200]. The study wanted to assess the effects of L-citrulline supplementation on performance and fatigue during an intense exercise session. Mice were put through a swimming regiment with 5 % body weight resistance and timed until exhaustion, at which point blood was drawn and assessed. The group that received the citrulline supplement had a significantly longer performance time, decreased plasma blood lactate levels, and decreased blood ammonia levels. These findings provide implications that L-citrulline may be beneficial for athletes in prolonging exhaustion.

7.10.3 Application

Nitric oxide-enhancing supplements have not been linked to muscle hypertrophy or increases in lean body mass. Nitric oxide supplements are typically associated with increases in nitric oxide production and increases in blood flow; however, there is not enough scientific evidence to prove this to be true, particularly in human research. Theoretically, some believe nitric oxide supplements may lead to more intense training sessions, resulting in hypertrophy; again, this is not currently supported by the scientific literature.

7.11 Conclusion

Gaining and maintaining lean mass and optimizing body composition are two common goals among many athletes. These processes can be achieved by influencing the body through food, exercise, and supplements. A basic understanding of the biochemical and physiological bases of muscle hypertrophy provides a foundation for assessing supplement claims. In conjunction with knowledge of supplements, the importance of whole-food nutrition cannot be overstated in promoting gains in lean mass and optimizing body composition. Protein and creatine are two supplements that have shown consistent promise promoting gains in muscle mass, while many other supplements still need more research to formulate more definitive conclusions concerning their effect on muscle mass development.

7.12 Key Points

- When meals contain adequate protein as sources of amino acids in addition to carbohydrates to stimulate insulin activity, muscle protein synthesis is increased with simultaneous decreases in muscle protein breakdown. As a result, a significant boost in positive protein balance and muscle protein growth occurs.
- Some sports nutrition supplements affect muscle biochemical processes during transcription and translation of genetic material into mRNA (e.g., IGF-1 via creatine or vitamin D_3 supplementation), while others affect muscle biochemical pathways posttranscription as they claim to increase muscle mass by driving a faster rate of amino acid incorporation into formal muscle protein under the guidance of mRNA (e.g., leucine supplementation). Still other sports nutrition supplements do not affect the transcription and translation process at all, but rather claim to expedite nutrient delivery to working skeletal muscle.
- In order to build lean body mass, it is necessary to incorporate high-quality protein as part of the normal diet in addition to a proper resistance training program. A quality protein source is also necessary to optimize cellular and tissue repair in addition to usage as a substrate for numerous hormonal and metabolic activities during the recovery process.
- When attempting to promote lean muscle mass accretion, supplementation with whey protein is one great option due to its rapid absorption characteristics, high branched-chain amino acid content, and health benefits.
- A combination of both whey and casein protein supplements may be even more effective for promoting gains in lean muscle mass.
- Due to the lower glycemic index of soy protein and its intermediate rate of digestion (relative to casein and whey), supplementation may be beneficial in isolated situations or in conjunction with the primary milk proteins.
- The variable effects that soy protein supplementation can have on different sexes leads to a difference in supplementation recommendations. With the nonhormonal estrogen-like properties, soy protein can be an excellent source of high-quality protein for both pre- and postmenopausal female athletes. The lower saturated fat and cholesterol content of soy may also help to promote more nutrient-dense caloric intake when used by female athletes as a supplement. For male athletes, however, the lower muscle protein fractional synthesis rate of soy protein compared to whey may be less advantageous. Additional research needs to be conducted to answer

questions concerning soy protein ingestion effects on male hormone levels and semen quality.

- Vegan athletes, however, may need to consider specific meal planning strategies that focus on plant sources rich in protein such as legumes, nuts and seeds, rice, and other whole-grain products in order to achieve proper nitrogen balance during periods of muscular growth.
- Despite its decrease in popularity and regular incorporation into newer nutritional supplements due to its higher cost compared to other protein forms, egg white protein is another great option for athletes.
- Under certain circumstances, nutrient timing can be important for optimizing training responses. The combination of carbohydrate and protein provides a surge of amino acids and insulin, both of which are necessary for maximizing gains in lean mass and recovery. For endurance athletes as well as strength-power athletes that engage in multiple workouts per day, nutrient timing will likely expedite recovery.
- Creatine monohydrate, at doses of 3–5 g per day × 4–6 weeks, is a safe and effective way to boost strength, lean mass, and performance.
- Studies analyzing the physiological effects of creatine on lean body mass development strongly indicate that gains are not solely attributed to greater water retention in the muscle, but rather that creatine actually promotes skeletal muscle hypertrophy by altering the level of gene expression within the muscle itself.
- Testosterone and human growth hormone are two anabolic hormones that influence the development of lean mass and strength. Despite the claims of many supplements, none of them have conclusively been shown to directly affect testosterone or GH in a manner consistent with improvements in body composition or performance. IGF-1 is another important factor for muscle protein synthesis, where recent research suggests that creatine and possibly vitamin D3 supplementation may increase IGF-1 levels and indirectly effect GH levels.
- Some supplements are used to reduce muscle catabolism. Glutamine does not appear to be effective in this regard, HMB shows promise, and further research is needed to determine if KIC is worthwhile.
- Nitric oxide supplements are theoretically associated with greater intensity training sessions which may lead to increased muscle mass; however, more research needs to be done in this area.

References

1. Tipton K, Ferrando A. Improving muscle mass: response of muscle metabolism to exercise, nutrition and anabolic agents. Essays Biochem. 2008;44: 85–98.
2. Biolo G, Maggi SP, Williams BD, Tipton KD, Wolfe RR. Increased rates of muscle protein turnover and amino acid transport after resistance exercise in humans. Am J Physiol. 1995;31(3), E514.
3. Phillips SM, Tipton K, Ferrando AA, Wolfe RR. Resistance training reduces the acute exercise-induced increase in muscle protein turnover. Am J Physiol. 1999;276(1):E118–24.
4. Phillips SM, Tipton KD, Aarsland A, Wolf SE, Wolfe RR. Mixed muscle protein synthesis and breakdown after resistance exercise in humans. Am J Physiol. 1997;36(1), E99.
5. Wagenmakers AJ. Tracers to investigate protein and amino acid metabolism in human subjects. Proc Nutr Soc. 1999;58(04):987–1000.
6. Biolo G, Tipton KD, Klein S, Wolfe RR. An abundant supply of amino acids enhances the metabolic effect of exercise on muscle protein. Am J Physiol. 1997;36(1), E122.
7. Hulmi JJ, Kovanen V, Selänne H, Kraemer WJ, Häkkinen K, Mero AA. Acute and long-term effects of resistance exercise with or without protein ingestion on muscle hypertrophy and gene expression. Amino Acids. 2009;37(2):297–308.
8. Hulmi JJ, Lockwood CM, Stout JR. Effect of protein/essential amino acids and resistance training on skeletal muscle hypertrophy: A case for whey protein. Nutr Metab. 2010;7(51).
9. Tipton KD, Ferrando AA, Phillips SM, Doyle D, Wolfe RR. Postexercise net protein synthesis in human muscle from orally administered amino acids. Am J Physiol. 1999;276(4):E628–34.
10. Pitkanen H, Nykanen T, Knuutinen J, Lahti K, Keinanen O, Alen M, et al. Free amino acid pool and muscle protein balance after resistance exercise. Med Sci Sports Exerc. 2003;35(5):784–92.
11. Trumbo P, Schlicker S, Yates AA, Poos M. Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein and amino acids. J Am Diet Assoc. 2002;102(11):1621–30.
12. Kreider RB, Wilborn CD, Taylor L, Campbell B, Almada AL, Collins R, et al. ISSN exercise & sport

nutrition review: research & recommendations. J Int Soc Sports Nutr. 2010;7(7):2–43.
13. Forslund AH, El-Khoury AE, Olsson RM, Sjödin AM, Hambraeus L, Young VR. Effect of protein intake and physical activity on 24-h pattern and rate of macronutrient utilization. Am J Physiol. 1999;276(5):E964–76.
14. Friedman J, Lemon P. Effect of chronic endurance exercise on retention of dietary protein. Int J Sports Med. 1989;10(2):118–23.
15. Lamont LS, Patel DG, Kalhan SC. Leucine kinetics in endurance-trained humans. J Appl Physiol. 1990;69(1):1–6.
16. Meredith C, Zackin M, Frontera W, Evans W. Dietary protein requirements and body protein metabolism in endurance-trained men. J Appl Physiol. 1989; 66(6):2850–6.
17. Phillips SM, Atkinson SA, Tarnopolsky MA, MacDougall J. Gender differences in leucine kinetics and nitrogen balance in endurance athletes. J Appl Physiol. 1993;75(5):2134–41.
18. Lemon P. Protein and amino acid needs of the strength athlete. Int J Sport Nutr. 1991;1(2):127–45.
19. Lemon P, Tarnopolsky M, MacDougall J, Atkinson S. Protein requirements and muscle mass/strength changes during intensive training in novice bodybuilders. J Appl Physiol. 1992;73(2):767–75.
20. Tarnopolsky M, Atkinson S, MacDougall J, Chesley A, Phillips S, Schwarcz H. Evaluation of protein requirements for trained strength athletes. J Appl Physiol. 1992;73(5):1986–95.
21. Chesley A, MacDougall J, Tarnopolsky M, Atkinson S, Smith K. Changes in human muscle protein synthesis after resistance exercise. J Appl Physiol. 1992;73:1383.
22. Kreider RB. Dietary supplements and the promotion of muscle growth with resistance exercise. Sports Med. 1999;27(2):97–110.
23. Tarnopolsky MA, MacDougall JD, Atkinson SA. Influence of protein intake and training status on nitrogen balance and lean body mass. J Appl Physiol. 1988;64(1):187–93.
24. Kreider RB, Leutholtz BC, Katch FI, Katch VL. Exercise and sport nutrition. Santa Barbara, CA: Fitness Technologies Press; 2009.
25. Kreider RB, Fry AC, O'Toole MLE, editors. Overtraining in sport. International conference on overtraining in sport, Jul, 1996, U Memphis, Memphis, TN, US; 1998: Human Kinetics.
26. Holwerda AM, van Vliet S, Trommelen J. Refining dietary protein recommendations for the athlete. J Physiol. 2013;591(12):2967–8.
27. Moore DR, Robinson MJ, Fry JL, Tang JE, Glover EI, Wilkinson SB, et al. Ingested protein dose response of muscle and albumin protein synthesis after resistance exercise in young men. Am J Clin Nutr. 2009;89(1):161–8.
28. Bucci L, Unlu L. Proteins and amino acid supplements in exercise and sport. Driskell L, Wolinsky I (eds). Energy-yielding macronutrients and energy metabolism in sports nutrition. Boca Raton, FL: CRC Press; 2000. pp. 191–212.
29. Etzel MR. Manufacture and use of dairy protein fractions. J Nutr. 2004;134(4):996S–1002.
30. Ha E, Zemel MB. Functional properties of whey, whey components, and essential amino acids: mechanisms underlying health benefits for active people (review). J Nutr Biochem. 2003;14(5):251–8.
31. Krissansen GW. Emerging health properties of whey proteins and their clinical implications. J Am Coll Nutr. 2007;26(6):713S–23.
32. Elliot TA, Cree MG, Sanford AP, Wolfe RR, Tipton KD. Milk ingestion stimulates net muscle protein synthesis following resistance exercise. Med Sci Sports Exerc. 2006;38(4):667.
33. Carunchia Whetstine M, Croissant A, Drake M. Characterization of dried whey protein concentrate and isolate flavor. J Dairy Sci. 2005;88(11): 3826–39.
34. Tipton KD, Elliott TA, Cree MG, Wolf SE, Sanford AP, Wolfe RR. Ingestion of casein and whey proteins result in muscle anabolism after resistance exercise. Med Sci Sports Exerc. 2004;36:2073–81.
35. Mahé S, Messing B, Thuillier F, Tome D. Digestion of bovine milk proteins in patients with a high jejunostomy. Am J Clin Nutr. 1991;54(3):534–8.
36. Boirie Y, Dangin M, Gachon P, Vasson M-P, Maubois J-L, Beaufrère B. Slow and fast dietary proteins differently modulate postprandial protein accretion. Proc Natl Acad Sci USA. 1997;94(26):14930–5.
37. Frühbeck G. Protein metabolism: slow and fast dietary proteins. Nature. 1998;391(6670):843–5.
38. Phillips SM, Tang JE, Moore DR. The role of milk- and soy-based protein in support of muscle protein synthesis and muscle protein accretion in young and elderly persons. J Am Coll Nutr. 2009;28(4): 343–54.
39. Katsanos CS, Chinkes DL, Paddon-Jones D, Zhang X-J, Aarsland A, Wolfe RR. Whey protein ingestion in elderly persons results in greater muscle protein accrual than ingestion of its constituent essential amino acid content. Nutr Res. 2008;28(10):651–8.
40. Katsanos CS, Kobayashi H, Sheffield-Moore M, Aarsland A, Wolfe RR. A high proportion of leucine is required for optimal stimulation of the rate of muscle protein synthesis by essential amino acids in the elderly. Am J Physiol. 2006;291(2):E381–7.
41. Koopman R, Wagenmakers AJ, Manders RJ, Zorenc AH, Senden JM, Gorselink M, et al. Combined ingestion of protein and free leucine with carbohydrate increases postexercise muscle protein synthesis in vivo in male subjects. Am J Physiol. 2005;288(4):E645–53.
42. Tipton KD, Elliott TA, Ferrando AA, Aarsland AA, Wolfe RR. Stimulation of muscle anabolism by resistance exercise and ingestion of leucine plus protein. Appl Physiol Nutr Metab. 2009;34(2):151–61.
43. Dangin M, Boirie Y, Garcia-Rodenas C, Gachon P, Fauquant J, Callier P, et al. The digestion rate of protein is an independent regulating factor of

postprandial protein retention. Am J Physiol. 2001;280(2):E340–8.
44. Mahe S, Roos N, Benamouzig R, Davin L, Luengo C, Gagnon L, et al. Gastrojejunal kinetics and the digestion of [15 N] beta-lactoglobulin and casein in humans: the influence of the nature and quantity of the protein. Am J Clin Nutr. 1996;63(4):546–52.
45. Wilborn CD, Taylor LW, Outlaw J, Williams L, Campbell B, Foster CA, et al. The effects of pre-and post-exercise whey vs. casein protein consumption on body composition and performance measures in collegiate female athletes. J Sports Sci Med. 2013; 12(((1):74.
46. Cribb PJ, Williams AD, Carey MF, Hayes A. The effect of whey isolate and resistance training on strength, body composition, and plasma glutamine. Int J Sports Nutr Exerc Metab. 2006;16(5).
47. Demling RH, DeSanti L. Effect of a hypocaloric diet, increased protein intake and resistance training on lean mass gains and fat mass loss in overweight police officers. Ann Nutr Metab. 2000;44(1):21–9.
48. Kerksick CM, Rasmussen CJ, Lancaster SL, Magu B, Smith P, Melton C, et al. The effects of protein and amino acid supplementation on performance and training adaptations during ten weeks of resistance training. J Strength Cond Res. 2006;20(3): 643–53.
49. Driskell JA, Wolinsky I. Energy-yielding macronutrients and energy metabolism in sports nutrition. New York: CRC Press; 1999.
50. Wilkinson SB, Tarnopolsky MA, MacDonald MJ, MacDonald JR, Armstrong D, Phillips SM. Consumption of fluid skim milk promotes greater muscle protein accretion after resistance exercise than does consumption of an isonitrogenous and isoenergetic soy-protein beverage. Am J Clin Nutr. 2007;85(4):1031–40.
51. Brown EC, DiSilvestro RA, Babaknia A, Devor ST. Soy versus whey protein bars: effects on exercise training impact on lean body mass and antioxidant status. Nutr J. 2004;3(1):22.
52. Bos C, Metges CC, Gaudichon C, Petzke KJ, Pueyo ME, Morens C, et al. Postprandial kinetics of dietary amino acids are the main determinant of their metabolism after soy or milk protein ingestion in humans. J Nutr. 2003;133(5):1308–15.
53. Fouillet H, Mariotti F, Gaudichon C, Bos C, Tomé D. Peripheral and splanchnic metabolism of dietary nitrogen are differently affected by the protein source in humans as assessed by compartmental modeling. J Nutr. 2002;132(1):125–33.
54. Kurzer MS. Hormonal effects of soy in premenopausal women and men. J Nutr. 2002;132(3): 570S–3.
55. Pino AM, Valladares LE, Palma MA, Mancilla AM, Yáñez M, Albala C. Dietary isoflavones affect sex hormone-binding globulin levels in postmenopausal women. J Clin Endocrinol Metab. 2000;85(8): 2797–800.
56. Rosenberg Zand RS, Jenkins DJ, Brown TJ, Diamandis EP. Flavonoids can block PSA production by breast and prostate cancer cell lines. Clin Chim Acta. 2002;317(1):17–26.
57. Kreider R, Kleiner S. Protein supplements for athletes: need vs convenience. Your Patient Fitness. 2000;14(6):12–8.
58. Cox G. Special needs: the vegetarian athlete. In: Burke LM, Deakin V, editors. Clinical sports nutrition. Sydney: McGraw-Hill Book; 2000. p. 656–71.
59. Venderley AM, Campbell WW. Vegetarian diets. Sports Med. 2006;36(4):293–305.
60. Nieman DC. Physical fitness and vegetarian diets: is there a relation? Am J Clin Nutr. 1999;70(3):570 s–5s.
61. Barr SI, Rideout CA. Nutritional considerations for vegetarian athletes. Nutrition. 2004;20(7):696–703.
62. Craig WJ, Mangels AR. Position of the American Dietetic Association: vegetarian diets. J Am Diet Assoc. 2009;109(7):1266–82.
63. Young VR, Pellett PL. Plant proteins in relation to human protein and amino acid nutrition. Am J Clin Nutr. 1994;59(5):1203S–12.
64. Maughan RJ. Creatine supplementation and exercise performance. Int J Sport Nutr. 1995;5(2):94–101.
65. Beelen M, Tieland M, Gijsen AP, Vandereyt H, Kies AK, Kuipers H, et al. Coingestion of carbohydrate and protein hydrolysate stimulates muscle protein synthesis during exercise in young men, with no further increase during subsequent overnight recovery. J Nutr. 2008;138(11):2198–204.
66. Wolfe RR. Effects of amino acid intake on anabolic processes. Can J Appl Physiol. 2001;26(S1):S220–7.
67. Bolster DR, Jefferson LS, Kimball SR. Regulation of protein synthesis associated with skeletal muscle hypertrophy by insulin-, amino acid-and exercise-induced signalling. Proc Nutr Soc. 2004;63(02): 351–6.
68. Hillier TA, Fryburg DA, Jahn LA, Barrett EJ. Extreme hyperinsulinemia unmasks insulin's effect to stimulate protein synthesis in the human forearm. Am J Physiol. 1998;274(6):E1067–74.
69. Kimball S, Jurasinski C, Lawrence J, Jefferson L. Insulin stimulates protein synthesis in skeletal muscle by enhancing the association of eIF-4E and eIF-4G. Am J Physiol. 1997;272(2):C754–9.
70. Biolo G, Fleming RD, Wolfe R. Physiologic hyperinsulinemia stimulates protein synthesis and enhances transport of selected amino acids in human skeletal muscle. J Clin Investig. 1995;95(2):811.
71. Biolo G, Williams BD, Fleming R, Wolfe RR. Insulin action on muscle protein kinetics and amino acid transport during recovery after resistance exercise. Diabetes. 1999;48(5):949–57.
72. Gore DC, Wolf SE, Sanford AP, Herndon DN, Wolfe RR. Extremity hyperinsulinemia stimulates muscle protein synthesis in severely injured patients. Am J Physiol. 2004;286(4):E529–34.
73. Denne SC, Liechty EA, Liu Y, Brechtel G, Baron AD. Proteolysis in skeletal muscle and whole body

in response to euglycemic hyperinsulinemia in normal adults. Am J Physiol. 1991;261(6 Pt 1): E809–14.
74. Gelfand RA, Barrett EJ. Effect of physiologic hyperinsulinemia on skeletal muscle protein synthesis and breakdown in man. J Clin Investig. 1987;80(1):1.
75. Heslin M, Newman E, Wolf R, Pisters P, Brennan M. Effect of hyperinsulinemia on whole body and skeletal muscle leucine carbon kinetics in humans. Am J Physiol. 1992;262(6):E911–8.
76. Floyd JC, Fajans SS, Pek S, Thiffault CA, Knopf RF, Conn JW. Synergistic effect of essential amino acids and glucose upon insulin secretion in man. Diabetes. 1970;19(2):109–15.
77. Floyd Jr JC, Fajans SS, Conn JW, Knopf RF, Rull J. Stimulation of insulin secretion by amino acids. J Clin Investig. 1966;45(9):1487.
78. van Loon LJ, Kruijshoop M, Verhagen H, Saris WH, Wagenmakers AJ. Ingestion of protein hydrolysate and amino acid–carbohydrate mixtures increases postexercise plasma insulin responses in men. J Nutr. 2000;130(10):2508–13.
79. van Loon LJ, Saris WH, Kruijshoop M, Wagenmakers AJ. Maximizing postexercise muscle glycogen synthesis: carbohydrate supplementation and the application of amino acid or protein hydrolysate mixtures. Am J Clin Nutr. 2000;72(1):106–11.
80. van Loon LJ, Saris WH, Verhagen H, Wagenmakers AJ. Plasma insulin responses after ingestion of different amino acid or protein mixtures with carbohydrate. Am J Clin Nutr. 2000;72(1):96–105.
81. Biolo G, Wolfe RR. Insulin action on protein metabolism. Bailliere Clin Endocrinol Metab. 1993;7(4):989–1005.
82. Miller SL, Tipton KD, Chinkes DL, Wolf SE, Wolfe RR. Independent and combined effects of amino acids and glucose after resistance exercise. Med Sci Sports Exerc. 2003;35(3):449–55.
83. Roy B, Tarnopolsky M, MacDougall J, Fowles J, Yarasheski K. Effect of glucose supplement timing on protein metabolism after resistance training. J Appl Physiol. 1997;82(6):1882–8.
84. Aragon AA, Schoenfeld BJ. Nutrient timing revisited: is there a post-exercise anabolic window. J Int Soc Sports Nutr. 2013;10(1):5.
85. Staples AW, Burd NA, West D, Currie KD, Atherton PJ, Moore DR, et al. Carbohydrate does not augment exercise-induced protein accretion versus protein alone. Med Sci Sports Exerc. 2011;43(7):1154–61.
86. Tipton KD, Phillips SM. Protein and amino acid supplements in exercise and sport. van Loon LJC, Meeusen R (eds). Dietary protein for muscle hypertrophy. Basel, Switzerland: Karger Medical and Scientific Publishers; 2013. pp. 73–84.
87. Rasmussen BB, Tipton KD, Miller SL, Wolf SE, Wolfe RR. An oral essential amino acid-carbohydrate supplement enhances muscle protein anabolism after resistance exercise. J Appl Physiol. 2000;88(2):386–92.
88. Breen L, Phillips SM. Nutrient interaction for optimal protein anabolism in resistance exercise. Curr Opin Clin Nutr Metab Care. 2012;15(3):226–32.
89. Yang Y, Breen L, Burd NA, Hector AJ, Churchward-Venne TA, Josse AR, et al. Resistance exercise enhances myofibrillar protein synthesis with graded intakes of whey protein in older men. Br J Nutr. 2012;108(10):1780–8.
90. Wilson JM, Fitschen PJ, Campbell B, Wilson GJ, Zanchi N, Taylor L, et al. International society of sports nutrition position stand: beta-hydroxy-betamethylbutyrate (HMB). J Int Soc Sports Nutr. 2013;10(1):1–14.
91. Burd NA, West DW, Moore DR, Atherton PJ, Staples AW, Prior T, et al. Enhanced amino acid sensitivity of myofibrillar protein synthesis persists for up to 24 h after resistance exercise in young men. J Nutr. 2011;141(4):568–73.
92. Andersen LL, Tufekovic G, Zebis MK, Crameri RM, Verlaan G, Kjær M, et al. The effect of resistance training combined with timed ingestion of protein on muscle fiber size and muscle strength. Metabolism. 2005;54(2):151–6.
93. Esmarck B, Andersen J, Olsen S, Richter E, Mizuno M, Kjaer M. Timing of post-exercise protein intake is important for muscle hypertrophy with resistance training in elderly humans. Scand J Med Sci Sports. 2002;12(1):60.
94. Josse AR, Tang JE, Tarnopolsky MA, Phillips SM. Body composition and strength changes in women with milk and resistance exercise. Med Sci Sports Exerc. 2010;42(6):1122–30.
95. Phillips SM, Hartman JW, Wilkinson SB. Dietary protein to support anabolism with resistance exercise in young men. J Am Coll Nutr. 2005;24(2):134S–9.
96. Poole C, Wilborn C, Taylor L, Kerksick C. The role of post-exercise nutrient administration on muscle protein synthesis and glycogen synthesis. J Sports Sci Med. 2010;9(3):354.
97. Tipton KD, Rasmussen BB, Miller SL, Wolf SE, Owens-Stovall SK, Petrini BE, et al. Timing of amino acid-carbohydrate ingestion alters anabolic response of muscle to resistance exercise. Am J Physiol. 2001;281(2):E197–206.
98. Tipton KD, Elliott TA, Cree MG, Aarsland AA, Sanford AP, Wolfe RR. Stimulation of net muscle protein synthesis by whey protein ingestion before and after exercise. Am J Physiol. 2007;292(1): E71–6.
99. Kumar V, Atherton P, Smith K, Rennie MJ. Human muscle protein synthesis and breakdown during and after exercise. J Appl Physiol. 2009;106(6): 2026–39.
100. Zawadzki K, Yaspelkis B, Ivy J. Carbohydrate-protein complex increases the rate of muscle glycogen storage after exercise. J Appl Physiol. 1992; 72(5):1854–9.
101. Greenhaff PL, Karagounis L, Peirce N, Simpson EJ, Hazell M, Layfield R, et al. Disassociation between the effects of amino acids and insulin on signaling, ubiquitin ligases, and protein turnover in human muscle. Am J Physiol. 2008;295(3):E595–604.
102. Rennie MJ, Bohé J, Smith K, Wackerhage H, Greenhaff P. Branched-chain amino acids as fuels

and anabolic signals in human muscle. J Nutr. 2006;136(1):264S–8.
103. Power O, Hallihan A, Jakeman P. Human insulinotropic response to oral ingestion of native and hydrolysed whey protein. Amino Acids. 2009;37(2):333–9.
104. Levenhagen DK, Gresham JD, Carlson MG, Maron DJ, Borel MJ, Flakoll PJ. Postexercise nutrient intake timing in humans is critical to recovery of leg glucose and protein homeostasis. Am J Physiol. 2001;280(6):E982–93.
105. Staples AW, Burd NA, West D, Currie KD, Atherton PJ, Moore DR, et al. Carbohydrate does not augment exercise-induced protein accretion versus protein alone. Med Sci Sports Exerc. 2011;43(7):1154–61.
106. Kreider RB. Effects of creatine supplementation on performance and training adaptations. Mol Cell Biochem. 2003;244(1–2):89–94.
107. Chromiak JA, Antonio J. Use of amino acids as growth hormone-releasing agents by athletes. Nutrition. 2002;18(7):657–61.
108. Kreider RB, Leutholtz BC, Greenwood M. Creatine. Wolinsky I, Driskel J (eds). Nutritional ergogenic aids. Boca Raton, FL: CRC Press; 2004. pp. 81–104.
109. Green A, Hultman E, Macdonald I, Sewell D, Greenhaff P. Carbohydrate ingestion augments skeletal muscle creatine accumulation during creatine supplementation in humans. Am J Physiol. 1996;271(5):E821–6.
110. Greenhaff P, editor. Muscle creatine loading in humans: procedures and functional and metabolic effects. 6th international conference on Guanidino compounds in biology and medicine. Cincinnati, OH; 2001.
111. Steenge G, Simpson E, Greenhaff P. Protein-and carbohydrate-induced augmentation of whole body creatine retention in humans. J Appl Physiol. 2000;89(3):1165–71.
112. Hultman E, Soderlund K, Timmons J, Cederblad G, Greenhaff P. Muscle creatine loading in men. J Appl Physiol. 1996;81(1):232–7.
113. Burke DG, Smith-Palmer T, Holt LE, Head B, Chilibeck PD. The effect of 7 days of creatine supplementation on 24-hour urinary creatine excretion. J Strength Cond Res. 2001;15(1):59–62.
114. Williams MH, Kreider RB, Branch JD. Creatine: the power supplement. Champaign: Human Kinetics; 1999.
115. Kreider RB, Ferreira M, Wilson M, Grindstaff P, Plisk S, Reinardy J, et al. Effects of creatine supplementation on body composition, strength, and sprint performance. Med Sci Sports Exerc. 1998;30:73–82.
116. Earnest CP, Snell P, Rodriguez R, Almada A, Mitchell T. The effect of creatine monohydrate ingestion on anaerobic power indices, muscular strength and body composition. Acta Physiol Scand. 1995;153(2):207.
117. Antonio J, Stout JR. Sports supplements. Philadelphia: Lippincott Williams & Wilkins; 2001.
118. Kreider RB, Klesges R, Harmon K, Grindstaff P, Ramsey L, Bullen D, et al. Effects of ingesting supplements designed to promote lean tissue accretion on body composition during resistance training. Int J Sport Nutr. 1996;6:234–46.
119. Stout J, Eckerson J, Noonan D, Moore G, Cullen D. Effects of 8 weeks of creatine supplementation on exercise performance and fat-free weight in football players during training. Nutr Res. 1999;19(2): 217–25.
120. Stout J, Eckerson J, Noonan D, Moore G, Cullen D. The effects of a supplement designed to augment creatine uptake on exercise performance and fat-free mass in football players 1429. Med Sci Sports Exerc. 1997;29(5):251.
121. Vandenberghe K, Goris M, Van Hecke P, Van Leemputte M, Vangerven L, Hespel P. Long-term creatine intake is beneficial to muscle performance during resistance training. J Appl Physiol. 1997; 83(6):2055–63.
122. Mihic S, MacDonald JR, McKenzie S, Tarnopolsky MA. Acute creatine loading increases fat-free mass, but does not affect blood pressure, plasma creatinine, or CK activity in men and women. Med Sci Sports Exerc. 2000;32(2):291–6.
123. Bessman S, Savabi F. The role of the phosphocreatine energy shuttle in exercise and muscle hypertrophy. San Diego, CA: Academic; 1988. p. 185–98.
124. Volek JS, Duncan ND, Mazzetti SA, Staron RS, Putukian M, Gomez A, et al. Performance and muscle fiber adaptations to creatine supplementation and heavy resistance training. Med Sci Sports Exerc. 1999;31:1147–56.
125. Willoughby DS, Rosene J. Effects of oral creatine and resistance training on myosin heavy chain expression. Med Sci Sports Exerc. 2001;33(10):1674–81.
126. Willoughby DS, Rosene JM. Effects of oral creatine and resistance training on myogenic regulatory factor expression. Med Sci Sports Exerc. 2003;35(6):923–9.
127. Lowe DA, Lund T, Alway SE. Hypertrophy-stimulated myogenic regulatory factor mRNA increases are attenuated in fast muscle of aged quails. Am J Physiol. 1998;275(1):C155–62.
128. Schultz E, McCormick KM. Skeletal muscle satellite cells. Rev Physiol Biochem Pharmacol. 1994;Volume 123:p. 213–57. Springer.
129. Hawke TJ. Muscle stem cells and exercise training. Exerc Sport Sci Rev. 2005;33(2):63–8.
130. Olsen S, Aagaard P, Kadi F, Tufekovic G, Verney J, Olesen JL, et al. Creatine supplementation augments the increase in satellite cell and myonuclei number in human skeletal muscle induced by strength training. J Physiol. 2006;573(2):525–34.
131. Vingren JL, Kraemer WJ, Ratamess NA, Anderson JM, Volek JS, Maresh CM. Testosterone physiology in resistance exercise and training. Sports Med. 2010;40(12):1037–53.
132. Antonio J, Stout JR. Supplements for strength-power athletes. Champaign: Human Kinetics; 2002.
133. Lukaski HC. Magnesium, zinc, and chromium nutriture and physical activity. Am J Clin Nutr. 2000;72(2):585 s–93s.

134. Shils ME, Shike M. Modern nutrition in health and disease. Philadelphia: Lippincott Williams & Wilkins; 2006.
135. Buchman AL, Keen C, Commisso J, Killip D, Ou C-N, Rognerud CL, et al. The effect of a marathon run on plasma and urine mineral and metal concentrations. J Am Coll Nutr. 1998;17(2):124–7.
136. Kikukawa A, Kobayashi A. Changes in urinary zinc and copper with strenuous physical exercise. Aviat Space Environ Med. 2002;73(10):991–5.
137. Lukaski HC. Micronutrients (magnesium, zinc, and copper): are mineral supplements needed for athletes? Int J Sport Nutr. 1995;5:S74-S.
138. Nielsen FH, Lukaski HC. Update on the relationship between magnesium and exercise. Magnes Res. 2006;19(3):180–9.
139. Brilla L, Conte V. Effects of a novel zinc-magnesium formulation on hormones and strength. J Exerc Physiol Online. 2000;3(4).
140. Koehler K, Parr M, Geyer H, Mester J, Schänzer W. Serum testosterone and urinary excretion of steroid hormone metabolites after administration of a high-dose zinc supplement. Eur J Clin Nutr. 2009;63(1):65–70.
141. Wilborn CD, Kerksick CM, Campbell BI, Taylor LW, Marcello BM, Rasmussen CJ, et al. Effects of zinc magnesium aspartate (ZMA) supplementation on training adaptations and markers of anabolism and catabolism. J Int Soc Sports Nutr. 2004;1(2): 12–20.
142. Qureshi A, Naughton DP, Petroczi A. A systematic review on the herbal extract *Tribulus terrestris* and the roots of its putative aphrodisiac and performance enhancing effect. J Diet Suppl. 2014;11(1):64–79.
143. Neychev VK, Mitev VI. The aphrodisiac herb *Tribulus terrestris* does not influence the androgen production in young men. J Ethnopharmacol. 2005; 101(1):319–23.
144. Rogerson S, Riches CJ, Jennings C, Weatherby RP, Meir RA, Marshall-Gradisnik SM. The effect of five weeks of *Tribulus terrestris* supplementation on muscle strength and body composition during preseason training in elite rugby league players. J Strength Cond Res. 2007;21(2):348–53.
145. West D, Phillips SM. Anabolic processes in human skeletal muscle: restoring the identities of growth hormone and testosterone. Phys Sports Med. 2010;38(3):97–104.
146. Ahmad AM, Hopkins MT, Thomas J, Ibrahim H, Fraser WD, Vora JP. Body composition and quality of life in adults with growth hormone deficiency; effects of low-dose growth hormone replacement. Clin Endocrinol. 2001;54(6):709–17.
147. Alba-Roth J, Müller OA, Schopohl J, Werder KV. Arginine stimulates growth hormone secretion by suppressing endogenous somatostatin secretion. J Clin Endocrinol Metab. 1988;67(6):1186–9.
148. Fernholm R, Bramnert M, Hägg E, Hilding A, Baylink DJ, Mohan S, et al. Growth hormone replacement therapy improves body composition and increases bone metabolism in elderly patients with pituitary disease. J Clin Endocrinol Metab. 2000;85(11):4104–12.
149. Merimee TJ, Rabinowitz D, Riggs L, Burgess JA, Rimoin DL, McKusick VA. Plasma growth hormone after arginine infusion: clinical experiences. N Engl J Med. 1967;276(8):434–9.
150. Thorén M, Hilding A, Baxter RC, Degerblad M, Wivall-Helleryd I-L, Hall K. Serum insulin-like growth factor I (IGF-I), IGF-binding protein-1 and-3, and the acid-labile subunit as serum markers of body composition during growth hormone (GH) therapy in adults with GH deficiency 1. J Clin Endocrinol Metab. 1997;82(1):223–8.
151. Brennan BP, Kanayama G, Hudson JI, Pope Jr HG. Human growth hormone abuse in male weightlifters. Am J Addict. 2011;20(1):9–13.
152. Schaefer A, Piquard F, Geny B, Doutreleau S, Lampert E, Mettauer B, et al. L-arginine reduces exercise-induced increase in plasma lactate and ammonia. Int J Sports Med. 2002;23(06):403–7.
153. Zajac A, Poprzecki S, Zebrowska A, Chalimoniuk M, Langfort J. Arginine and ornithine supplementation increases growth hormone and insulin-like growth factor-1 serum levels after heavy-resistance exercise in strength-trained athletes. J Strength Cond Res. 2010;24(4):1082–90.
154. Isidori A, Lo Monaco A, Cappa M. A study of growth hormone release in man after oral administration of amino acids. Curr Med Res Opin. 1981; 7(7):475–81.
155. Besset A, Bonardet A, Rondouin G, Descomps B, Passouant P. Increase in sleep related GH and Prl secretion after chronic arginine aspartate administration in man. Acta Endocrinol (Copenh). 1982;99(1):18–23.
156. Colombani P, Bitzi R, Frey-Rindova P, Frey W, Arnold M, Langhans W, et al. Chronic arginine aspartate supplementation in runners reduces total plasma amino acid level at rest and during a marathon run. Eur J Nutr. 1999;38(6):263–70.
157. Alvares TS, Conte-Junior CA, Silva JT, Paschoalin VMF. L-arginine does not improve biochemical and hormonal response in trained runners after 4 weeks of supplementation. Nutr Res. 2014;34(1):31–9.
158. Corpas E, Blackman MR, Roberson R, Scholfield D, Harman SM. Oral arginine-lysine does not increase growth hormone or insulin-like growth factor-I in old men. J Gerontol. 1993;48(4):M128-M.
159. da Silva DVT, Conte-Junior CA, Paschoalin VMF, da Silveira AT. Hormonal response to L-arginine supplementation in physically active individuals. Food Nutr Res. 2014;58.
160. Forbes SC, Harber V, Bell GJ. Oral L-arginine prior to resistance exercise blunts growth hormone in strength trained males. Int J Sport Nutr Exerc Metab. 2013;24(2):236–44.
161. Forbes SC, Harber V, Bell GJ. The acute effects of L-arginine on hormonal and metabolic responses during submaximal exercise in trained cyclists. Int J Sports Nutr Exerc Metab. 2013;23:369–77.

162. Nassar E, Mulligan C, Taylor L, Kerksick C, Galbreath M, Greenwood M, et al. Effects of a single dose of N-Acetyl-5-methoxytryptamine (Melatonin) and resistance exercise on the growth hormone/IGF-1 axis in young males and females. J Int Soc Sports Nutr. 2007;4(1):1–13.
163. Meeking D, Wallace J, Cuneo R, Forsling M, Russell-Jones D. Exercise-induced GH secretion is enhanced by the oral ingestion of melatonin in healthy adult male subjects. Eur J Endocrinol. 1999;141(1):22–6.
164. Mero AA, Vähälummukka M, Hulmi JJ, Kallio P, von Wright A. Effects of resistance exercise session after oral ingestion of melatonin on physiological and performance responses of adult men. Eur J Appl Physiol. 2006;96(6):729–39.
165. Laron Z. Somatomedin-1 (recombinant insulin-like growth factor-1). BioDrugs. 1999;11(1):55–70.
166. Laron Z. Insulin-like growth factor 1 (IGF-1): a growth hormone. Mol Pathol. 2001;54(5):311–6.
167. Spangenburg EE. IGF-I isoforms and ageing skeletal muscle: an 'unresponsive' hypertrophy agent? J Physiol. 2003;547((1):2.
168. Mero A, Kähkönen J, Nykänen T, Parviainen T, Jokinen I, Takala T, et al. IGF-I, IgA, and IgG responses to bovine colostrum supplementation during training. J Appl Physiol. 2002;93(2):732–9.
169. Mero A, Miikkulainen H, Riski J, Pakkanen R, Aalto J, Takala T. Effects of bovine colostrum supplementation on serum IGF-I, IgG, hormone, and saliva IgA during training. J Appl Physiol. 1997;83(4):1144–51.
170. Deldicque L, Louis M, Theisen D, Nielens H, Dehoux M, Thissen J-P, et al. Increased IGF mRNA in human skeletal muscle after creatine supplementation. Med Sci Sports Exerc. 2005;37(5):731–6.
171. Burke DG, Candow DG, Chilibeck PD, MacNeil LG, Roy BD, Tarnopolsky MA, et al. Effect of creatine supplementation and resistance-exercise training on muscle insulin-like growth factor in young adults. Int J Sport Nutr. 2008;18(4):389.
172. Ameri P, Giusti A, Boschetti M, Bovio M, Teti C, Leoncini G, et al. Vitamin D increases circulating IGF1 in adults: potential implication for the treatment of GH deficiency. Eur J Endocrinol. 2013;169(6):767–72.
173. Fabian C. The what, why and how of aromatase inhibitors: hormonal agents for treatment and prevention of breast cancer. Int J Clin Pract. 2007;61(12):2051–63.
174. Fryburg DA, Barrett EJ, Louard RJ, Gelfand RA. Effect of starvation on human muscle protein metabolism and its response to insulin. Am J Physiol. 1990;259(4):E477–82.
175. Curthoys NP, Watford M. Regulation of glutaminase activity and glutamine metabolism. Annu Rev Nutr. 1995;15(1):133–59.
176. Blomstrand E, Essén-Gustavsson B. Changes in amino acid concentration in plasma and type I and type II fibres during resistance exercise and recovery in human subjects. Amino Acids. 2009;37(4):629–36.
177. Gleeson M, Walsh N, Blannin A, Robson P, Cook L, Donnelly AE, et al. The effect of severe eccentric exercise-induced muscle damage on plasma elastase, glutamine and zinc concentrations. Eur J Appl Physiol Occup Physiol. 1998;77(6):543–6.
178. Street B, Byrne C, Eston R. Glutamine supplementation in recovery from eccentric exercise attenuates strength loss and muscle soreness. J Exerc Sci Fitness. 2011;9(2):116–22.
179. Jówko E, Ostaszewski P, Jank M, Sacharuk J, Zieniewicz A, Wilczak J, et al. Creatine and β-hydroxy-β-methylbutyrate (HMB) additively increase lean body mass and muscle strength during a weight-training program. Nutrition. 2001;17(7):558–66.
180. Knitter A, Panton L, Rathmacher J, Petersen A, Sharp R. Effects of β-hydroxy-β-methylbutyrate on muscle damage after a prolonged run. J Appl Physiol. 2000;89(4):1340–4.
181. Pellegrinotti I, Cesar MC, Rochelle M, Rochelle SA, Borin J, Rosa R, et al. Effect of oral glutamine supplementation on exercise performance in endurance swimmers. Pensar a Prática. 2012;15(2):317–30.
182. Ramallo B, Charro MA, Foschini D, Prestes J, Pithon-Curi T, Evangelista A, et al. ACUTE glutamine supplementation does not affect muscle damage profile after resistance training. Int J Sports Sci. 2013;3(1):4–9.
183. Nissen S, Sharp R, Ray M, Rathmacher J, Rice D, Fuller J, et al. Effect of leucine metabolite β-hydroxy-β-methylbutyrate on muscle metabolism during resistance-exercise training. J Appl Physiol. 1996;81(5):2095–104.
184. Davis G, Lowery RP, Duncan N, Sikorski E, Rathmacher J, Baier S, et al. The effects of beta-hydoxy-beta-methylbutyrate free acid supplementation on muscle damage, hormonal status, and performance following a high volume 2-week overreaching cycle. J Int Soc Sports Nutr. 2012;9 Suppl 1:4.
185. Van Someren KA, Edwards AJ, Howatson G. Supplementation with B-hydroxy-B-methylbutyrate (HMB) and a-ketoisocaproic acid (KIC) reduces signs and symptoms of exercise-induced muscle damage in man. Int J Sports Nutr Exerc Metab. 2005;15(4).
186. Lowery RP, Joy JM, Rathmacher JA, Baier SM, Fuller Jr J, Shelley M, et al. Interaction of beta-hydroxy-beta-methylbutyrate free acid (HMB-FA) and adenosine triphosphate (ATP) on muscle mass, strength, and power in resistance trained individuals. J Strength Cond Res. 2014.
187. Dunsmore K, Lowery RP, Duncan N, Davis G, Rathmacher J, Baier S, et al. Effects of 12 weeks of beta-hydroxy-beta-methylbutyrate free acid Gel supplementation on muscle mass, strength, and

power in resistance trained individuals. J Int Soc Sports Nutr. 2012;9 Suppl 1:5.
188. Lowery RP, Joy J, Rathmacher JA, Baier SM, Fuller JC, Jäger R, et al. Effects of 12 weeks of beta-hydroxy-beta-methylbutyrate free acid, adenosine triphosphate, or a combination on muscle mass, strength, and power in resistance trained individuals. J Int Soc Sports Nutr. 2013;10 Suppl 1:17.
189. Stamler JS, Meissner G. Physiology of nitric oxide in skeletal muscle. Physiol Rev. 2001;81(1):209–37.
190. KINGWELL BA. Nitric oxide-mediated metabolic regulation during exercise: effects of training in health and cardiovascular disease. FASEB J. 2000; 14(12):1685–96.
191. Moncada S, Higgs E, Hodson H, Knowles R, López-Jaramillo P, McCall T, et al. The L-arginine: nitric oxide pathway. J Cardiovasc Pharmacol. 1991;17:S1.
192. Campbell B, Roberts M, Kerksick C, Wilborn C, Marcello B, Taylor L, et al. Pharmacokinetics, safety, and effects on exercise performance of L-arginine α-ketoglutarate in trained adult men. Nutrition. 2006;22(9):872–81.
193. Reid J, Skelton G, Clark M, Boucher A, Willoughby DS. Effects of 7 days of arginine-alpha-ketoglutarate supplementation using NO2 Platinum on brachial artery blood flow and the levels of plasma L-arginine, nitric oxide, and eNOS after resistance exercise. J Int Soc Sports Nutr. 2010;7 Suppl 1:22.
194. Álvares TS, Conte Jr CA, Paschoalin VMF, Silva JT, Meirelles CM, Bhambhani YN, 1, et al. Acute l-arginine supplementation increases muscle blood volume but not strength performance. Appl Physiol Nutr Metab. 2012;37(1):115–26.
195. Willoughby DS, Boucher T, Reid J, Skelton G, Clark M. Effects of 7 days of arginine-alpha-ketoglutarate supplementation on blood flow, plasma L-arginine, nitric oxide metabolites, and asymmetric dimethyl arginine after resistance exercise. Int J Sports Nutr Exerc Metab. 2011;21(4):291.
196. Sureda A, Córdova A, Ferrer MD, Pérez G, Tur JA, Pons A. L-citrulline-malate influence over branched chain amino acid utilization during exercise. Eur J Appl Physiol. 2010;110(2):341–51.
197. Schwedhelm E, Maas R, Freese R, Jung D, Lukacs Z, Jambrecina A, et al. Pharmacokinetic and pharmacodynamic properties of oral L-citrulline and L-arginine: impact on nitric oxide metabolism. Br J Clin Pharmacol. 2008;65(1):51–9.
198. Ochiai M, Hayashi T, Morita M, Ina K, Maeda M, Watanabe F, et al. Short-term effects of l-citrulline supplementation on arterial stiffness in middle-aged men. Int J Cardiol. 2012;155(2):257–61.
199. Hecker M, Sessa WC, Harris HJ, Anggård E, Vane JR. The metabolism of L-arginine and its significance for the biosynthesis of endothelium-derived relaxing factor: cultured endothelial cells recycle L-citrulline to L-arginine. Proc Natl Acad Sci USA. 1990;87(21):8612–6.
200. Takeda K, Machida M, Kohara A, Omi N, Takemasa T. Effects of citrulline supplementation on fatigue and exercise performance in mice. J Nutr Sci Vitaminol. 2011;57(3):246–50.

Weight Loss Nutritional Supplements

8

Joan M. Eckerson

Abstract

Obesity is a major public health concern in the United States and is related to a considerable number of chronic diseases including hypertension, type 2 diabetes, stroke, heart disease, degenerative joint disease, and several types of cancer. Because of the medical implications and health-care costs associated with obesity, as well as the negative social and psychological impacts, many individuals turn to nonprescription nutritional weight loss supplements hoping for a quick fix, and the weight loss industry has responded by offering a variety of products that generates billions of dollars each year in sales.

Most nutritional weight loss supplements are purported to work by increasing energy expenditure, modulating carbohydrate or fat metabolism, increasing satiety, or blocking fat or carbohydrate absorption. To review the literally hundreds of nutritional weight loss supplements available on the market today is well beyond the scope of this chapter. Therefore, several of the most commonly used supplements were selected for critical review, and practical recommendations are provided based upon the findings of well-controlled, randomized clinical trials that examined their efficacy.

In the majority of cases, the nutritional supplements reviewed either elicited no clinically meaningful effect (i.e., ≥5 % change in body weight) or resulted in changes in body weight and composition that are similar to that which occurs through a restricted diet and exercise program. There is evidence to suggest that herbal forms of ephedrine, such as ma huang, combined with caffeine or caffeine and aspirin (i.e., ECA stack) are effective for inducing moderate weight loss in overweight adults. However, because of the ban on ephedra, it is not practical to recommend it for

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weight loss, and ephedra-free supplements, such as bitter orange, do not appear to be as effective. Green bean coffee extract, capsaicinoids, and white kidney bean extract (*Phaseolus vulgaris*) do appear to hold some promise as possible adjuvant treatments for weight loss; however, most dietary weight loss supplements used alone or in combination are largely ineffective.

Keywords

Dietary supplements • Ephedra • Obesity • Overweight • Complementary medicine • Alternative medicine • Herbal medicine • Chromium • Calcium • Chitosan • Pyruvate • Garcinia • Psyllium • *Citrus aurantium* • Bitter orange • Guarana • Herbal caffeine • Green tea • Conjugated linoleic acid • Capsaicinoid • Green coffee bean extract • *Phaseolus vulgaris* • Glucomannan

8.1 Introduction

Obesity is a major public health concern in the United States and is related to a considerable number of chronic diseases including hypertension, type 2 diabetes, stroke, heart disease, degenerative joint disease, and several types of cancer [1]. According to data from the 2011 to 2012 National Health and Nutrition Examination Survey released by the Centers for Disease Control, 68.5 % of adults in the United States were overweight or obese, 34.9 % were obese (BMI $\geq$ 30 kg·m^2), and 6.4 % were extremely obese (grade 3 obesity = BMI $\geq$ 40 kg·m^2). Because of the medical implications and healthcare costs associated with obesity, as well as the negative social and psychological impacts, many individuals turn to nonprescription nutritional weight loss supplements hoping for a quick fix or the answer to their unsuccessful attempts at dieting and exercise to lose weight. In fact, it has been suggested that many individuals prefer dietary supplements and prescription weight loss drugs to making healthier lifestyle changes [2].

The weight loss industry has responded to the rising rates of obesity and generates billions of dollars each year through the sale of a variety of products and commercial weight loss businesses. In 2014, Americans spent over $60 billion on books, exercise videos, low-calorie foods and drinks, sugar substitutes, medical treatments, commercial weight loss centers, bariatric surgery, and nutritional supplements to assist in their battle to lose weight [3]. Retail sales of over-the-counter (OTC) nutritional weight loss supplements alone were estimated to be more than $1.45 billion in 2013 [3].

Given that obesity is a growing public health concern and that the use of OTC nutritional weight loss supplements by obese and overweight individuals is commonplace, it is important for health professionals to understand the physiological mechanisms by which these products are purported to result in weight loss, as well as their safety and efficacy. Most OTC weight loss supplements are claimed to work by increasing energy expenditure, modulating carbohydrate or fat metabolism, increasing satiety (feeling of fullness), or blocking fat or carbohydrate absorption.

8.2 Nutritional Supplements that Increase Energy Expenditure

8.2.1 Ephedra Alkaloids and Herbal Caffeine

Ephedra, also known as *ma huang*, is probably one of the most commonly recognized nutritional supplements used for weight loss and was widely

used in the 1990s. Because of several safety concerns including hypertension, arrhythmias, heart attack, stroke, and even death, the Food and Drug Administration (FDA) removed ephedra products from the US market in 2004, since its risk of use was deemed greater than its benefits on weight loss. Ephedra is derived from a shrub that is native to China (*Ephedra sinica*) and has been used for over 5,000 years as a natural treatment for asthma and other conditions [4]. The ephedrine alkaloids present in the plant contain sympathomimetic compounds (i.e., central nervous system (CNS) stimulants) and are a source of ephedrine and pseudoephedrine, which are used in many decongestants and cold medicines. The history of ephedrine as a weight loss supplement goes back to 1972 when a Danish physician in Elsinore, Denmark, who was treating his asthmatic patients with a compound that contained ephedrine and caffeine noticed that they were experiencing unintentional weight loss. His compound became known as the "Elsinore Pill," and, by 1977, it was being used by over 70,000 patients [5]. Before they were taken off the market in 2004, dietary supplements that contained ephedrine alkaloids were regulated by the DSHEA; however, ephedrine and pseudoephedrine are regulated by the government as drugs.

Ephedrine and norephedrine are analogs of methamphetamine and amphetamine, respectively, and, therefore, are potent CNS stimulants that act as both alpha- and beta-adrenergic agonists and release epinephrine from sympathetic neurons [6]. The action of ephedra on adrenergic receptors increases thermogenesis and suppresses hunger which, in turn, promotes weight loss [7]. In animal studies, it has been shown that ephedrine stimulates thermogenesis in brown adipose tissue via the activation of beta-receptors; however, because humans have very little brown adipose, it is believed that thermogenesis primarily occurs in the skeletal muscle [4].

A meta-analysis by Shekelle et al. [8] that examined the efficacy and safety of ephedra- and ephedrine-containing products found that they have modest short-term benefits (up to 6 months) and are associated with an increased risk of experiencing an adverse event. The findings of the meta-analysis showed that ephedra resulted in weight loss that was only 0.9 kg (~2 lb) more per month compared to placebo, but led to a 2.2–3.6 fold increase in the odds of experiencing psychiatric, autonomic, or gastrointestinal problems, as well as arrhythmias of the heart.

In an effort to maximize fat burning, ephedrine has been used in combination with caffeine and aspirin, which is often referred to as an ECA stack. It is believed that when these three compounds are taken together (recommended ratio: 60 mg ephedrine/200 mg caffeine/300 mg aspirin), it results in an even greater thermogenic effect compared to ephedra alone and may be more effective for inducing weight loss [9, 10]. Herbal equivalents that are often used as a substitute for caffeine in nutritional weight loss supplements include guarana, kola nut, yerba mate, green tea, and yohimbe. Similarly, willow bark is often used in place of aspirin. Hydroxycut™ is an example of a well-known OTC product that contained an ECA stack (ma huang, guarana, and willow bark) prior to the FDA ban in 2004. Interestingly, Hydroxycut™ has been reformulated at least twice since that time and, in 2009, recalled several of their products as a result of an FDA warning to consumers to stop using their products after they received 23 reports of serious liver-related health issues [11].

There is some evidence to suggest that the combination of ephedra with caffeine and/or aspirin (or their herbal constituents) may, indeed, be more effective for inducing weight loss than ephedra alone. In his extensive review, Greenway [5] examined the safety and efficacy of ephedrine and caffeine (EC) and reported that the combination was as effective as some prescription weight loss drugs and was associated with fewer side effects. In the studies reviewed by Greenway [5], the acute side effects for EC were considered mild and transient, and following continuous treatment for 4–12 weeks, the reported side effects were not significantly different from placebo. As a result, Greenway [5] suggested that the benefits of EC outweigh the associated risks and pointed out that many of the serious adverse events that have been reported in the literature are voluntary case reports that have no placebo (PL)

or control (CTRL) groups for comparison. Therefore, in his opinion [5], the argument for removing herbal products containing ephedrine was somewhat unfounded. Hutchins [12] also indicated that many of the ephedra alkaloid-related deaths reported in the literature occurred in individuals with preexisting cardiovascular conditions or risks, and, therefore, the dangers associated with ephedra use in healthy individuals may be widely speculative. In addition, Dulloo [13] suggested that mixtures of ephedrine and caffeine may offer a viable and cost-effective approach to the treatment of obesity and has recommended that more large-scale clinical trials be conducted to gain a better understanding of the risks and benefits associated with the combination of ephedrine and caffeine.

In two separate studies, Boozer et al. [4, 14] also reported that ma huang (herbal ephedra) combined with either guarana [4] or kola nuts [14] was more effective for weight loss in overweight men and women compared to PL and resulted in no adverse events and minimal side effects. In the study that examined the effects of ma huang and guarana [4], the treatment was a commercial herbal mixture called Metabolife-356®, which contained an equivalent of 72 mg of ephedrine and 240 mg of caffeine. Following 8 weeks of supplementation, the treatment group lost significantly more body weight (−4.0 ± 3.4 kg) and percent body fat (−2.1 ± 3.0 % fat) vs. the PL group (−0.8 ± 2.4 kg and 0.2 ± 2.3 % fat, respectively). In the other study by Boozer et al. [14] that examined the effects of ma huang and kola nut on weight loss, the herbal preparation was equivalent to 90 mg of ephedrine and 192 mg of caffeine and, when compared to PL, resulted in significant decreases in body weight (−5.3 ± 5.0 vs. −2.6 ± 3.2 kg) and fat weight (−4.3 ± 3.3 vs. −2.7 ± 2.8 kg). In both studies [4, 14], the herbal preparations also resulted in significant improvements in the blood lipid profiles of the subjects. Kalman and Minsch [15] also showed that supplementation of an ECA stack (20 mg ephedrine + 200 mg caffeine + 325 mg aspirin) for 6 weeks in overweight men resulted in weight loss that was significantly greater when compared to PL (4.17 kg vs. 0.68 kg, respectively). In agreement, Daly et al. [16] also reported that an ECA combination (75–150 mg ephedrine + 150 mg caffeine + 330 mg aspirin) resulted in modest sustained weight loss (2.2–5.2 kg) in 24 obese individuals compared to PL and reported that the doses were well-tolerated and had no meaningful effects on heart rate, blood pressure, insulin and glucose concentrations, or cholesterol levels.

In a more recent study, Liu et al. [17] examined the effect of leptin, EC, and the combination of the three on visceral fat mass and weight loss in obese men and women (BMI = 30–40 $kg \cdot m^2$) between the ages of 18 and 60 years. Subjects were randomized to one of three groups and received either 200 mg of caffeine + 20 mg ephedrine three times per day ($n = 17$), 20 mg of leptin A-200 administered subcutaneously (recombinant methionyl human Fc-leptin molecule, Amgen®) once per day, and two PL pills twice per day ($n = 26$) or a combination of the leptin A-200 and EC in the doses described above ($n = 18$) for 24 weeks. At baseline, subjects were provided with a walking program (goal: 30 min 5 × week) and a calorie-restricted diet that was 1,200 kcal for women and 1,500 kcal for men; however, compliance data for the exercise and diet were not collected over the course of the study. Body fat was assessed at baseline, 12 weeks, and 24 weeks by dual x-ray absorptiometry (DEXA), and abdominal visceral fat mass was obtained via computed tomography. The results showed that the groups that received the EC and the combination of leptin with EC lost significant ($p < 0.05$) amounts of weight (−5.9 ± 1.2 % and −6.5 ± 1.1 %, respectively) and whole body fat mass (−4.3 ± 0.9 kg and −4.9 ± 0.9 kg, respectively) compared to the leptin only group (−1.8 ± 0.9 % and −0.6 ± 0.8 kg for change in body weight and body fat, respectively). Only treatment with the leptin in combination with EC resulted in a significant reduction in visceral fat mass (−11.0 ± 3.3 %). The authors [17] concluded that EC was a moderately effective weight loss agent and that leptin A-200 did not have any synergistic effect compared to EC alone.

In contrast to the studies described above, Vukovich et al. [18] reported that acute administration (3 h) of herbal ephedrine and caffeine at

doses of 20 mg and 150 mg, respectively, significantly increased heart rate (22.7 ± 5.5 %), systolic blood pressure (9.1 ± 2.2 %), and resting energy expenditure (REE) (8.5 ± 2.0 %) compared to baseline values. Although the authors [18] did not directly examine the effects of the herbal mixture on body weight, they suggested that the increase in REE would be negligible in terms of weight loss.

Based upon the majority of the findings in the literature, it appears that herbal ephedrine (ma huang) combined with caffeine or with caffeine and aspirin is effective for inducing moderate weight loss in overweight adults that are otherwise healthy and have no preexisting cardiovascular or cerebrovascular conditions. Because of safety concerns, and considering that many individuals might be unaware of underlying conditions that may predispose them to an increased risk from herbal preparations that mimic both caffeine and ephedra, consultation with a physician prior to their use may be warranted as a precaution. It is also important to note that ephedra and ephedra alkaloids are on the World Anti-Doping Agency Prohibited List and urine concentrations >10 $\mu g \cdot ml^{-1}$ would lead to disqualification in most sanctioned sports.

8.2.2 Bitter Orange (*Citrus aurantium*)

The ban of ephedra by the FDA in 2004 led to the proliferation of a number of "ephedra-free" dietary supplements. Many of these products contained bitter orange, which is also known as *Citrus aurantium*, Zhi shi, Seville orange, or sour orange, and refers to a small citrus tree (*C. aurantium*) and its peel and fruit [19]. The active components in bitter orange are synephrine and octopamine, which are structurally similar to epinephrine and norepinephrine, respectively. Therefore, these compounds are also chemically related to ephedrine and are believed to affect alpha-receptors and beta-3 receptors, but not beta-1 or beta-2 receptors. Because synephrine does not affect beta-1 and beta-2 receptors, it is reportedly less active on the CNS than ephedrine and is theorized to have fewer adverse effects [19].

There is some confusion within the literature regarding the action of synephrine. For example, as mentioned above, Fugh-Berman and Myers [19] have reported that synephrine (and octopamine) activates beta-3 adrenoreceptors, and not beta-1 or beta-2 receptors, which act to stimulate the heart (beta-1 and beta-2) and result in systemic vasodilation (beta-2). However, Bent et al. [20] and Penzak et al. [21] reported that the extracts contained in bitter orange primarily stimulate alpha-1 adrenergic receptors because they resemble phenylephrine (a selective alpha receptor agonist commonly used as a nasal decongestant that is also known as neosynephrine) and would result in vasoconstriction and increased blood pressure.

It appears that much of the confusion lies in the fact that there are several isomers of synephrine including para (p)-synephrine, meta (m)-synephrine, and ortho-synephrine and that it is not exactly known which of these isomers or combination of isomers are present in nutritional weight loss supplement products. In addition, there is some confusion as to which synephrine alkaloids are actually present in bitter orange itself [22]. This information is critical to know, since these various isoforms exhibit different pharmacological properties. The differences in the studies [19–21] mentioned above regarding the exact mechanism of action of bitter orange is related to the different synephrine isoforms that each author suggests is contained in the extract. For example, Penzak et al. [21] and Bent et al. [20] state that it contains m-synephrine (i.e., phenylephrine), whereas Fugh-Berman and Myers [16] specifically state that m-synephrine (phenylephrine) is *not* present in *C. aurantium* and that its most active component is p-synephrine. Blumenthal [7] has also stated that the type of synephrine in bitter orange peel is p-synephrine and has been incorrectly characterized as m-synephrine by various authors. However, in their technical report of the constituents of bitter orange, Allison et al. [22] stated that they were unable to find any convincing data that bitter orange solely contains m-synephrine or p-synephrine.

Considering for a moment that bitter orange contains only p-synephrine and, therefore,

selectively activates beta-3 receptors, it seems reasonable to suggest that this isoform would be able to induce weight loss with fewer side effects than other CNS stimulants, including m-synephrine. However, because of their selective activation of beta-3 receptors, these compounds may actually be ineffective in humans. Animal studies using fat cells from rats, hamsters, and dogs have shown that beta-3 agonists, such as synephrine and octopamine, have potent lipolytic effects; however, they are weak stimulators in human fat cells [19]. Human adipocytes respond to activation of beta-1 or beta-2 receptors and have very little expression for beta-3 receptors. Therefore, it requires very high concentrations of synephrine (0.1–1 mM) to stimulate fat cells in humans [23].

As indicated by Allison et al. [22], it is likely the case that most weight loss products containing bitter orange contain both p- and m-synephrines. In their technical report, Allison et al. [22] analyzed a weight loss supplement called Ultimate Thermogenic Fuel™, which stated on the label that it contained m-synephrine from bitter orange, and the authors did, indeed, find that the product contained both the p- and m- isoforms. Therefore, if bitter orange only contains p-synephrine, then the manufacturers of these weight loss products are either adding synthetic m-synephrine or are including other CNS stimulants [22]. As evidence of this, one only needs to read the label on commonly used OTC weight loss supplements to see that most do, in fact, include several CNS stimulants as a proprietary blend to boost the thermogenic effect. For example, in addition to bitter orange, many products also include ingredients such as caffeine, green coffee bean extract, green tea, yerba mate, and yohimbe bark extract, which are all purported to have an effect on weight loss. Bitter orange extract alone in pill form is also available OTC; however, it appears that no studies have examined the effect of bitter orange alone on weight loss.

In one of the first clinical studies to investigate the effect of bitter orange on weight loss, Colker et al. [24] examined the effect of an herbal mixture that contained 975 mg of *C. aurantium* extract (6 % synephrine alkaloid), 900 mg of St. John's wort (3 % hypericum), and 528 mg of caffeine on body fat in 20 overweight (BMI > 25 kg/m^2), but otherwise, healthy adults. The subjects were randomly placed into a CTRL group ($n=4$), a PL group that ingested maltodextrin ($n=7$), or the active treatment group ($n=9$) and, if applicable, ingested their respective supplement once daily for 6 weeks. All subjects participated in a circuit training exercise program 3 × week^{-1} for 45 min per session and received individual counseling from a registered dietitian to comply with an 1,800 kcal·day^{-1} diet recommended by the American Heart Association.

The change in body weight from baseline to 6 weeks for the group taking the *C. aurantium* was 1.4 kg compared to 0.9 kg in the PL group and 0.4 kg in the CTRL group, and the change in body fat and percent fat (via bioelectrical impedance analysis (BIA)) for each of the three groups was −3.1 kg/−2.9 %,–0.63 kg / 0.8 %, and −1.8 kg/−2.2 %, respectively. The loss in body fat and percent fat was significantly greater in the *C. aurantium* group compared to both the PL and CTRL groups; however, there were no significant differences between groups for body weight, basal metabolic rate, blood pressure, HR, or EKG measurements.

Based upon the findings, the authors [24] suggested that the combination of *C. aurantium* with St. John's wort and caffeine was safe and effective when combined with a diet and exercise program for inducing weight loss and fat loss in healthy, overweight adults. These results should be interpreted with caution, however, because the change in percent body fat (−2.9 %) over the 6-week supplementation period was less than the error that is typically associated with BIA (~3–5 %), and this technique is not typically regarded as a criterion measure of body composition [25].

In another early study by Armstrong et al. [26], the authors examined the effect of an herbal weight loss preparation containing ma huang, bitter orange, guarana, white willow bark extract, and ginger root on REE, blood chemistries (blood lipids and glucose), and body composition (measured via DEXA) in 20 obese men ($n=5$) and women ($n=15$). Subjects randomly received the supplement ($n=12$) or a PL ($n=8$) for 6 weeks

and also participated in an aerobic exercise program 3 days·wk^{-1}. The only significant ($p<0.05$) difference was for fat mass with the supplement group demonstrating a 2.57 kg loss, which is equivalent to approximately 1.2 lb, compared to a 0.49 kg loss in the PL group.

In 2006, Sale et al. [27] examined the acute effects of a commercially available supplement containing bitter orange, green tea, and guarana on metabolism and substrate utilization during rest and during treadmill walking in 10 overweight males (>20 % fat). To gather resting data, the subjects ingested the supplement and laid supine for 7 h. Baseline measurements were taken during the first hour, and expired gases, blood pressure, HR, and a venous blood sample were measured every 30 min for the remaining 6 h. During the exercise arm of the study [27], the subjects ingested the supplement or a PL and at 1 h post-ingestion exercised on a treadmill for 1 h at 60 % of their estimated HR reserve. Venous blood was analyzed for nonesterified fatty acids (NEFA), glycerol, glucose, and lactate, and expired gases were used to calculate energy (ATP) production and substrate utilization from carbohydrate and NEFA for both the resting and exercise conditions.

The results showed that there was no significant effect of the supplement on total ATP utilization during 6 h of rest or during 60 min of treadmill walking. However, there was a shift in ATP production and substrate utilization in both phases of the study, which demonstrated an increase in ATP production from carbohydrate and a decrease in NEFA, as well as an increase in carbohydrate oxidation. In fact, the increase in carbohydrate oxidation at rest was shown to be as high as 30 %. Although many weight loss supplements are typically promoted to increase fat utilization, these findings suggest that a combination of bitter orange, green tea, and guarana stimulated carbohydrate use and actually *decreased* ATP production from fat. One positive finding from the study [27] was that the formula had no effect on resting HR or blood pressure (both SBP and DBP).

In a related study, Zenk et al. [28] also reported that a commercial weight loss product called the Lean System 7 (iSatori Global Technologies, Inc), which contained bitter orange, guarana, dehydroepiandrosterone (DHEA), and yerba mate among its seven ingredients, had no effect on HR or blood pressure (SBP and DBP) following 8 weeks of supplementation in 47 overweight adults who were also following a low-calorie diet and exercise program. Zenk et al. [28] also reported that this product, which was recently discontinued by the manufacturer, had no effect on BMI, body weight, fat weight, or fat-free weight compared to PL, even though the resting metabolic rate was significantly ($p=0.03$) increased in the treatment group (7.2 ± 1.6 kcal·day^{-1}).

In a more recent study, Lopez et al. [29] examined the safety and effectiveness of a multi-ingredient weight loss product as an adjunct to an 8-week diet and exercise program on body composition (DEXA) and blood chemistries (including blood lipids, glucose, and leptin) in 45 obese men and women. Subjects randomly received a PL ($n=18$) or a supplement that contained bitter orange, raspberry ketone, caffeine, capsaicin (cayenne pepper extract), garlic, and ginger ($n=27$) daily for 8 weeks. At the end of the 8-week intervention, the results showed that the supplement was significantly ($p<0.05$) more effective than PL for inducing positive changes in body weight (−1.9 kg vs. −0.4 kg), fat mass (−2.9 kg vs. −0.9 kg), lean mass (+1.8 kg vs. +0.4 kg), and waist (−2.1 cm vs. −0.3 cm) and hip circumference (−1.9 cm vs. −0.4 cm). There were no significant differences in blood pressure or blood chemistries between the two groups nor were there any serious adverse events reported, which suggests that the supplement was relatively safe. Although the supplement did appear to significantly augment the effects of the diet and exercise program, the magnitude of the changes in body composition was less than robust when you consider that this was an obese population with an average BMI ≥ 30 kg·m^2.

Based upon the available research, it does not appear that bitter orange is effective for weight loss when used in combination with a variety of other ingredients, including other CNS stimulants. Although the studies reviewed above would appear to suggest that products containing bitter

orange are relatively safe and do not result in adverse effects on blood pressure, it is important to note that the subjects used in these studies were normotensive. Many individuals who are overweight or obese are also hypertensive; therefore, safety studies utilizing hypertensive populations are warranted. In addition, there appear to be no studies that have examined the effect of bitter orange-containing products on more serious endpoint conditions such as myocardial infarction or stroke [30]. Because questions still remain regarding the safety of bitter orange and the weight loss induced through supplementation is marginal at best, it is difficult to recommend with confidence. In addition, individuals with preexisting cardiac problems and/or hypertension should proceed with caution before using weight loss supplements containing bitter orange, since it is most commonly used in herbal mixtures that contain several other CNS stimulants.

8.2.3 Green Tea and Caffeine

Next to water, tea is the most widely consumed beverage in the world. Black, green, and oolong tea are all derived from the *Camellia sinensis* plant, which contains a class of polyphenols known as catechins [31]. Catechins, particularly those found in green tea, have been shown to exert positive effects on energy expenditure (i.e., thermogenesis) and fat oxidation, and, therefore, consumption of green tea or green tea extracts may be beneficial for weight loss [32]. The process by which green tea is produced (heat treatment shortly after harvest) results in less oxidation and, as a result, preserves the highest concentration of catechins, which include epigallocatechin gallate (EGCG), epigallocatechin, and epicatechin gallate [32]. Green tea also contains caffeine; therefore, the two active ingredients in green tea believed to potentially induce weight loss are caffeine and catechins, particularly EGCG.

A recent study by Wang et al. [31] examined the effects of catechin-enriched green tea on body composition in 182 moderately overweight Chinese subjects (BMI range = 26.8–27.2 $kg \cdot m^2$). Using a randomized, placebo-controlled design, the subjects were placed into one of four groups and received either (1) two servings of a CTRL drink (total = 30 mg catechins/10 mg caffeine; $n = 43$), (2) one serving of the CTRL drink and one serving of high-catechin green tea (total = 458 mg catechins/104 mg caffeine, GT1; $n = 47$), (3) two servings of high-catechin green tea (total = 468 mg catechins/126 mg caffeine, GT2; $n = 49$), or (4) two servings of an extra high-catechin green tea (total = 886 mg catechins/198 mg caffeine, GT3; $n = 43$) twice per day for 90 days. Whole body fat and intra-abdominal fat were measured using DEXA, and a tape measure was used to measure waist and hip circumferences at baseline, 30, 60, and 90 days. There were no differences between groups at baseline or over the course of the study for reported energy intakes and macronutrient composition. At 90 days, there was a significant ($p < 0.05$) decrease in body weight (−1.2 kg), waist circumference (−1.9 cm), and intra-abdominal fat (−5.6 cm^2) in the GT3 group compared to the CTRL group (+0.1 kg, −0.2 cm, and −1.1 cm^2, respectively). Based upon these findings, the authors [31] concluded that consuming two servings of green tea containing 500–900 mg of catechins and moderate amounts of caffeine (<200 mg) for 3 months results in positive effects on body composition and reduces intra-abdominal fat in moderately overweight Chinese subjects.

Two recent meta-analyses [32, 33] also suggest that the catechins and caffeine in green tea result in small, but positive effects on body composition and BMI. Hursel et al. [32] conducted a systematic review and meta-analysis of long-term studies (≥12 weeks) that examined the effect of EGCG on weight loss and weight maintenance and included potential moderators such as regular caffeine intake and ethnicity to determine if those factors influence the effect of EGCG + caffeine on body weight. Eleven of forty-nine studies identified met the inclusion criteria for the meta-analysis. The results showed a moderate, but significant ($p < 0.001$) positive effect of catechins on both weight loss and weight maintenance. It was estimated that individuals in the treatment groups lost 1.31 kg more weight (~0.6 lb) compared to the CTRL groups. When the effects of habitual caffeine use and ethnicity were taken into account, the results showed that

individuals who consumed caffeine in quantities >300 mg experienced less of an effect on weight loss (−0.27 kg) compared to low caffeine users (−1.61 kg). In addition, Caucasians experienced a smaller effect (−0.82 kg) compared with Asians (−1.51 kg). However, none of these differences reached statistical significance. Based upon the findings, the authors [32] suggested that a catechin/caffeine mixture had positive effects on weight loss and that ethnicity and habitual caffeine use may moderate their effects.

In a related study, Phlung et al. [33] performed a systematic review and meta-analysis to determine the effect of catechins with or without caffeine on anthropometric variables including BMI, body weight, waist circumference, and waist-to-hip ratio. Of 341 citations retrieved through their search strategy, 15 trials ($n = 1{,}243$) met the inclusion criteria and were included in the meta-analysis. The results showed that catechins + caffeine decreased BMI (−0.55 $kg \cdot m^2$), body weight (−1.38 kg), and waist circumference (−1.93 cm), but had no effect on waist-to-hip ratio compared to caffeine alone. In addition, catechin + caffeine ingestion resulted in a significant decrease in body weight (−0.44 kg) compared with a caffeine-free CTRL. However, there was no effect of catechins alone on any parameter when compared to caffeine-free CTRL, suggesting that catechin ingestion alone is ineffective for weight loss.

Although these studies [31–33] indicate that catechins work synergistically with caffeine to elicit significant reductions in body weight, BMI, and waist circumference, the magnitude of the changes is modest at best and is not clinically relevant. There do not appear to be any adverse side effects associated with green tea consumption, and, although it has modest effects on weight loss, there is evidence that green tea has antioxidant components that benefit health and has been shown to improve cholesterol profiles, decrease platelet aggregation, and lower blood pressure [10].

8.2.4 Caffeine

Caffeine (1,3,7-trimethylxanthine) is an active ingredient in coffee, which is another one of the most common beverages consumed worldwide, but caffeine is also found in many other foods and beverages including dark chocolate, soda, and sports and energy drinks. Caffeine has been widely studied for its potential thermogenic effects and has been shown to increase REE and reduce energy intake; however, these acute effects have not resulted in meaningful long-term weight loss [34, 35]. Caffeine is usually studied in combination with other thermogenic ingredients for their effects on weight loss versus its effects alone; however, one 12-year longitudinal study [36] showed that men and women who increased their caffeine consumption (143–213 mg) experienced slightly smaller weight gain (2.79–3.22 kg) compared to individuals who decreased their caffeine intake (3.87–4.28 kg) over the 12-year period. A lack of sensitivity to caffeine as a result of increased tolerance may explain, in part, why it is ineffective for weight loss over time [34, 35].

8.2.5 Capsaicin

Capsaicinoids are chemicals in plants that give foods and spice their pungency and are found in chili peppers, tobasco sauce versus tobacco, and mustard. Capsaicin and dihydrocapsaicin account for approximately 90 % of capsaicinoids present in nature and have been shown to increase REE and fat oxidation, most likely by stimulating the sympathetic nervous system or via increased secretion of catecholamines [37]. Capsaicin binds to the same receptors (nociceptors) that lead to the sensation of pain from heat and acid, which explains why eating chili peppers produces a strong sensation of heat [38]. In fact, chili peppers are so spicy that many people cannot eat them or can only eat them in small quantities. Another independent group of compounds that are structurally similar to capsaicin are capsinoids and are found in a non-pungent cultivar of the red chili pepper called the "CH-19 Sweet" pepper [37–39]. Because of their different structure, they stimulate receptors in the intestines versus nociceptors in the mouth [39]. Capsaicin, chili peppers, and the CH-19 Sweet have all been studied for their effect on weight loss.

Whiting et al. [38] recently performed a systematic review of the literature to determine the

potential benefits of capsaicinoids and capsinoids on weight loss and weight management. Of 90 trials identified, 20 met their inclusion criteria ($n = 563$). Three main areas of potential benefit for weight management were identified including increased energy expenditure, increased fat oxidation, and decreased appetite. The interventions in the studies reviewed included capsaicinoid-rich red pepper, CH-19 Sweet pepper, capsaicin supplements, dihydrocapsiate supplements, and cayenne peppers. It was observed that regular consumption of capsaicinoids significantly decreased intra-abdominal fat and decreased appetite and energy intake. The review of the literature also determined that the consumption of capsaicinoids increased REE by approximately 50 kcal·day^{-1}, which would result in clinically significant weight loss in 1–2 years. Based upon the findings [38], it was suggested that capsaicinoids could play a positive role in weight management programs.

In a recent clinical trial, Clegg et al. [40] also reported that chili pepper combined with medium-chain triglycerides (MCT) increased diet-induced thermogenesis by over 50 %, which they suggested could induce clinically significant weight loss over time. In their study [40], seven healthy volunteers were tested on four occasions after an overnight fast and were randomly fed a breakfast (egg omelet with tomato, mushroom, sausage, and bacon, toast and orange juice) containing (1) chili and MCT oil, (2) chili and sunflower oil, (3) bell pepper and sunflower oil, or (4) bell pepper and MCT oil. The chili mix consisted of a cayenne and habanero pepper blend containing 2,000 ppm capsaicin that was added to the omelet. Resting energy expenditure, diet-induced thermogenesis, and fat oxidation were measured for 6 h following each breakfast condition. There were no statistically significant differences between conditions for satiety or gastrointestinal discomfort ratings or fat oxidation, and all four breakfasts resulted in an increase in REE. However, the combined effect of the chili-MCT oil combination had a cumulative effect to increase thermogenesis by 51 % compared to the other conditions.

Based upon the available evidence, it appears that capsaicinoids and capsinoids found in chili peppers and other pungent foods and spices are effective for increasing REE, which could lead to clinically significant weight loss over time. The most commonly reported doses used in clinical trials appears to be 30 mg for red chili pepper, 135 mg for capsaicin supplements, 3–12 mg for capsinoids, and up to 1 g·kg^{-1} body weight for CH-19 Sweet pepper [38]. However, questions remain regarding the ability of capsaicinoids and capsinoids to result in significant amounts of weight loss over time, since few long-term studies (>12 weeks) using human subjects have been conducted to date.

8.2.6 Pyruvate

Pyruvate (PYR) is a three-carbon compound synthesized in the body via glycolysis and has been studied for its effects on weight loss since the late 1970s when Stanko et al. [41] found that PYR, and a related three-carbon compound known as dihydroxyacetone (DHA), reduced the development of fatty livers in rats fed with ethanol. Follow-up studies performed by the same research group [42, 43] using rat and pig models also showed that PYR and DHA supplementation resulted in increased energy expenditure and fat reduction, possibly through the result of increased thermogenesis. Stanko et al. [44, 45] have also reported significant effects of PYR and DHA on weight loss in humans. In one study [45] that examined the effect of PYR (19 g·day^{-1}) and DHA (12 g·day^{-1}) supplementation for 3 weeks in 21 obese women ingesting a low-calorie diet, it was found that the combination of PYR-DHA resulted in significantly greater losses in body weight (6.5 kg) and fat weight (4.3 kg) compared to PL (5.6 kg and 3.5 kg, respectively), which represented a difference of ~ 2 lb between groups. In a related study, Stanko et al. [44] also found that, when obese women who first lost weight on a low-calorie diet were subsequently placed on a high-calorie diet with PYR, they regained weight at a significantly ($p < 0.05$) slower rate compared to a high-calorie diet without PYR. Based upon these findings, it was concluded that PYR and PYR-DHA when combined with a low-calorie

diet results in greater weight loss vs. calorie restriction alone [45] and attenuates weight gain during hypercaloric conditions [44].

Although many of the studies conducted by Stanko and colleagues [44–47] resulted in positive findings, it is important to note that he owns several patents [42] for PYR-DHA, and while many researchers use patents as a means to protect their intellectual property, it may be considered by some to represent a conflict of interest. In addition, the dosages recommended in the patients were large (i.e., 22–44 g·day^{-1}) representing up to 20 % of daily energy intake and were ingested concurrently with a low-calorie diet [44, 46]. To gain a better understanding of the efficacy of PYR on weight loss without caloric restriction, Kalman et al. [48] determined the effect of low-dose PYR on body composition in 51 overweight (BMI > 25 kg·m^2) men and women consuming a 2,000 kcal·day^{-1} diet.

In their study [48], the subjects randomly received weight loss product that contained PYR (6 g·day^{-1}) and DHA (50 mg·day^{-1}) ($n = 18$) or a PL (6 g·day^{-1} maltodextrin; $n = 18$) for 6 weeks, and another 15 subjects served as a CTRL group. Subjects in the PYR and PL groups met with a registered dietitian every 2 weeks and received counseling to follow a 2,000 kcal·day^{-1} diet (50 % carbohydrate, 20 % protein, and 30 % fat), and all subjects completed a circuit training protocol three times a week for ~45 min at 60 % of their predicted maximal HR. Body composition was tested at baseline and every 2 weeks, thereafter, using BIA. There were no significant differences between the three groups at baseline, and, at the end of the 6-week period, the results showed that none of the groups experienced a significant change in body weight. However, PYR resulted in a significant decrease in fat weight (−2.1 kg) and percent fat (−2.6 %), as well as a significant increase in fat-free weight (1.5 kg). There were no significant differences in fat weight and fat-free weight from baseline to 6 weeks for the PL and CTRL groups, and it is unknown if any of the differences in body composition were significantly different between groups, since it does not appear that a statistical analysis was performed to determine between group differences after baseline. The authors [49] stated that 6 g·day^{-1} PYR supplementation for 6 weeks results in modest decreases in fat weight and a concomitant increase in fat-free weight when performed in conjunction with exercise. These results should be interpreted with caution, however, since body composition was not assessed using a criterion method, and it appears that incomplete statistical analyses were performed.

Kalman et al. [50] performed a similar study to examine the effects of exercise (45–60 min; 3 × week) and 6 g·day^{-1} PYR for 6 weeks on body composition in 26 overweight men and women compared to PL. The results of this study [50] showed that PYR resulted in a statistically significant ($p < 0.001$) decrease in body weight (1.2 kg), fat weight (−2.5 kg), and percent fat (−3.0 %), whereas the PL group experienced no changes over the 6-week supplementation and training period.

In contrast to the findings of Kalman et al. [48, 50], Koh-Banerjee et al. [51] examined the effect of PYR during training on body composition and reported no significant effects compared to PL. In this study [51], 23 untrained women were assigned to receive either 10 g·day^{-1} of PYR or a PL for 30 days while participating in a supervised exercise program. Prior to and following supplementation, body weight, fat weight, and percent fat were assessed using underwater weighing, which is a commonly accepted criterion method for assessing body composition. Although the PYR group gained less weight (PYR = 0.3 ± 0.3 kg; PL = 1.2 ± 0.3 kg), lost more fat weight (PYR = −0.4 ± 0.5 kg; PL = 1.1 ± 0.5 kg), and lost a greater percentage of body fat (PYR = −0.65 ± 0.6 %; PL = 0.1 ± 0.5 %), the results were not statistically significant ($p = 0.16$) when compared to PL. These findings [51] are in agreement with Stone et al. [52] who also reported that PYR supplementation (~9 g·day^{-1}) for 5 weeks had no significant effect on body composition or training adaptations in college football players.

Onakpoya et al. [53] recently performed a systematic review and meta-analysis of randomized clinical trials to examine the efficacy of PYR for reducing body weight. Only 9 trials were

identified as potentially relevant and, of those, six met the inclusion criteria for analysis, but all six were reported to have methodological weaknesses. The results of the meta-analysis showed that PYR did result in a small, but statistically significant difference in body weight compared to PL (mean difference = −0.72 kg). Adverse events reported in the various studies included gas, bloating, diarrhea, and an increase in LDL cholesterol. The decrease in body weight was clinically insignificant and suggests that PYR is ineffective for reducing body weight.

Although many studies have shown that PYR, both with and without DHA, results in positive effects on body weight and body composition [44–48, 50], the majority of these studies were performed in the same laboratory, and supplementation occurred in conjunction with extremely low-calorie diets [43–46]. In contrast, the results of other well-controlled studies in which subjects maintained their normal diet [51, 52] showed no effect of PYR when compared to PL. In addition, considering that the subjects used in the majority of the studies that showed positive results were overweight or obese, the weight loss induced by PYR was what may be considered modest at best. Based upon the available evidence, PYR cannot be recommended with confidence as a treatment for weight loss.

8.3 Supplements that Modify Carbohydrate and Fat Metabolism

8.3.1 Green Coffee Bean Extract

Green coffee bean extract (GCBE) has been gaining popularity as potential weight loss supplement and is being used in many OTC formulations and can also be purchased separately as a stand-alone supplement. Green coffee beans are beans that have not been roasted and contain high amounts of both caffeine and the phenolic compound, chlorogenic acid (CGA). The roasting process destroys most of the CGA; however, roasted coffee beans do contain small amounts, with daily intake ranging from 0.5 to 1.0 $g \cdot day^{-1}$ in coffee drinkers [54]. Chlorogenic acid is also naturally occurring in plums, apples, and berries [55].

The CGA in GCBE is largely responsible for its pharmacological effects, and its mechanism of action related to weight loss may be due to its ability to modulate glucose metabolism by inhibiting hepatic glucose-6-phosphatase, a rate-limiting enzyme in gluconeogenesis, inhibiting fat accumulation, and/or altering adipokine levels and fat distribution [56, 57]. Shimoda et al. [57] showed that GCBE administered to mice for 2 weeks reduced visceral fat accumulation and body weight gain compared to caffeine or CGA alone. The authors [57] conducted additional experiments to determine the effect of GCBE and CGA on the liver and serum triglyceride levels, as well as the antiobesity effect of GCBE on dietary fat absorption using mice loaded with olive oil. The results of these experiments suggested that the caffeine in GCBE suppressed fat absorption, while the CGA reduced hepatic triglyceride content and serum triglyceride levels, and, therefore, the two constituents work synergistically. In a related study, Cho et al. [58] also reported that CGA improved body weight, fat metabolism, and obesity-related hormone concentrations (leptin, insulin) in mice fed with a high-fat diet.

Studies examining the effect of GCBE on body composition in human subjects have also showed promising results. Thom [59] conducted two separate clinical trials to examine the effect of GCA-rich coffee on glucose absorption in healthy subjects ($n = 12$, BMI < 25 $kg \cdot m^2$) and also determined its effects on weight loss when added to the regular diet of overweight and obese subjects for 12 weeks ($n = 30$, BMI 27.5–32.0 $kg \cdot m^2$). The test coffee product used for both studies was Coffee Slender® (Med-Eq Ltd., Tonsberg, Norway), which is enriched with 200 mg of CGA from GCBE, and Nescafe® Gold Norwegian instant caffeinated and decaffeinated coffee blends were used as comparative products. For the glucose absorption study, subjects received each of the three beverages using a randomized, double-blind, crossover design with a 1-week washout between trials. Following an overnight fast, each subject first completed a 2 h glucose tolerance test

upon arrival to the laboratory to serve as a CTRL. Subjects then randomly received one of the three test beverages, and blood glucose was then monitored at regular intervals for 2 h following consumption (15, 30, 45, 60, 90, and 120 min). The results showed that the area under the curve for plasma glucose was significantly lower for the Coffee Slender® trial (724 ± 8 mmol·L·min^{-1}) compared with the control (glucose tolerance test; 778 ± 10 mmol·L·min^{-1}), which represented a 6.9 % reduction. There were no significant effects observed between the CTRL and both caffeinated (788 ± 10 mmol·L·min^{-1}) and decaffeinated (818 ± 11 mmol·L·min^{-1}) Nescafe® blends.

In the second study [59], 30 volunteers were randomly placed into one of two groups and received Coffee Slender® ($n = 15$) or the Nescafe® Norwegian instant caffeinated coffee blend ($n = 15$). Each group was asked to consume 5 c black coffee per day (equivalent to 11 g) for 12 weeks. Body weight and percent body fat (via BIA) were measured at baseline, 4 weeks, and 12 week. The results showed that, following the 12 weeks intervention, subjects in the Coffee Slender® group experienced significant ($p < 0.05$) decreases in body weight (-5.4 ± 0.6 kg) and percent fat (-3.6 ± 0.3 %) compared to the group that received caffeinated coffee (-1.7 ± 0.6 kg and -0.7 ± 0.4 %, respectively).

In another recent study, Vinson et al. [60] conducted a 22-week crossover study to examine the efficacy of a commercially available GCBE product containing CGA on weight loss in 16 overweight adults (8 men, 8 women; mean BMI ± SD $= 28.22 \pm 0.91$ kg·m^2). The subjects randomly received high-dose CGA (1,050 mg), low-dose CGA (700 mg), or a PL in three separate 6-week treatment periods each followed with a 2-week washout. Subjects were measured at baseline, 6, 8, 14, 16, and 22 weeks to assess body weight, body fat (via BIA), blood pressure, and HR. The results showed that the GCBE product resulted in significant reductions in body weight (-8.4 ± 2.31 kg), percent body fat (-4.44 ± 2.00 %), and HR (-2.56 ± 2.85 bmin-1) for two-thirds of the 22-week study, with no reported changes in blood pressure. Although GCBE was shown to induce significant decreases in body weight and had no adverse effects on heart rate and blood pressure, the study [60] has several methodological weaknesses, and, therefore, the results should be interpreted with some caution.

Onakpoya et al. [54] also recently completed a systematic review and meta-analysis to examine the effectiveness of GCBE on weight loss using human trials. Only three of five eligible trials were included in the analyses, but the results showed a significant mean difference in body weight of −2.47 kg in GCBE-treated groups compared with placebo.

Based upon the available evidence, it appears that GCBE with CGA may hold some promise for reducing body weight. However, more rigorous, long-term clinical trials are necessary to gain a better understanding of the efficacy and safety of GCBE as a weight loss supplement.

8.3.2 Chromium Picolinate

Chromium is an essential trace mineral that enhances insulin activity and, therefore, is involved in carbohydrate, protein, and fat metabolism. Dietary weight loss supplements typically contain chromium in the form of chromium picolinate (CrP), an organic compound of trivalent chromium and picolinate, which is a derivative of tryptophan [61, 62]. Because CrP facilitates the action of insulin, it is believed to decrease body fat, increase lean mass, and increase basal metabolism [61, 62]. However, most studies that have examined the effect of CrP on body weight and lean mass using humans have not shown many positive effects.

Pittler et al. [62] conducted a meta-analysis of 10 randomized clinical trials that examined the effect of CrP on body weight reduction, and the results showed that body weight decreased 1.1–1.2 kg (−0.08 to −0.2 kg·wk^{-1}) compared to PL during an intervention period ranging from 6 to 14 weeks, with daily dosages ranging from 188 to 924 ug. In addition, no adverse events were reported in the studies that also examined the potential adverse side effects of chromium supplementation [62].

Lukaski et al. [61] examined the effect of CrP on body weight and body composition (fat weight

and fat-free weight) via DEXA in 83 women (age range = 19–50 years) with a BMI range of 18–30 kg·m^2. The subjects in the treatment group (n = 27) ingested an equivalent of 200 ug of CrP for 12 weeks, and the other subjects either randomly received picolinic acid (1,720 ug; n = 27) or PL (n = 29). All subjects were counseled by a registered dietitian and maintained a 2,000 kcal diet (51 % carbohydrate, 18 % protein, and 31 % fat) to control for chromium intake during the 12-week study.

The results showed that body weight (−1.0 kg (PL) to −1.3 kg (CrP)) and fat weight (−1.1 kg (CrP) to −1.4 kg (PL)) significantly decreased over the 12-week intervention; however, there were no significant differences between the three groups, which indicates that the calorie restriction, not CrP, was responsible for the weight loss. There were no significant effects across time for any of the groups for fat-free weight or bone mineral density determined from DEXA. These findings support those of Pittler et al. [62] and suggest that CrP is a safe, but ineffective dietary weight loss supplement.

A more recent randomized, double-blind, placebo-controlled trial performed by Yazaki et al. [63] also reported that supplementation with 1,000 μg of CrP alone or in combination with a nutrition education program for 24 weeks had no effect on weight loss in a population of 80 overweight and obese adults. Supplementation with CrP also had no effect on blood chemistries, including serum lipid, glucose, and insulin concentrations. Given the findings of the study by Yazaki et al. [63], as well as the studies described above, CrP appears to be an ineffective weight loss supplement for humans and, therefore, is not recommended.

8.3.3 Chitosan (Chitin)

Chitosan is a positively charged polysaccharide that is a polymer of glucosamine and is derived from the shells of crustaceans (i.e., crabs, shrimp, and lobster) [22, 64]. It is purported to block fat absorption, and, although there is some data using animals [65, 66] to suggest that it might be an effective weight loss supplement, there is little support for its use in humans.

In their review article, Pittler and Ernst [64] performed a meta-analysis on five randomized clinical trials that examined the effect of chitosan on body weight in obese and overweight individuals and reported that in three of the five studies, chitosan had no significant effect on body weight compared to a PL. The dosages used in the studies ranged from 0.48 g·day^{-1} to 3.1 g·day^{-1} and were 4–12 weeks in duration; however, in the study that used the lowest dose, chitosan was also combined with *Garcinia cambogia* (1.1 g·day^{-1}), which is also commonly used in many dietary weight loss supplements. When examining the other four studies that used chitosan only, three resulted in no significant findings. All five studies used in the meta-analysis reported minor adverse gastrointestinal effects following chitosan supplementation including constipation, flatulence, bloating, nausea, and heartburn [64].

In another review and meta-analysis, Jull et al. [67] examined the effect of chitosan as a treatment for weight loss. Fifteen studies that ranged in duration from 4 to 24 weeks (n = 1,219) met the inclusion criteria. Results of the data analysis showed that chitosan resulted in significantly greater weight loss (−1.7 kg) and also lowered total cholesterol (−0.2 mmol·L^{-1}) compared to PL. Although, the results were statistically significant, the weight loss (<1.0 lb) has little clinical significance.

As previously mentioned, chitosan is a positively charged polymer of glucosamine that is believed to block, or "trap," the absorption of fat by binding with negatively charged fat molecules in the lumen of the intestine [68]. If malabsorption of fat does result from products containing chitosan, then it would be expected that there would be an increase in fecal fat excretion. To test this hypothesis, Gades and Stern [69] quantified the fecal fat content in subjects who supplemented with an OTC product called Absorbitol® (Natrol Inc, Chatsworth, CA). Fifteen males (26.3 ± 5.9 years; BMI = 25.6 ± 2.3 kg·m^2) consumed five meals per day containing 15 g fat (total 75 g·day^{-1}) for 12 days. The first 4 days served as a CTRL period, followed by a 4-day

supplementation period in which the subjects received 4.5 g·day^{-1} of chitosan, and then the subjects were placed back onto the CTRL diet for another 4 days. All fecal matter on days 2–12 was collected to be analyzed for fat content.

The results showed that chitosan supplementation significantly ($p=0.02$) increased fecal fat excretion by 1.1 ± 1.8 g·day^{-1} (from 6.1 ± 1.2 to 7.2 ± 1.8 g·day^{-1}), which the authors [69] considered clinically negligible and stated that the product would have no meaningful effect on energy balance or weight loss. Given these findings [69], as well as those of Pittler and Ernst [64] and Jull et al. [67], chitosan does not appear to be effective for reducing body weight in humans and is associated with gastrointestinal discomfort, including constipation, flatulence, and bloating.

8.3.4 Garcinia Cambogia (Hydroxycitric Acid)

Garcinia cambogia, also known as brindleberry, is a tropical tree native to India that bears yellowish, pumpkin-shaped fruit. Both the natural fruit and rind contain hydroxycitric acid (HCA), which has been shown to decrease fat synthesis (lipogenesis), spare carbohydrate, suppress food intake, and attenuate body weight gain [70]. The extract of *G. cambogia* is a component of many dietary supplements including Citrimax™ and Citrilean™. Most of these products claim that when ingested 30 min prior to a meal, they suppress appetite and block carbohydrate absorption.

In general, the results for HCA as a dietary weight loss supplement for humans are not promising. In their article that examined the effect of HCA as a potential antiobesity agent, Heymsfield et al. [70] reviewed seven other studies that had examined the effect of HCA alone or in combination with other ingredients on body weight and fat weight in overweight humans including two peer-reviewed articles, four abstracts, and one open-label study from an industrial publication. Of the seven studies reviewed, five reported significant ($p<0.05$) effects of HCA alone or in combination with another weight loss agent on weight loss and fat loss and one study that failed to include statistics reported that subjects who ingested HCA + chromium for 8 weeks lost ~ 7 more pounds versus subjects on PL (HCA = 11.14 lb vs. 4.20 lb for PL). However, Heymsfield et al. [70] noted that in five of the studies, HCA was taken in combination with other active ingredients that could also potentially result in weight loss (i.e., CrP, L-carnitine, chitosan, and herbal forms of caffeine); therefore, the studies offered little insight into the specific weight loss effects of HCA. Other limitations included a lack of a PL group or double blinding in one study and the use of near-infrared interactance to assess body composition in another, which is considered by many to be an invalid method for measuring body composition [70].

To gain a better understanding of the effect of HCA alone on body composition, as well as overcome some of the limitations previously reported in the literature, Heymsfield et al. [70] conducted their own 12-week double-blind placebo-controlled study using overweight subjects (age range = 18–65 years; BMI range ≥ 27–38 kg·m^2) who were either randomized to receive 1,500 mg·day^{-1} HCA ($n=42$; 3 × 500 mg·day^{-1} 30 min prior to meals) or a PL ($n=42$). Body weight and fat weight (via DEXA) were assessed at baseline and 12 weeks, and all subjects were provided with 5,040 kJ/day diet plan (i.e., ~1,200 kcal) with 50, 30, and 20 % as carbohydrate, protein, and fat, respectively.

The results showed that subjects in both groups lost a significant amount of weight over the 12 weeks; however, there was no significant difference between the two groups (PL = −4.1 ± 3.9 kg vs. HCA = −3.2 ± 3.3 kg, $p=0.14$). In addition, there was no significant difference in percent body fat lost between the HCA and PL groups (−2.16 ± 2.06 % vs. −1.44 ± 2.15 %, respectively). Based upon these results, HCA was no more effective than PL for reducing body weight and fat weight in overweight individuals.

Kovacs et al. [71] also found that supplementation with 500 mg·day^{-1} of HCA alone or in combination with MCT for 2 weeks did not result in increased satiety, fat oxidation, 24 h REE, or body weight loss (−1.0 kg for PL to −1.5 kg for HCA alone) compared to PL in 11 overweight

male subjects (BMI = 27.4 ± 8.2 kg·m^2). However, in a follow-up study that was also 2 weeks in duration, but used a larger dose, investigators from this same laboratory [72] reported that HCA (900 mg·day^{-1}) reduced energy intake by 15–30 %, but did not result in any significant changes in satiety or body weight. The authors [72] suggested that HCA may not serve as a weight loss agent, but could be effective for preventing weight regain in overweight individuals, since it resulted in a reduced energy intake.

In another related study, Kriketos et al. [73] examined the effect of HCA on fat oxidation and the metabolic rate in 10 sedentary men (age range = 22–38 years; BMI range = 22.4–37.6 kg·m^2) using a double-blind, crossover design. The subjects visited the laboratory on four separate occasions to examine the effects of HCA (3.0 g·day^{-1} × 3 days) and a PL on metabolic parameters both with and without moderately intense exercise (30 min at 40 % VO_2 max followed by 15 min at 60 % VO_2 max). The results showed that HCA had no effect on the respiratory exchange ratio or energy expenditure at rest or during exercise, indicating that it had no effect on fat oxidation. Although their study did not directly examine the effect of HCA on body weight loss, the authors [73] commented that the lack of metabolic changes suggests that HCA would be ineffective for inducing weight loss in individuals consuming a typical mixed diet. In agreement, van Loon et al. [74] also reported that acute HCA supplementation (18 g·day^{-1}) had no significant effects on total carbohydrate and fat oxidation in 10 trained cyclists at rest or during submaximal exercise.

Although the results of several early studies (as reported by Heymsfield [70]) suggested that HCA in combination with other ingredients, including CrP and herbal caffeine, enhanced weight loss, more rigorous well-controlled studies that used HCA alone suggest that it is not an effective dietary weight loss supplement compared to PL. In support of this, a recent systematic review conducted by Marquez et al. [75] that evaluated the safety and efficacy of HCA or *Garcinia cambogia* extracts in humans also cautioned against their effectiveness for decreasing body weight, but did indicate that the dosages used in the studies reviewed (55–2,400 mg·day^{-1}) did not result in adverse effects or toxicity compared to PL.

8.3.5 Conjugated Linoleic Acid

Conjugated linoleic acid (CLA) is a collective term used to describe a group of positional and geometric conjugated (i.e., alternating single and double bonds) isomers of linoleic acid (a fatty acid (FA)) that are naturally found in animal fat, dairy, and partially hydrogenated vegetable oils [76, 77] and is also sold commercially as a dietary weight loss supplement. Most CLA products sold OTC have a 40 %:40 % content of *cis*-9,*trans*-11 (c9t11) and *trans*-10,*cis*-12 (t10c12) FA, while the remaining 20 % is typically composed of other conjugated FA (~1–4 %) and other nonconjugated FA (~15–19 %). The c9t11 CLA isomer accounts for 85–90 % of the total natural CLA content in the diet, whereas dietary intake of the t10c12 isomer is negligible [78]. When these two CLA isomers are combined in approximately equal amounts, several animal studies have shown strong evidence that they have anticarcinogenic and antiatherogenic effects, as well as positive effects on body composition and blood lipid profiles [76, 77, 79, 80]. The mechanisms of action which may explain how CLA promotes weight loss are not well understood, but it has been theorized that CLA may elicit positive effects on body composition by (1) inhibiting hormone-sensitive lipoprotein lipase which, in turn, inhibits lipogenesis (fat synthesis); (2) promoting adipocyte apoptosis (programmed cell death); (3) preventing triglyceride (TG) accumulation in adipocytes; (4) downregulating the expression of leptin; and (5) modulating glucose and fat metabolism to increase energy expenditure [81]. As previously mentioned, it is well-documented that CLA elicits very favorable effects on body composition and lipid profiles in animals; however, the effect of CLA on body weight and body composition in humans has resulted in conflicting findings.

Tricon and Yaqoob [77] reviewed 18 studies that examined the effect of body weight and body

composition using human subjects and found that the results were much less promising than those found for animal studies using mice and pigs. The amount used in the studies reviewed ranged from 0.7 g·day^{-1} to 6.8 g·day^{-1}, the majority of which contained a 1:1 mixture of c9t11 and t10c12 CLA isomers. Of the 18 studies, four demonstrated modest reductions in fat weight, two studies were deemed inconsistent because a dose-response relationship was not found, and the remaining 12 studies showed no effect of CLA on body composition [77]. Although four studies reviewed by Tricon and Yaqoob [77] did show positive results for CLA on body composition, upon closer examination, some of the findings are less than dramatic. For example, Riserus et al. [82] examined the effect of 4.2 g·day^{-1} CLA for 4 weeks on abdominal fat and cardiovascular risk factors in 25 obese men with syndrome-X type symptoms (i.e., abdominal obesity, hypertension, dyslipidemia, impaired fasting glucose) and reported a significant ($p=0.04$) decrease in sagittal abdominal diameter compared to PL. However, the change was less than 1 cm (−0.57 cm), and there were no significant differences between groups for body weight, waist circumference, waist-to-hip ratio, or blood lipid concentrations (cholesterol, HDL, LDL, and TG) following supplementation.

In agreement, Larsen et al. [83] reported that CLA had no effect on body weight, body fat, or lean mass in a systematic review of the literature that included 13 studies that ranged from 4 to 24 weeks in duration and dosages ranging from 0.7 to 9.8 g·day^{-1}. Conversely, in another meta-analysis conducted 4 years later by Whigham [84], the authors reviewed 18 randomized clinical trials and reported that CLA in a dose of 3.2 g· day^{-1} resulted in a modest loss in body fat (−0.09 ± 0.08 kg·wk^{-1}) compared to placebo ($p<0.001$). In a more recent systematic review and meta-analysis of randomized clinical trials conducted by Onakpoya et al. [85], the authors reported that CLA resulted in significantly greater reductions in body weight (mean difference: −0.70 kg) and fat weight (−1.33 kg) compared to PL. The authors [85] noted that the magnitude of these effects was small and also reported that several adverse events were reported including soft stools, constipation, and diarrhea.

In a long-term independent clinical trial showing positive results, Gaullier et al. [81] reported that supplementation with two different isomers of CLA for 1 year reduced body fat in overweight (BMI range = 25–30 kg·m^2), but otherwise healthy adult men and women ($n=180$). In their study [81], subjects ingested TG-CLA ($n=60$; 4.5 g·day^{-1}), FA-CLA ($n=61$; 4.5 g·day^{-1}), or a PL ($n=59$; 4.5 g·day^{-1} olive oil). After 1 year of supplementation, both CLA groups demonstrated significant decreases in body weight (ΔFA-CLA = −1.1 ± 3.7 kg; ΔTG-CLA = −1.8 ± 3.4 kg) compared to PL (Δ 0.2 ± 3.0 kg), which only represents an approximate weight loss of 2.4–4.0 lb over the entire year or 0.20–0.33 lb per month. The fact that the standard deviation was greater than the mean change value for each group also suggests that there may have been considerable variation in body weight exhibited by the subjects during the 1-year period, with some likely demonstrating notable increases.

In contrast to the findings of Gaullier et al. [81], Tricon et al. [80] used a crossover design to examine the effect of three different doses of high-grade c9t11 (0.59 g·day^{-1}, 1.19 g·day^{-1}, or 2.38 g·day^{-1}) and t10c12 CLA (0.63 g·day^{-1}, 1.26 g·day^{-1}, or 2.52 g·day^{-1}) for three consecutive 8-week periods separated by a 6-week washout period. The results showed that there was no significant effect of either isomer on body weight, BMI, or body composition (via skinfolds and BIA) at any dose. In agreement, Malpeuch-Brugere et al. [76] also reported no effect of high-grade c9t11 or t10c12 CLA supplementation at dosages of 1.5 g·day^{-1} or 3.0 g·day^{-1} administered in a dairy drink for 18 weeks on body weight or body composition (via DEXA) in 81 overweight men.

Although animal studies have provided strong evidence to indicate that CLA has positive effects on body composition, its potential as an anti-obesity treatment for humans is much less promising. Brown and McIntosh [79] have suggested that the conflicting findings in human research may be due, in part, to the fact that the mechanism of action of CLA is isomer specific and that the dosages used in human trials are much less than those used in animal studies. Research from

their own laboratory [79] has shown that the t10c12 CLA isomer decreases human adipocyte TG content and differentiation, whereas the c9t11 isomer increases TG accumulation and adipocyte-specific gene expression in human fat cells. In a related study, Tricon et al. [80] showed that these same two CLA isomers also had opposing effects on blood lipid profiles in healthy adults, with t10c12 resulting in increases in LDL/HDL cholesterol and total/HDL cholesterol, while c9t11 resulted in a decrease in these ratios. Given that the c9t11 and t10c12 CLA isomers appear to have opposite effects on adiposity, Brown and McIntosh [79] speculated that the inconclusive findings in human studies could be due to the use of mixed isomers for supplementation, which may negate each other and, thus, result in no significant change in body fat. Although future studies are warranted to examine the effect of isomer-specific doses of CLA on body composition, there is no conclusive evidence to date to suggest that supplementation with either a mixture of CLA isomers or single CLA isomers results in any meaningful effects on body composition in humans.

8.3.6 Calcium

Calcium is typically known for its role in maintaining bone density and bone mineral homeostasis. However, there is some evidence to suggest that calcium may also play a role in adipocyte lipid kinetics to help decrease body fat. The potential of calcium to induce weight loss was first reported in the late 1980s when Metz et al. [86] showed a reduction in fat weight in hypertensive rats that were ingesting high amounts of calcium and sodium, and Bursey et al. [87] found that increasing dietary calcium from 0.1 to 2.0 % resulted in less weight gain in both lean and obese Zucker rats. Interestingly, it wasn't until 1999 with the publication of two abstracts [88, 89] that more research began to focus upon this unexpected relationship between calcium and body fat.

The exact mechanism of action by which calcium exerts its effect on body weight is not entirely clear; however, Zemel et al. [90] have proposed that low dietary calcium intake stimulates dihydroxy vitamin D and parathyroid hormone (PTH) which, in turn, simulates the uptake of calcium into adipocytes. This influx of intracellular calcium results in an increase in lipogenesis (i.e., fat synthesis) and a decrease in lipolysis (i.e., fat breakdown), and the net result is an increase in body fat. In contrast, a high dietary intake of calcium has the opposite effect and inhibits vitamin D and PTH, which decreases the uptake of calcium into the adipocytes and, in turn, increases lipolysis and decreases lipogenesis resulting in weight loss [90].

The discovery of an apparent inverse relationship between dietary calcium intake and body weight has led to several original investigations, as well as the reevaluation of previously published data, to examine the efficacy of both dietary and supplemental calcium on body composition. For example, Davies et al. [91] re-analyzed five clinical trials that included 780 women between their third and eighth decade of life and found that in each of the five studies, the calcium/protein ratio negatively predicted BMI and/or change in body weight. In contrast, Shapses et al. [92] combined data from three separate 25-week randomized, double-blind placebo-controlled trials to re-examine the effect of 1,000 mg·day^{-1} calcium supplementation (calcium citrate) on body weight and fat weight in pre- and postmenopausal women (total $n = 100$) and found no significant differences for calcium versus PL and no significant interaction of calcium supplementation on menopausal status. The results from several original investigations [49, 93–96] designed to specifically examine the effect of calcium on body composition have also resulted in conflicting findings.

Zemel et al. [96] placed 32 obese subjects (18–60 years; BMI = 30.0–39.9 kg·m^2) on a calorie-restricted diet (500 kcal·day^{-1} deficit) for 24 weeks and randomized them to a standard diet (400–500 mg dietary calcium per day supplemented with PL), a high-calcium diet (standard diet with 800 mg·day^{-1} calcium carbonate), or a high-dairy diet (1,200–1,300 mg·day^{-1} dietary calcium in the form of dairy products supplemented with PL). The results showed that all subjects lost body weight as a result of caloric restriction; however, those assigned to the high-

calcium (supplemental) and high-dairy diet lost 8.58 ± 1.1 kg and 11.07 ± 1.63 kg of body weight, respectively, which was greater than the loss demonstrated by the subjects in the standard diet (−6.60 ± 2.58 kg). A similar trend also occurred for fat weight with the high-calcium and high-dairy groups experiencing greater losses (−5.61 ± 0.98 kg and −7.16 ± 1.22 kg, respectively) compared to the standard diet (−4.81 ± 1.22 kg), with a significant portion of the fat loss in each group occurring in the trunk region. Although the sample size in the study by Zemel et al. [96] was relatively small, their findings indicate that calcium significantly augments weight loss secondary to calorie restriction and that dairy products have a greater effect than supplemental forms of calcium. Based upon these results, as well as their finding that calcium regulates lipogenesis and lipolysis within the adipocyte [90], Zemel and colleagues submitted a patent for treating obesity with calcium [97].

In contrast to the findings of Zemel et al. [96] several clinical trials using a larger number of subjects [49, 93–95] have failed to find a significant relationship between calcium intake and body composition. Gunther et al. [49] determined the effect of long-term (1 year) supplementation with dairy calcium using 135 healthy, normal weight women (age range = 18–30 years) as subjects and found no significant changes in body weight or fat weight between groups that consumed a CTRL diet (<800 mg·day^{-1}), a moderate dairy diet (1,000–1,100 mg·day^{-1}), or a high-dairy diet (1,300–1,400 mg·day^{-1}). In agreement, Haub et al. [95] also showed that a calcium-fortified beverage (1,125 mg·day^{-1}) supplemented over 1 year had no effect on body weight, fat weight, or abdominal fat in 37 postmenopausal women (age range = 48–75 years) even though supplementation more than doubled the calcium/protein ratio. Barr et al. [93] also showed that three servings per day of milk had no effect on weight loss or other metabolic risk factors in older adults, and, in a 1-year study using 178 preschool children (ages 3–5 years), DeJongh et al. [94] reported that there were no significant correlations between percent body fat and fat mass changes and dietary calcium intake and no significant differences between calcium-supplemented groups (1,000 mg·day^{-1}) vs. PL.

The results of several systematic reviews and meta-analyses [98–100] also suggest that calcium supplementation has small and clinically insignificant effects on body weight and body fat. In a review of 13 randomized controlled trials, Trowman et al. [100] found no statistically significant association between the consumption of either calcium supplements or dairy products on body weight and concluded that it was ineffective for weight loss. In their systematic review of 49 randomized trials, Lanou and Barnard [98] reported that 41 showed no effect, two resulted in weight gain, one showed a lower rate of weight gain, and only five resulted in weight loss. In a more recent review, Onakpoya et al. [99] reported that a meta-analysis of seven randomized clinical trials showed that calcium resulted in a small, but significant ($p < 0.05$) reduction in body weight and body fat compared to PL (mean difference: −0.74 kg and −0.93 kg, respectively); however, they questioned the clinical relevance of the results.

There is an overwhelming amount of evidence which shows that calcium has beneficial effects on bone health and metabolism; however, the majority of the current evidence suggests that calcium supplementation or dairy intake has no meaningful effects on body weight or body fat loss. Although many individuals who are attempting to lose weight tend to eliminate dairy products, only two studies mentioned herein reported a significant increase in body weight following increased calcium or dairy intake. Therefore, as long as energy intake is less than energy expenditure, it does not appear that the addition of calcium-rich dairy sources to the diet would lead to any substantial increases in body weight and may help many individuals meet their daily calcium requirements.

8.3.7 White Kidney Bean (*Phaseolus vulgaris*)

Carbohydrates are the major source of calories in most diets. Digestion of carbohydrates starts in the mouth with salivary amylase (released from

salivary glands), followed by amylase secretion by the pancreas for further digestion in the small intestine. The end products of carbohydrate digestion are their breakdown to monosaccharides (glucose, fructose, and galactose), which are absorbed into the bloodstream from the intestinal wall, subsequently resulting in an increase in serum insulin concentrations. It has been theorized that slowing the absorption of carbohydrates via amylase inhibitors may result in favorable effects on insulin and, in turn, reduce fat accumulation [101]. Products available on the market purported to slow the absorption of carbohydrates through the inhibition of enzymes involved in their digestion include alpha-amylase and glucosidase inhibitors [102]. Alpha-amylase inhibitors are also present in plants. For example, raspberries, green and black tea, beans, and grains, including wheat and rice, have all been reported to inhibit and amylase activity [102]. Most of the recent research attention, however, has focused on alpha-amylase inhibitors from beans, particularly white kidney beans (*Phaseolus vulgaris*).

White kidney bean extract (WKBE) can come in the form of a powder, tablets and capsules, and chewables, and it has been reported by Barrett and Udani [102] that approximately 200 brands of nutritional supplements, including weight loss supplements, contain some form of WKBE. In addition, WKBE is also being added to food products including mashed potatoes, chewing gum, and bread and pizza dough and has been shown to maintain its activity without altering the texture, appearance, or taste of the food [102]. Most clinical trials that have examined the effect of WKBE on weight loss have used a proprietary product called Phase 2® Carb Controller (Pharmachem Laboratories, Kearny, NJ), and several clinical trials have shown very promising data regarding its effect on weight loss.

Rothacker [103] examined the effect of a supplement soft chew containing WKBE on weight loss in 60 overweight men and women (BMI range = 24–32 $kg \cdot m^2$) for 12 weeks. Subjects randomly received either 2 soft chews with WKBE (1,000 mg) or 2 PL chews before each of their meals for a total of 6 chews per day. Subjects received counseling about proper nutrition and the importance of exercise, but neither diet nor exercise was monitored. Body weight was measured at baseline and 6, 8, and 12 weeks. At the end of the 12-week supplementation period, the results showed that subjects that received the active soft chew lost 6.9 ± 7.9 lb compared to a weight gain of 0.8 ± 6.1 lb in the PL group ($p = 0.029$). These results are promising since subjects who supplemented with WKBE lost a significant amount of weight without a strict diet or exercise intervention.

In a related study, Celleno et al. [104] examined the effect of a dietary supplement containing WKBE on body composition in 60 overweight men and women. Subjects randomly received an 800 mg tablet containing 445 mg of WKBE or an 800 mg placebo tablet that was identical in appearance and contained cellulose and maltodextrin for 30 days. The subjects were also given nutrition counseling and received a menu plan with nutritional recommendations that provided 2,000–2,200 $kcal \cdot day^{-1}$. They were instructed to take one tablet per day with one of two carbohydrate-rich meals provided with their menu for 30 consecutive days. Body weight, percent body fat (via BIA), and waist-to-hip ratio were measured at baseline and 30 days. The results showed that the subjects who received the WKBE supplement demonstrated significant ($p < 0.001$) decreases in body weight (−2.93 ± 1.16 kg), fat weight (−2.40 ± 0.67 kg), and waist (−2.93 ± 2.13 cm) and hip (−1.48 ± 0.66 cm) compared to placebo (body weight = −0.35 ± 0.38 kg; fat weight = −0.16 ± 0.33 kg; waist = −0.47 ± 0.39 cm; hip = −0.10 ± 0.47 cm). The weight loss experienced by subjects in the current study [104] over ~4 weeks (6.45 lb) was similar to that reported in the 12-week study by Rothacker [103] (6.9 lb).

A recent review of 10 clinical trials by Barrett and Udani [102] that included the studies described above [103, 104] largely showed that doses of WKBE ranging from 500 to 3,000 $mg \cdot day^{-1}$ in either single or divided doses led to clinically significant weight loss and reduced postprandial spikes in blood glucose

compared to placebo. The authors [102] also reported that gastrointestinal side effects were rare and that, to date, no serious side effects had been reported. Although more long-term, randomized, placebo-controlled studies using more robust methods of body composition are warranted, it appears that WKBE has strong potential to elicit clinically significant weight loss and modulate glucose metabolism via its ability to inhibit amylase activity.

8.4 Supplements That Increase Satiety

8.4.1 Glucomannan, Guar Gum, and Psyllium

A number of dietary weight loss supplements contain water-soluble fiber, which is theorized to absorb water in the gut and, therefore, decrease feelings of hunger and, in turn, reduce food intake ultimately leading to weight loss. Examples of some of the most common sources of fiber in these products are glucomannan, psyllium, and guar gum.

8.4.2 Glucomannan

Glucomannan (*Amorphophallus konjac*) is a highly viscous dietary fiber native to Asia that is derived from the konjac root (also known as elephant yam) and is composed of a polysaccharide chain of glucose and mannose [64]. An early study by Walsh et al. [105] that examined the effect of glucomannan (3 g·day^{-1} × 8 weeks taken before meals) on obese patients (≥20 % of ideal body weight) found that it was more effective than PL for inducing weight loss, resulting in a mean loss of 2.49 kg (~5.5 lb). A review published in 2005 by Keithly and Swanson [106] also reported that at doses of 2–4 g·day^{-1}, glucomannan resulted in significant weight loss in overweight individuals by increasing satiety and appears to be well-tolerated. However, in a recent clinical study published by the same authors [107], it was reported that 1.33 g of glucomannan in capsule form administered 1 h before meals for 8 weeks resulted in no significant difference in weight loss (−0.40 ± 0.06 kg) compared to placebo (−0.43 ± 0.07 kg). It was also reported that glucomannan was well-tolerated, but did not have any effect on satiety or lipid and glucose chemistries [107].

Lyon et al. [108] examined the effect of a recently developed high-viscous polysaccharide (HVP) containing three natural fibers (konjac, sodium alginate, and xanthan gum) for 3 months on anthropometric measures (body weight, waist and hip circumference) in non-dieting overweight and obese men and women (BMI 27–35 kg · m^2). The study was conducted using a randomized double-blind design and subjects ingested either 5–15 g per day of HVP in powder form added to yogurt (n = 29) or inulin as PL (n = 30) for 15 weeks. Modest, but significant, decreases were observed for HVP compared to PL for body weight (−1.6 ± 3.2 kg) and hip circumference (−2.8 ± 3.2 cm) for women only. Although the changes in anthropometry were modest at best with the change in body weight for women representing 2 % of their initial weight, the authors [108] suggested that HVP may have potential for weight loss as part of a comprehensive weight management program.

Onakpoya et al. [109] also recently published a systematic review and meta-analysis to determine the efficacy of glucomannan for weight loss for in overweight and obese individuals. The findings from 8 randomized control trials were used for analysis, and the results showed that there was a nonsignificant difference in weight loss between glucomannan and placebo (mean difference: −0.22 kg). In addition, several adverse events were reported including constipation, diarrhea, and abdominal discomfort.

8.4.3 Guar Gum

The dietary fiber guar gum is derived from the Indian cluster bean *Cyamopsis tetragonolobus* and is found in a number of natural weight loss

preparations. To determine its effectiveness for reducing body weight, Pittler and Ernst [110] conducted a meta-analysis of 11 randomized controlled trials that ranged from 3 weeks to 6 months and found that there was no significant difference in overweight subjects who received guar gum (7.5–21 g·day^{-1}) compared to those that received PL (mean difference between guar gum and PL = −0.04 kg). Seven of the eleven studies also reported several adverse gastrointestinal effects from guar gum including flatulence, diarrhea, gastric pain, and nausea. Because of the related adverse events, as well as the fact that it resulted in minimal weight loss compared to PL, Pittler and Ernst [110] did not recommend guar gum as a dietary treatment for weight loss.

In contrast, the results of a study by Birketvedt et al. [111] that examined the effect of three different dietary fiber supplements containing glucomannan and/or guar gum on weight loss reported positive findings. In their study [111], 176 men and women randomly received one of three different dietary fiber supplements or a PL for 5 weeks, while consuming a balanced 1,200 kcal·day^{-1} diet. The fiber supplements included (1) glucomannan, (2) glucomannan and guar gum, or (3) glucomannan, guar gum, and alginate. The results showed that all three fiber supplements in conjunction with the low-calorie diet resulted in significantly more weight loss compared to PL and diet alone; however, there were no significant differences between the three treatments (−3.8 ± 0.9 kg, −4.4 ± 2.0 kg, and −4.1 ± 0.6 kg, respectively), which resulted in an average weight loss of approximately −0.8 kg·wk^{-1}.

Anderson et al. [112] also reported somewhat positive findings for the effects of fiber on weight loss. Sixteen randomized control trials were reviewed, and, for most trials, fiber intake ranged from 4.5 to 20 g · day^{-1} and averaged 2.5 g per meal 3 × day^{-1}. In the majority of the trials, fiber was primarily in insoluble form, but several also used glucomannan and guar gum. It was found that fiber supplementation in conjunction with an energy-restricted diet resulted in moderately greater weight loss compared to PL. Compared to initial body weight, the percentage of weight loss for PL and fiber-supplemented diets over 4, 8, and 12 weeks were as follows: 4 weeks, 2.0 % vs. 3.2 %; 8 weeks, 2.9 % vs. 4.9 %; and 12 weeks, 2.7 % vs. 4.9 %, respectively.

8.4.4 Psyllium

Psyllium is derived from the husks of ripe seeds from the plant *Plantago ovata* or *Plantago psyllium* [113] and is the active ingredient in many non-prescription laxatives and fiber supplements including the well-known brand Metamucil®. Although psyllium has been shown to be effective for lowering total cholesterol and LDL cholesterol, it does not appear to be as effective as other fiber types for reducing body weight and is associated with gastrointestinal disturbances including bloating and flatulence [113].

Dietary fiber is well known for its benefits on colon health and is commonly recommended for the treatment of high cholesterol [112, 113]. Although there is some evidence to suggest that fiber supplements may be useful for increasing satiety and producing reductions in body weight, the results are equivocal and the weight loss is modest at best.

8.5 Other Dietary Supplements

Other dietary supplements that have been purported to induce weight loss as either their primary or secondary action include herbal preparations such as dandelion, hoodia, curcumin, bladderwrack, sunflower, germander, and St. John's wort; the prohormone DHEA; β-hydroxy-β-methylbutyrate (HMB), which is a metabolite of the amino acid leucine; and yerba mate, which would have similar actions to ma huang, citrus aurantium, and guarana [9, 68]. Still others include licorice, vitamin B_5, MCT, and L-carnitine [68]. Research regarding the efficacy of these supplements for weight loss has primarily resulted in nonsignificant findings, and, in some cases, supplementation has resulted in serious adverse effects [9, 68]. Therefore, the use of these dietary supplements as a treatment for obesity appears to be largely unwarranted.

8.6 Summary

Although the use of dietary supplements for weight loss is widespread, the evidence for their efficacy and safety is not overwhelmingly convincing. Although there is some controversy regarding the definition of "clinically significant weight loss," there is strong consensus that a weight loss change of at least 5 % of body weight is clinically relevant [114]. For a 200 lb individual, that would represent a loss of 10 lb. For the majority of supplements discussed in this chapter, few elicited changes in body weight that would meet this definition and were not comparable to changes in body weight and composition that may occur through a restricted diet and exercise program (1.5–2.5 $kg \cdot wk^{-1}$) [115]. There is some evidence to suggest that herbal forms of ephedrine, such as ma huang, combined with caffeine or as an ECA stack, are effective for inducing moderate weight loss in overweight adults. However, because of the ban on ephedra, it is only available through prescription, and, therefore, manufacturers must now use ingredients, such as bitter orange, which do not appear to be as effective and may still possess the potential for adverse effects. Green bean coffee extract, white kidney bean extract, and capsaicinoids also appear to hold some promise as a possible adjuvant treatment for weight loss; however, more long-term studies are warranted to examine their efficacy, particularly when consumed alone, to confirm the findings of preliminary research.

It is important to remember that dietary supplements are not regulated like drugs, which must undergo rigorous clinical testing using both animal and human models before entering the market. Therefore, the manufacturers of dietary weight loss supplements can make claims regarding the effectiveness of their products without necessarily conducting clinical research trials first. When making the decision to use dietary supplements, it is critical, therefore, to rely on evidence-based research and/or dietetics professionals versus infomercials and advertisements from fitness and body building magazines.

The future of dietary supplements for weight loss is dependent upon well-designed, large-scale clinical studies and more stringent regulation of the dietary supplement industry. Currently, however, there are few dietary supplements designed for weight loss that can be recommended with much confidence.

References

1. Dixon JB. The effect of obesity on health outcomes. Mol Cell Endocrinol. 2009;316:104–8.
2. Radimer KL, Subar AF, Thompson FE. Nonvitamin, nonmineral dietary supplements: issues and findings from NHANES III. J Am Diet Assoc. 2000; 100:447–54.
3. Marketdata Enterprises, Inc. Weight loss market sheds some dollars in 2013 (Press Release, 4 Feb 2014).
4. Boozer CN, Nasser JA, Heymsfield SB, Wang V, Chen C, Solomon JL. An herbal supplement containing ma huang-guarana for weight loss: a randomized, double-blind trial. Int J Obes. 2001;25:316–24.
5. Greenway FL. The safety and efficacy of pharmaceutical and herbal caffeine and ephedrine use as a weight loss agent. Obes Rev. 2001;2:199–211.
6. Young R, Glennon RA. Discriminative stimulus properties of (-) ephedrine. Pharmacol Biochem Behav. 1998;60(3):771–5.
7. Blumenthal M. Bitter orange peel and synephrine: Part 1. HerbalGram 2005;66: American Botanical Council. http://cms.herbalgram.org/herbalgram/issue66/article2833.html. Accessed 26 May 2014.
8. Shekelle PG, Hardy ML, Morton SC, Maglione M, Mojica WA, Suttorp MJ, Rhodes RL, Jungvig L, Gagne J. Efficacy and safety of ephedra and ephedrine for weight loss and athletic performance: a meta-analysis. JAMA. 2003;289:1537–45.
9. Allison DB, Fontaine KR, Heshka S, Mentore JL, Heymsfield SB. Alternative treatments for weight loss: a critical review. Crit Rev Food Sci Nutr. 2001;41(1):1–28.
10. Kovacs EMR, Mela DJ. Metabolically active functional food ingredients for weight control. Obes Rev. 2006;7:59–78.
11. FDA Consumer Health Information. Warning on Hydroxycut Products. 1 May 2009. www.fda.gov/consumer/updates/hydroxycut050109.html
12. Hutchins GM. Dietary supplements containing ephedra alkaloids. N Engl J Med. 2001;344(14): 1095–7.
13. Dulloo AG. Herbal stimulation of ephedrine and caffeine in the treatment of obesity. Int J Obes. 2002;26:590–2.
14. Boozer CN, Daly PA, Homel P, Solomon JL, Blanchard D, Nasser JA, Strauss R, Meredith T. Herbal ephedra/caffeine for weight loss: a 6-month randomized safety and efficacy trial. Int J Obes. 2002;26:593–604.

15. Kalman CM, Minsch A. Ephedrine, caffeine, and aspirin enhance fat loss under nonexercising conditions. J Am Coll Nutr. 1997;16 Suppl 2:S149. Abs.
16. Daly PA, Krieger DR, Dulloo AG, Young JB, Landsberg L. Ephedrine, caffeine, and aspirin: safety and efficacy for treatment of obesity. Int J Obes. 1993;17(Suppl1):S73–8.
17. Liu AG, Smith SR, Fujioka K, Greenway FL. The effect of leptin, caffeine/ephedrine and their combination upon visceral fat mass and weight loss. Obesity. 2013;21:1991–6.
18. Vukovich MD, Schoorman R, Heilman C, Jacob P, Benowitz NL. Caffeine-herbal ephedra combination increases resting energy expenditure, heart rate, and blood pressure. Clin Exp Pharmacol Physiol. 2005;32(1-2):47–53.
19. Fugh-Berman A, Myers A. Citrus aurantium, an ingredient of dietary supplements marketed for weight loss: current status of clinical and basic research. Exp Biol Med. 2004;229:698–704.
20. Bent S, Padula A, Neuhaus J. Safety and efficacy of citrus aurantium for weight loss. Am J Cardiol. 2004;94:1359–61.
21. Penzak SR, Jann MW, Cold JA, Hon YY, Desai HD, Gurley BJ. Seville (sour) orange juice: synephrine content and cardiovascular effects in normotensive adults. J Clin Pharmacol. 2001;41:1059–63.
22. Allison DB, Cutter G, Poehman ET, Moore DR, Barnes S. Exactly which synephrine alkaloids does citrus aurantium (bitter orange) contain? Int J Obes (Lond). 2005;29:443–6.
23. Carpene C, Galitzky J, Fontana E, Atgie C, Lafontan M, Berlan M. Selective activation of beta3-adrenoreceptors by octopamine: comparative studies in mammalian fat cells. Naunyn Schmiedebergs Arch Pharmacol. 1999;359(4):310–21.
24. Colker CM, Kalman DS, Torina GC, Perlis T, Street C. Effects of Citrus aurantium, caffeine, and St. John's Wort on body fat loss, lipid levels, and mood states, in overweight healthy adults. Curr Ther Res. 1999;60(3):145–52.
25. Heyward VH, Stolarczyk LM. Applied body composition assessment. Champaign, IL: Human Kinetics; 1996. p. 47–54.
26. Armstrong WJ, Johnson P, Duhme S. The effect of commercial thermogenic weight loss supplement on body composition and energy expenditure in obese adults. J Exer Physiol Online. 2001;4(2):28–35.
27. Sale C, Harris RC, Delves S, Corbett J. Metabolic and physiological effects of ingesting extracts of bitter orange, green tea and guarana at rest and during treadmill walking in overweight males. Int J Obes. 2006;30:764–73.
28. Zenk JL, Liekam SA, Kassen LJ, Kuskowski MA. Effect of Lean System 7 on metabolic rate and body composition. Nutrition. 2005;21:179–85.
29. Lopez HL, Ziegenfuss TN, Hofheins JE, Habowski SM, Arent SM, Weir JP, Ferrando AA. Eight weeks of supplementation with a multi-ingredient weight loss product enhances body composition, reduces hip and waist girth, and increases energy levels in overweight men and women. J Int Soc Sport Nutr. 2013;10:22.
30. Haaz S, Fontaine KR, Cutter G, Limdi N, Perumean-Chaney S, Allison DB. Citrus aurantium and synephrine alkaloids in the treatment of overweight and obesity: an update. Obes Rev. 2006;7:79–88.
31. Wang H, Wen Y, Du Y, et al. Effect of catechin enriched green tea on body composition. Obesity. 2010;18(4):773–9.
32. Hursel R, Viechtbauer W, Westerterp-Plantenga MS. The effects of green tea on weight loss and weight maintenance: a meta-analysis. Int J Obes. 2009;33:956–61.
33. Phung OJ, Baker WL, Matthews LJ, Lanosa M, Thorne A, Coleman CI. Effect of green tea catechins with or without caffeine on anthropometric measures: a systematic review and meta-analysis. Am J Clin Nutr. 2010;91:73–81.
34. Hursel R, Westerterp-Plantenga MS. Thermogenic ingredients and body weight regulation. Int J Obes. 2010;34:659–69.
35. Manore MM. Dietary supplements for improving body composition and reducing body weight: where is the evidence? Int J Sport Nutr Exerc Metab. 2012;22:139–54.
36. Lopez-Garcia E, van Dam RM, Rajpathak S, Willett WC, Manson JE, Hu FB. Changes in caffeine intake and long-term weight change in men and women. Am J Clin Nutr. 2006;83:674–80.
37. Galgani JE, Ravussin E. Effect of dihydrocapsiate on resting metabolic rate in humans. Am J Clin Nutr. 2010;92:1089–93.
38. Whiting S, Derbyshire E, Tiwari BK. Capsaicinoids and capsinoids. A potential for weight management? A systematic review of the evidence. Appetite. 2012;59:341–8.
39. Luo XJ, Peng J, Li YJ. Recent advances in the study of capsaicinoids and capsinoids. Eur J Pharmacol. 2011;650:1–7.
40. Clegg ME, Golsorkhi M, Henry CJ. Combined medium-chain triglyceride and chili feeding increases diet-induced thermogenesis in normal-weight humans. Eur J Nutr. 2013;52:1579–85.
41. Stanko RT, Mendelow H, Shinozuka H, Adibi SA. Prevention of alcohol-induced fatty liver by natural metabolites and riboflavin. J Lab Clin Med. 1978;91:228–35.
42. Stanko RT. Methods for preventing body fat deposition in mammals. US Patent No. 4,812,479; 14 Mar 1989.
43. Stanko RT, Adibi SA. Inhibition of lipid accumulation and enhancement of energy expenditure by the addition of pyruvate and dihydroxyacetone to a rat diet. Metabolism. 1986;35:182–6.
44. Stanko RT, Arch JE. Inhibition of regain in body weight and fat wit addition of 3-carbon compounds to the diet with hyperenergetic refeeding after weight

reduction. Int J Obes Relat Metab Disord. 1996;20:925–30.
45. Stanko RT, Tietze DL, Arch JE. Body composition, energy utilization, and nitrogen metabolism with a severely restricted diet supplemented with dihydroxyacetone and pyruvate. Am J Clin Nutr. 1992;55:771–6.
46. Stanko RT, Reynolds HR, Hoyson R, Jonosky JE, Wolf R. Pyruvate supplementation on a low cholesterol, low fat diet: effects on plasma lipid concentrations and body composition in hyperlipidemic patients. Am J Clin Nutr. 1994;59:423–7.
47. Stanko RT, Ferguson TL, Newman CW, Newman RK. Reduction of carcass fat in swine with dietary addition of dihydroxyacetone and pyruvate. J Anim Sci. 1989;67:1272–8.
48. Kalman D, Colker CM, Stark R, Minsch A, Wilets I, Antonio J. Effect of pyruvate supplementation on body composition and mood. Curr Ther Res. 1998;59(11):793–802.
49. Gunther CW, Legowski AP, Lyle RM, McCabe GP, Eagan MS, Peacock M, Teegarden D. Dairy products do not lead to alterations in body weight or fat mass in young women in a 1-y intervention. Am J Clin Nutr. 2005;81:751–6.
50. Kalman D, Colker CM, Welets I, Roufs JB, Antonio J. The effects of pyruvate supplementation on body composition in overweight individuals. Nutrition. 1999;15(5):337–40.
51. Koh-Banerjee PK, Ferreira MP, Greenwood M, Bowden RG, Cowan PN, Almada AL, Kreider RB. Effects of calcium pyruvate supplementation during training on body composition, exercise capacity, and metabolic responses to exercise. Nutrition. 2005;21(3):312–9.
52. Stone MH, Sanborn K, Smith LL, et al. Effects of in-season (5 weeks) creatine and pyruvate supplementation on anaerobic performance and body composition in American football players. Int J Sport Nutr. 1999;9:146–65.
53. Onakpoya I, Hunt K, Wider B, Ernst E. Pyruvate supplementation for weight loss: a systematic review and meta-analysis of randomized clinical trials. Crit Rev Food Sci Nutr. 2014;54:17–23.
54. Onakpoya I, Rohini T, Ernst E. The use of green coffee extract as a weight loss supplement: a systematic review and meta-analysis of randomized clinical trials. Gastroenterol Res Pract. 2011;2011:6. Article ID 382852.
55. Quick M, Kiefer D. Weighing in: green coffee bean extract – a potential safe and effective weight loss supplement? Integr Med Alert;1 Sept 2013.
56. Flanagan J, Bily A, Rolland Y, Roller M. Lipolytic activity of Svetol, a decaffeinated green coffee bean extract. Phytother Res. 2014;28:946–8.
57. Shimoda H, Seki E, Aitani M. Inhibitory effect of green coffee bean extract on fat accumulation and body weight gain in mice. BMC Complement Altern Med. 2006;6:9.
58. Cho AS, Jeon SM, Kim MJ, et al. Chlorogenic acid exhibits anti-obesity property and improves lipid metabolism in high-fat diet-induced-obese mice. Food Chem Toxicol. 2010;48:937–43.
59. Thom E. The effect of chlorogenic acid enriched coffee on glucose absorption in health volunteers and its effect on body mass when used long-term in overweight and obese people. J Int Med Res. 2007;35:900–8.
60. Vinson JA, Burnham BR, Nagendran MV. Randomized, double-blind, placebo controlled, linear dose, crossover study to evaluate the efficacy and safety of a green coffee bean extract in overweight subjects. Diabetes Metab Syndr Obes. 2012;5:21–7.
61. Lukaski HC, Siders WA, Penland JG. Chromium picolinate supplementation in women: effects on body weight, composition, and iron status. Nutrition. 2007;23:187–95.
62. Pittler MH, Stevinson C, Ernst E. Chromium picolinate for body weight reduction: meta-analysis of randomized trials. Int J Obes. 2003;27(4):522–9.
63. Yazaki Y, Faridi Z, Ma Y, Ali A, Northrup V, Njike VY, Liberti L, Katz DL. A pilot study of chromium picolinate for weight loss. J Altern Complement Med. 2010;16(3):29–299.
64. Pittler MH, Ernst E. Dietary supplements for body-weight reduction: a systematic review. Am J Clin Nutr. 2004;79:529–36.
65. Han LK, Kimura Y, Okuda H. Reduction in fat storage during chitin-chitosan treatment in mice fed a high fat diet. Int J Obes. 1999;23:174–9.
66. Trautwein EA, Jurgensen U, Erbersdobler HF. Cholesterol-lowering and gallstone-preventing action of chitosans with different degrees of deacetylation in hamsters fed cholesterol rich-diets. Nutr Res. 1997;17:1053–65.
67. Jull AB, Mhurchu N, Bennett DA, Dunshea-Mooij CA, Rodgers A. Chitosan for overweight or obesity. Cochrane Database Syst Rev. 2008;3, CD003892.
68. Saper RB, Eisenberg DM, Phillips RS. Common dietary supplements for weight loss. Am Fam Physician. 2004;70:1731–8.
69. Gades MD, Stern JS. Chitosan supplementation and fecal fat excretion in men. Obes Res. 2003;11:683–8.
70. Heymsfield SB, Allison DB, Vasselli JR, Pietrobelli A, Greenfield D, Nunez C. Garcinia cambogia (HCA) as a potential anti-obesity agent. JAMA. 1998;280(18):1596–600.
71. Kovacs EMR, Westerterp-Plantega MS, Saris WHM. The effects of 2-week ingestion of (-)-hydroxycitrate and (-)-hydroxycitrate combined with medium-chain triglycerides on satiety, fat oxidation, energy expenditure and body weight. Int J Obes. 2001;25:1087–94.
72. Westerterp-Plantenga MS, Kovacs EMR. The effect of (-)-hydroxycitrate on energy intake and satiety in overweight humans. Int J Obes. 2002;26:870–2.

73. Kriketos AD, Thomson HR, Greene H, Hill JO. (-)-Hydroxycitric acid does not affect energy expenditure and substrate oxidation in adult males in a post-absorptive state. Int J Obes. 1999;23:867–73.
74. Van Loon LJC, van Rooijen JJM, Niesen B, Verhagen H, Saris WHM, Wagenmakers AJM. Effects of acute (-)-hydroxycitrate supplementation on substrate metabolism at rest and during exercise in humans. Am J Clin Nutr. 2000;72:1445–50.
75. Marquez F, Babio N, Bullo M, Salas-Salvado J. Evaluation of the safety and efficacy of hydroxycitric acid or *Garcinia cambogia* extracts in humans. Crit Rev Food Sci Nutr. 2012;52:585–94.
76. Malpuech-Brugere C, Wihelmine PHG, de Verboeket-van V, Mensink RP, et al. Effects of two conjugated linoleic acid isomers on body fat mass in overweight humans. Obes Res. 2004;12(4):591–8.
77. Tricon S, Yaqoob P. Conjugated linoleic acid and human health: a critical evaluation of the evidence. Curr Opin Clin Nutr Metab Care. 2006;9(2): 105–10.
78. Meinert Larsen T, Toubro S, Gudmundsen O, Astrup A. Conjugated linoleic acid supplementation for 1 y does not prevent weight or body fat regain. Am J Clin Nutr. 2006;83:606–12.
79. Brown JM, McIntosh MK. Conjugated linoleic acid in humans: regulation of adiposity and insulin sensitivity. J Nutr. 2003;133(10):3041–6.
80. Tricon S, Burdge GC, Kew S, Banerjee T, et al. Opposing effects of cis-9, trans-11 and trans-10, cis-12 conjugated linoleic acid on blood lipids in healthy humans. Am J Clin Nutr. 2004;80:614–20.
81. Gaullier JM, Halse J, Hoye K, Kristiansen K, Fagertun H, Vik H, Gudmundsen O. Conjugated linoleic acid supplementation for 1 y reduces body fat mass in healthy overweight humans. Am J Clin Nutr. 2004;79:1118–25.
82. Riserus U, Berglund L, Vessby B. Conjugated linoleic acid (CLA) reduced abdominal adipose tissue in obese middle-aged men with signs of the metabolic syndrome: a randomized controlled trial. Int J Obes. 2001;25:1129–35.
83. Larsen TM, Toubro S, Astrup A. Efficacy and safety of dietary supplements containing CLA for the treatment of obesity: evidence from animal and human studies. J Lipid Res. 2003;44(12):2234–41.
84. Whigham LD, Watras AC, Schoeller DA. Efficacy of conjugated linoleic acid for reducing fat mass: a meta-analysis in humans. Am J Clin Nutr. 2007;85(5):1203–11.
85. Onakpoya I, Posadzki PP, Watson LK, Davies LA, Ernst E. The efficacy of long-term conjugated linoleic acid (CLA) supplementation on body composition in overweight and obese individuals: a systematic review and meta-analysis of randomized clinical trials. Eur J Nutr. 2012;51:127–34.
86. Metz JA, Karanja N, Torok J, McCaron DA. Modification of total body fat in spontaneously hypertensive rats and Wistar-Kyoto rats by dietary calcium and sodium. Am J Hypertens. 1988; 1:58–60.
87. Bursey RG, Sharkey T, Miller GD. High calcium intake lowers weight in lean and fatty Zucker rats. FASEB J. 1989;3137:A265. Abs.
88. Teegarden D, Lin YC, Weaver CM, Lyle RM, McCabe GP. Calcium intake related to change in body weight in young women. FASEB J. 1999; 13:A873. Abs.
89. Zemel MB, Shi H, Zemel PC, DiRienzo D. Calcium and calcium-rich dairy products reduce body fat. FASEB J. 1999;12:LB211. abs.
90. Zemel MB, Shi H, Greer B, DiRienzo D, Zemel P. Regulation of adiposity by dietary calcium. FASEB J. 2000;14:1132–8.
91. Davies KM, Heaney RP, Recker RR, Lappe JM, Barger-Lux MH, Rafferty K, Hinders S. Calcium intake and body weight. J Clin Endocrinol Metab. 2000;85:4635–8.
92. Shapses SA, Stanley H, Heymsfield SB. Effect of calcium supplementation on weight and fat loss in women. J Clin Endocrinol Metab. 2004;89(2):632–7.
93. Barr SI, McCarron DA, Heaney RP, Dawson-Hughes B, Berga SL, Stern J, Oparil S. Effects of increased consumption of fluid milk on energy and nutrient intake, body weight, and cardiovascular risk factors in healthy older adults. J Am Diet Assoc. 2000;100:810–7.
94. DeJongh ED, Binkley TL, Specker BL. Fat mass gain is lower in calcium-supplemented than in unsupplemented preschool children with low dietary calcium intakes. Am J Clin Nutr. 2006;84(5):1123–7.
95. Haub MD, Simons TR, Cook CM, Remig VM, Al-Tamimi EK, Holcomb CA. Calcium-fortified beverage supplementation on body composition in postmenopausal women. Nutr J. 2005;4:21 (PubMed online).
96. Zemel MB, Thompson W, Milstead A, Morris K, Campbell P. Calcium and dietary acceleration of weight and fat loss during energy restriction in obese adults. Obes Res. 2004;12:582–90.
97. Zemel MB, et al. Materials and methods for the treatment or prevention of obesity. US Patent No. 6,384,087; 7 May 2002.
98. Lanou AJ, Barnard ND. Dairy and weight loss hypothesis: an evaluation of the clinical trials. Nutr Rev. 2008;66(5):272–9.
99. Onakpoya I, Perry R, Zhang J, Ernst E. Efficacy of calcium supplementation for management of overweight and obesity: systematic review of randomized clinical trials. Nutr Rev. 2011;69(6):335–43.
100. Trowman R, Dumville JC, Hahn S, Torgerson DJ. A systematic review of the effects of calcium supplementation on body weight. Br J Nutr. 2006;95: 1033–8.
101. Vinson JA, Kharrat HA, Shuta D. Investigation of an amylase inhibitor on human glucose absorption after starch consumption. Open Nutraceuticals J. 2009;2:88–91.

102. Barrett ML, Udani JK. A proprietary alpha-amylase inhibitor from white bean (Phaseolus vulgaris): a review of clinical studies on weight loss and glycemic control. Nutr J. 2011;10:24.
103. Rothacker D. Reduction in body weight with a starch blocking diet aid: StarchAway comparison with placebo. Leiner Health Products 2003; http://www.phase2info.com/pdf/Phase2_Study6.pdf (online source).
104. Celleno L, Tolaini MV, D'Amore A, Perricone NV, Preuss HG. A dietary supplement containing standardized Phaseolus vulgaris extract influences body composition in overweight men and women. Int J Med Sci. 2007;4(1):45–53.
105. Walsh DE, Yaghoubian V, Behforooz A. Effect of glucomannan on obese patients: a clinical study. Int J Obes. 1984;8(4):289–93.
106. Keithly J, Swanson B. Glucomannan and obesity: a critical review. Altern Ther Health Med. 2005;11(6):30–4.
107. Keithly JK, Swanson B, Mikolaitis SL, DeMeo M, Zeller JM, Fogg L, Adamji J. Safety and efficacy of glucomannan for weight loss in overweight and moderately obese adults. J Obes. 2013;2013:7.610908.
108. Lyon M, Wood S, Pelletier X, Donazzolo Y, Gahler R, Bellisle F. Effect of a 3-month supplementation with a novel soluble highly viscous polysaccharide on anthropometry and blood lipids in nondieting overweight or obese adults. J Hum Nutr Diet. 2011;24:351–9.
109. Onakpoya I, Posadzki P, Ernst E. The efficacy of glucomannan supplementation in overweight and obesity: a systematic review and meta-analysis of randomized clinical trials. J Am Coll Nutr. 2014;33(1):77–8.
110. Pittler MH, Ernst E. Guar gum for body weight reduction: Meta-analysis of randomized trials. Am J Med. 2001;110:724–30.
111. Birketvedt GS, Shimshi M, Erling T, Florholmen J. Experiences with three different fiber supplements in weight reduction. Med Sci Monit. 2005;11(1):I5–8.
112. Anderson JW, Baird P, Davis R, et al. Health benefits of dietary fiber. Nutr Rev. 2009;67(4):188–205.
113. Pittler MH, Schmidt K, Ernst E. Adverse events of herbal food supplements for body weight reduction: a systematic review. Obes Rev. 2005;6(2):93–111.
114. Stevens J, Truesdale KP, McClain JE, Cai J. The definition of weight management. Int J Obes. 2006;30:391–9.
115. Cowburn G, Hillsdon M, Hankey CR. Obesity management by life-style strategies. Br Med Bull. 1997;53:389–408.

Effective Nutritional Supplement Combinations

9

Matthew B. Cooke and Paul J. Cribb

Abstract

Few supplement combinations that are marketed to athletes are supported by scientific evidence of their effectiveness. Under the rigor of scientific investigation, we often see that the patented combination fails to provide any greater benefit when compared to an active (generic) ingredient. The focus of this chapter is supplement combinations and dosing strategies that are effective at promoting an acute physiological response that may improve/enhance exercise performance and/or influence chronic adaptations desired from training. In recent years, there has been a particular focus on two nutrition ergogenic aids—creatine monohydrate and protein/amino acids—in combination with specific nutrients in an effort to augment or add to their already established independent ergogenic effects. These combinations and others are discussed in this chapter.

Keywords

Acute • Chronic • Supplementation • Aerobic • Anaerobic • Exercise performance • Resistance training • Protein • Amino acids • Carbohydrate • Creatine monohydrate • Protein balance • Glycogen resynthesis • Sodium D-pinitol • β-Alanine • HMβ • Sodium bicarbonate • Caffeine • Ephedrine

9.1 Introduction

Since the ancient Greeks (300 BC) used "natural preparations" to enhance athletic prowess, it is probable that athletes have been combining various nutritional compounds in an effort to increase the ergogenic potential. An athlete's drive to outperform the competition or maximize personal potential, combined with a growing awareness that nutritional choices can influence

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athletic performance, has fueled an explosion in the interest of nutritional ergogenic aids, combinations of dietary supplement formulations that enhance athletic performance. Sports supplement companies often market various combinations to consumers based on the assumption that the supplement blend (or stack) will provide greater benefit than any single compound alone. However, very few supplement combinations that are marketed to athletes possess scientific evidence of their effectiveness. Quite often, under the rigor of scientific investigation, the patented blend is not examined against an active (generic) ingredient. From both scientific and practical perspectives, the focus of this chapter is supplement combinations and dosing strategies that are documented to be safe and effective at promoting an acute physiological response that may either improve/enhance exercise performance or influence the chronic adaptations desired from training.

9.2 Supplement Combinations that May Enhance the Phosphagen System

To fully appreciate the rationale behind the intense research focus on supplements that may enhance this system also known as the phosphocreatine–creatine (PCr–Cr) system within muscle, one has to appreciate its fundamental, multifaceted roles in relation to exercise metabolism. The PCr–Cr system as a whole integrates all the local pools (or compartments) of adenine nucleotides, i.e., the transfer of energy from mitochondrial compartments to that in myofibrils and cellular membranes as well as the feedback signal transmission from sites of energy utilization to sites of energy production. The availability of PCr is now generally accepted as most critical to the continuation of muscle force production and performance during repeated, short bouts of powerful activity [1, 2] as well as aerobic exercise at high intensity [3, 4].

The CK reaction during the resynthesis of ATP takes up protons [5]. Therefore, another function of this PCr–Cr system is the maintenance of pH in exercising muscle. In a reversible reaction (catalyzed by the site-specific CK), Cr and ATP form PCr and ADP (Fig. 9.1). The formation of the polar PCr "locks" Cr within the muscle and maintains the retention of Cr because the charge prevents partitioning through biological membranes [2]. When pH declines (i.e., during exercise when lactic acid accumulates), the reaction will favor the generation of ATP. Conversely, during recovery periods (i.e., periods of rest between exercise sets), where ATP is being generated aerobically, the reaction will proceed toward the right and increase PCr levels. The notion that the maintenance of PCr availability is crucial to continued force production and performance during high-intensity exercise is further supported by research that demonstrates the rate of PCr utilization is extremely high during the initial seconds of intense contraction—high anaerobic ATP regeneration rates result in a 60–80 % fall in PCr [10]. Not only is the depletion of muscle PCr associated with fatigue [9], the resynthesis of PCr and the restoration of peak performance are shown to proceed in direct proportion to one another, despite low muscle pH during recovery [10].

9.2.1 Why Creatine?

If we condense the information covered so far, the ergogenic potential of Cr becomes clear. Cr is a naturally occurring tripeptide found prominently in active muscle [1, 2]. However, under normal circumstances, muscle stores of Cr are not saturated [11]. Whether synthesized endogenously or consumed orally, Cr is phosphorylated and stored within muscle [3, 4]. Therefore supplementation represents a unique opportunity to increase cellular reserves to provide large amounts of energy that enhance the cellular bioenergetics of the PCr–Cr system by increasing PCr availability [2, 9, 12]. While metabolic investigations involving Cr date back to the 1830s, the exogenous use of Cr in published research can be found in the early 1900s [13]. Cr as a supplement used for medical interventions such as treating diabetes and gyrate atrophy is documented from the 1930s up to the 1960s and 1970s [1–3]. However, the earliest scientific investigations involving the deliberate use of Cr to enhance

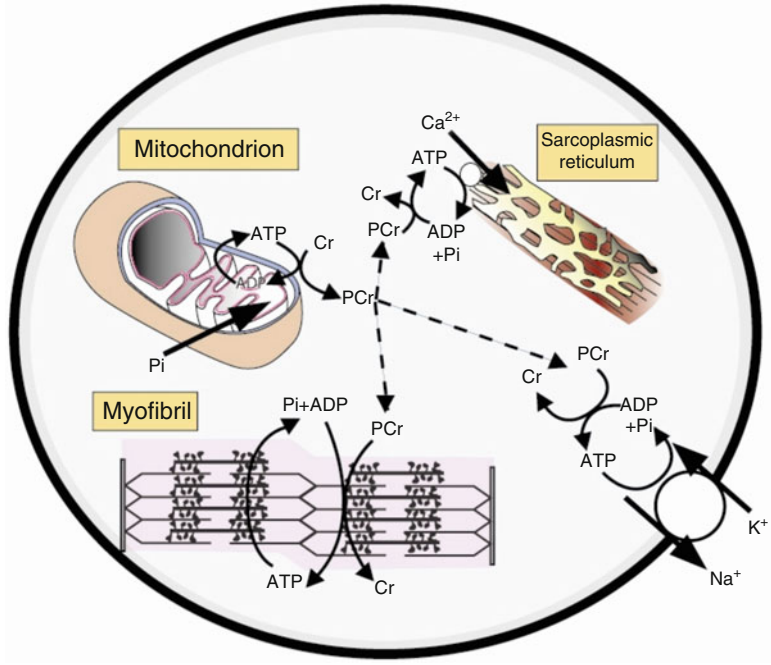

Fig. 9.1 The main roles of the PCr–Cr system are illustrated in this figure. The first is that of a temporal energy buffer for ATP regeneration achieved via anaerobic degradation of PCr to Cr and rephosphorylation of ADP. This energy buffering function is most prominent in the fast-twitch/glycolytic fibers; these fibers contain the largest pool size of PCr [6]. The ATP required for high-intensity exercise is met by the simultaneous breakdown of PCr and anaerobic glycolysis of which the PCr–Cr system provides up to one-third of the total energy required [7]. The second major function of the PCr–Cr system is that of a spatial energy buffer (or transport system). In this capacity, the PCr–Cr system serves as an intracellular energy carrier connecting sites of energy production (mitochondria) with sites of energy utilization (Na^+/K^+ pump, myofibrils, and the SR) (see figure). To describe the specificity of this system, it has been coined the creatine-phosphate ($Cr\text{-}P_i$) shuttle [8]. Meaning, Cr literally shuttles energy from the mitochondrion to highly specific sites via compartment-specific creatine kinase (CK) isoenzymes located at each of the energy-producing or energy-utilizing sites that transduce the PCr to ATP [5] and then returns to regenerate energy exactly equivalent to its consumption at those sites [8]. A third function of the PCr–Cr system is the prevention of a rise in ADP that would have an inhibitory effect on a variety of ATP-dependant processes, such as cross-bridge cycling. A rise in ADP production would also activate the kinase reactions that ultimately result in the destruction of muscle adenine nucleotides [2]. Therefore, the removal of ADP via the creatine kinase (CK) reaction-induced rephosphorylation serves to reduce the loss of adenine nucleotides while maintaining a high intracellular ATP/ADP ratio at the sites of high energy requirements [9]

athletic performance belong to Drs Eric Hultman, Karin Soderlund, and Roger Harris. These researchers pioneered the seminal work that showed large oral doses (20–30 g daily) of Cr in the form of creatine monohydrate (CrM) could increase plasma Cr and accumulation in skeletal muscle [1–3, 11, 12, 14]. Hultman was also one of the pioneers of CHO loading to enhance glycogen supercompensation and performance in the 1960s [15–17]. Hultman and colleagues applied the same loading principles with CrM supplementation [11, 12, 14].

CrM (n[aminoiminomethyl]-N-methylglycine) is a combination of Cr (anhydrous) and one water molecule. CrM is particularly stable even at high temperatures (stored over 60 °C for 3 years) and has slow degradation even at low pH levels [18]. Intestinal absorption of CrM is close to 100 % [19], Commercially, CrM is inexpensive to produce (compared to most supplements) and yields very high Cr purity (over 90 %) [18]. Probably for these reasons CrM supplementation has been the focus of well over 500 published investigations that have established that "loading" (4 × 5-g

servings · day^{-1}, 3–5 days) is a safe and effective way to elevate muscle Cr concentrations by 15–40 % [1, 11] and enhance athletic performance under a variety of circumstances [14, 20–25]. Regular use also appears to enhance the chronic adaptations desired from resistance training [26–28]. A large scientific body of literature continues to document this supplement's physiological [29–32] and performance-enhancing [33–37] effects as well as dispel concerns of adverse effects [27, 38]. For these reasons, there has always been interest in combining CrM with other compounds to enhance its ergogenic potential.

9.2.2 Why Combine Creatine with Other Compounds?

The beneficial effect of oral supplementation is thought to be dependent on the extent of Cr accumulation [12, 26, 28]. However, it is also apparent that this response can be highly variable between subjects [39]. Large variations in Cr accumulation (0–40 mmol · kg dm^{-1}) in response to supplementation can be partly accounted for by differences in pre-supplementation muscle concentrations [28] and possibly in muscle fiber-type distribution [6], but it remains unclear as to why muscle Cr accumulation can vary tremendously (up to sixfold) among individuals with similar pre-supplementation concentrations [21, 39, 40]. This variability in muscle Cr uptake among some individuals combined with the significance of the PCr–Cr system and CrM's potential to augment this all-important pathway is the underlining rational of studies that examine the effects of CrM supplementation in combination with other compounds.

9.2.3 The Effects of Other Compounds on Creatine Uptake

The presence of phosphatase enzymes in the blood and gut suggests that supplementation with other energy-yielding components of the phosphagen system, such as ATP or PCr, is not a viable option as these enzymes readily cleave the phosphate from the molecule [41]. Whereas the Cr portion of the monohydrate form consists of up to 92 % Cr, it only forms 50 % of the PCr molecule [42]. Oral supplementation with CrM enters the circulation intact where active uptake by tissues is facilitated by a Na^+-dependent transporter against a concentration gradient [43]. CrM's capacity to enhance the bioenergetics of the phosphagen system by increasing PCr availability is thought to reside in the extent of Cr accumulation within muscle [12, 26, 28]. To exert a beneficial effect on performance and metabolism, an increase in muscle total Cr (PCr + Cr) content by at least 20 mmol · kg dm^{-1} appears to be required [40]. While a loading phase is shown consistently to achieve this (as well as increase total Cr concentrations in other tissues with low baseline Cr content), it is also apparent that this response can be highly variable between subjects. For these reasons, a number of studies have assessed Cr uptake in the presence of other compounds. For example, Cr accumulation in muscle is enhanced by the presence of insulin [44] and possibly triiodothyronine [45] but may be depressed by the presence of some drugs such as ouabain or digoxin [46] or a vitamin E deficiency [47]. The findings from some investigations suggest that caffeine may impair the advantages of Cr loading [48], whereas other studies have involved caffeine-containing beverages (such as tea or coffee) to administer CrM and report significant elevations in muscle Cr as well as improvements in athletic performance [7, 9, 14, 21]. Other investigations report that muscle Cr uptake is not affected by PCr, creatinine, or cellular concentrations of various amino acids such as glycine, glutamine, alanine, arginine, leucine, and glycine or the sulfur-containing amino acids methionine and cysteine [49, 50].

9.2.4 Creatine with Macronutrients

Improved cellular retention of Cr has been attributed to a stimulatory effect of insulin on the Cr transporter protein [44]. Carbohydrates (CHO),

such as glucose and sucrose, generally evoke a high insulin response. Once it had been demonstrated that the presence of insulin (at supraphysiological levels) increased muscle Cr accumulation in humans [40], other investigations that examined the effects of combining CrM with CHO such as glucose soon followed. In two separate studies, Green et al. were the first to demonstrate reduced urine Cr losses [51] and a 60 % increase in muscle Cr accumulation [52] from combining a high dose of glucose (93 g) with each 5 g dose of CrM (4×5 g·day^{-1}, 2 days) compared to CrM alone. Robinson et al. [53] also showed that a high-CHO diet combined with CrM (4×5 g·day^{-1}, 5 days) after exercise provided effective ($P < 0.01$) Cr accumulation in the exercised limb. However, data from subsequent studies suggested that lower doses of CHO (glucose) may also be effective. For instance, Greenwood et al. [54] assessed whole-body Cr retention (via 24-h urine samples for 4 days) and reported that a 5-g dose of CrM combined with an 18-g dose of glucose (4×·day^{-1}, 3 days) resulted in significantly greater Cr retention than an equivalent dose of CrM only, or an effervescent Cr supplement (containing sodium and potassium bicarbonate). Along this line, Preen et al. [55] examined the effectiveness of 3 different CrM-loading procedures on total Cr accumulation in muscle. Eighteen physically active males were divided into three equal groups and provided either (a) CrM (4×5 g·day^{-1}, 5 days), (b) the same dose of CrM + glucose (1 g·kg^{-1}, twice·day^{-1}, 5 days), or (c) CrM combined with 60 min of daily exercise (repeated sprints) (CrM + E) for 5 days. Results showed that the combination of CrM + glucose provided a 7–9 % greater ($P < 0.05$) elevation in total muscle Cr concentrations than CrM only or CrM + E [55].

Supplementation with high insulin-stimulating CHO appears to be effective at promoting Cr uptake; however, combining CrM with a protein (PRO) supplement may also provide similar benefits. For example, using a group of recreational weight lifters, one study directly compared the effects of two CrM-containing supplements, CrM + CHO (glucose) and CrM + PRO (whey isolate) (1.5 g of supplement·kg·day^{-1}) during 11 weeks of resistance training [56]. After the 11-week program, the two different CrM-containing supplements provided a similar increase in total muscle Cr concentrations (~10 %). Additionally, the groups given the CrM + CHO and CrM + PRO supplements demonstrated greater ($P < 0.05$) strength improvements and muscle hypertrophy compared to an equivalent dose of CHO or PRO [56]. Other studies have reported similar benefits from combining CrM with whey PRO [57] or CHO (glucose) [24] during resistance training, but muscle Cr concentrations were not assessed. Whereas these studies utilized relatively large doses of PRO or CHO (70–100 g or more) in combination with CrM [56–58] and reported positive outcomes, the results of one study by Stout et al. [59] suggest that a smaller dose of CHO (35 g glucose) with each 5-g dose of CrM is also effective at improving training adaptations. However, no other studies have directly compared the effects of different CrM-containing PRO or CHO supplements on Cr accumulation and training adaptations.

Combining PRO, CHO, and CrM may be the most effective mix for promoting whole-body Cr accumulation, particularly if smaller doses of the macronutrients are desired. Steenge et al. [40] reported that the ingestion of CrM along with a PRO + CHO supplement (50 g dairy milk PRO, 50 g glucose) over 5 days resulted in similar insulin responses and (whole-body) percentage Cr accumulation values (~25 %) as the same CrM dose combined with 100 g of glucose [40]. Whole-body Cr accumulation is an indirect method assessing CrM uptake by tissues. Percent whole-body Cr retention can be calculated as Cr ingested (g)/urinary Cr excretion (g) × 100 [40]. The results obtained by Steenge et al. [40] suggest that the combination of PRO and CHO with CrM may be an effective way to improve Cr accumulation particularly when smaller doses of these macronutrients are desired. This combination may also have important implications for populations where the consumption of large amounts of CHO is undesirable, such as those with, or at risk of, type-II diabetes. This combination (CHO–PRO–CrM) has also been used to demonstrate that the timing of supplementation

may also be important to improving Cr accumulation in muscle and adaptations from training [60]. Other studies have shown that CrM supplementation close to exercise promotes muscle Cr uptake [53] and increases the girth and thickness of the exercised limb after resistance training [61]. Therefore, the use of a CrM-containing PRO–CHO supplement before and after resistance exercise may provide a higher degree of Cr accumulation and muscle anabolism and, therefore, promote better gains in strength and muscle mass. To summarize the research in this particular area, co-ingestion of CrM with CHO and/or PRO (namely, glucose or whey isolates, ~35–100 g) appears to enhance muscle Cr storage that may result in enhanced performance and better training adaptations. Greater accumulation within muscle appears to be due to a stimulatory effect of insulin on cell Cr transporter. In fact, combining CrM with a PRO and/or CHO supplement seems to reduce the individual variations in muscle Cr accumulation reported previously in studies involving acute loading [21, 39, 40]. Additionally, there is evidence to suggest that the timing of the supplement dose is important. The use of this supplement combination close to exercise (i.e., just before and/or after) appears to promote better Cr accumulation within muscle and influence training adaptations [53, 60]. Therefore, the use of a CrM-containing PRO–CHO supplement close to exercise represents a simple but highly effective strategy that promotes effective Cr accumulation (to increase PCr availability in muscle) and provides an ergogenic effect during training that results in greater adaptations. Further examination of dose–responses alongside the extent of Cr accumulation and adaptations would help define a clearer supplementation prescription.

9.2.5 Creatine with Insulin Mimickers

Aside from the use of macronutrients such as PRO and CHO, some studies have examined the effects of co-ingesting CrM with other compounds that affect insulin secretion and/or tissue sensitivity. For instance, in a single-blinded study, Greenwood et al. [62] examined whether co-ingestion of D-pinitol (a plant extract with insulin-sensitizing characteristics) [63] with CrM affected whole-body Cr retention (determined by 24-h urine samples for 4 days). Results revealed that whole-body Cr retention (and percentage of Cr retention) over the 3-day loading phase was greater ($P<0.05$) in the two groups given CrM combined with a low dose of D-pinitol (LP = 4 × 5 g CrM + 2 × 0.5 g D-pinitol) (PreP = D-pinitol 2 × 0.5 g D-pinitol 5 days prior to and during CrM supplementation 4 × 5 g CrM) compared to equivalent dose of glucose (placebo) or CrM alone. However, another group given a high dose of D-pinitol (4 × 0.5 g D-pinitol) with the same dose of CrM showed no greater Cr retention when compared to the group given CrM alone [62]. Interestingly, the group pre-dosing with D-pinitol (PreP) demonstrated the same results as the LP group suggesting that no further benefit seems to be gained by taking D-pinitol prior to supplementation [62]. In a follow-up study, Kerksick et al. [64] examined whether co-ingestion of D-pinitol with CM would affect training adaptations, body composition, and/or whole-body Cr retention in resistance-trained males. In the study, 24 resistance-trained males were randomly assigned in a double-blind manner to CM + D-pinitol or CM alone prior to beginning a supervised 4-week resistance-training program. Subjects ingested a typical loading phase (i.e., 20 $g \cdot day^{-1}$ for 5 days) before ingesting 5 $g \cdot d^{-1}$ for the remaining 23 days. The researchers reported that Cr retention increased in both groups as a result of supplementation. However, no significant differences were observed between groups in training adaptations. The authors concluded that ingesting Cr with D-pinitol may augment whole-body Cr retention in a similar manner to that reported with CHO or CHO and PRO supplementation [40]. Due to the conflicting nature of the results regarding the high vs. low doses of D-pinitol, further research is necessary before a clear conclusion can be drawn.

Another insulin mimicker that has shown potential to enhance Cr uptake and accumulation in muscle is α-lipoic acid (ALA). Supplementation

with ALA is shown to increase the expression of glucose transporter proteins (GLUT4) and enhance glucose uptake in muscle [65, 66]. In light of the fact that Cr uptake is influenced by insulin and that ALA can increase glucose disposal, Burke et al. [67] examined the effects of combining ALA with CrM on muscle Cr accumulation. In this study muscle biopsies were obtained to determine total Cr concentration from16 male subjects before and after the 5-day supplementation intervention. Results showed a greater increase ($P < 0.05$) in PCr and total Cr in the group given ALA combined with CrM + CHO (20 $g \cdot day^{-1}$ CrM + 100 $g \cdot day^{-1}$ sucrose + 1,000 $mg \cdot day^{-1}$ ALA) compared with a group given the same dose of CrM + CHO or CrM alone. The authors concluded that co-ingestion of ALA with CrM (and a small amount of sucrose) can enhance muscle Cr concentrations content compared to an equivalent dose of CrM + CHO or CHO alone [67]. However, the authors also acknowledge that a limitation of this study was the high baseline muscle Cr concentrations exhibited by the participants; the groups were ~10 % higher than starting values reported in other studies (~135 $mmol \cdot kg^{-1}$ vs. ~125 $mmol \cdot kg^{-1}$). Initial muscle Cr content is an important determinant of muscle Cr uptake [40]. That is, study participants with lower muscle Cr concentrations tend to show the largest increases after supplementation; conversely, those with higher muscle Cr concentrations show little or no increase. Burke et al. [67] suggest that the higher starting values of the participants may have been the reason for the lack of increase in PCr and total Cr experienced by two of the three groups in this study. As is the case with D-pinitol, a very limited amount of work has examined the effects of ALA on Cr accumulation.

The herb Russian tarragon (RT) is an ethanolic extract that may have antihyperglycemic activity when combined with CM ingestion. To support this hypothesis, Jäger et al. [68] reported that RT influences plasma creatine levels during the ingestion of CM in a similar manner to glucose and PRO. The authors suggest that theoretically, ingesting RT extract prior to Cr loading may enhance insulin sensitivity and thereby promote greater Cr absorption/retention. In a follow-up study by this group, Oliver et al. [69] used a double-blind, randomized, and crossover manner to examine the effect of consuming RT during 5 days of CrM loading. Recreationally trained males ingested 500 mg of aqueous RT extract or 500 mg placebo 30 min prior to ingesting 5 g of CrM twice per day for 5 days and then repeated after a 6-week washout period. Muscle and whole-body Cr retention was assessed. Results showed that in these healthy adults, short-term CrM supplementation (10 $g \cdot day^{-1}$ for 5 days) significantly increased whole-body Cr retention and muscle free Cr content. However, ingesting 500 mg of RT 30 min prior to CrM supplementation did not affect whole-body Cr retention, muscle free Cr content, or anaerobic sprint capacity in comparison to ingesting CrM with a placebo. After showing initial promise nearly 15 years ago, the evidence on insulin mimickers and their ability to enhance muscle Cr accumulation during CrM supplementation is still scarce. At this point, more investigations are required before evidence-based recommendations, if any, can be made.

9.2.6 Creatine Salts

Cr has been combined with different organic acids to form Cr salts with the intention of using acids that will create a synergistic effect or simply improve the properties of Cr. For example, creatine salts such as citrate, maleate, pyruvate, ketoisocaproate, and orotate have been available to consumers since as the late 1990s [18]. A limitation of combining Cr with organic acids to form a Cr salt is that effective daily doses of Cr and the acid will have to match CrM to achieve meaningful physiological effects. For example, the amount of Cr in different forms of Cr salts will vary. For example, CrM contains 87.9 % creatine, whereas Cr citrate, maleate, pyruvate, ketoisocaproate, and orotate contain 66, 66, 60, 50 and 45.8 % creatine, respectively [18].

Several investigations have used Cr salts to demonstrate a performance-enhancing effect. For example, Jager et al. [70] examined the effect of the administration of two different Cr salts

compared to CrM don plasma Cr concentrations and pharmacokinetics. In a balanced crossover designed study, six healthy subjects were assigned to ingest a single dose of isomolar amounts of creatine (4.4 g) in the form of CM, tricreatine citrate (TCC), or creatine pyruvate (CPY), followed by the measurement of the plasma creatine levels. Mean peak concentrations and area under the curve (AUC) were significantly higher with CPY (17 and 14 %, respectively) in comparison to CM. Although a small number of blood samples were taken, the findings suggested that different forms of creatine may result in slightly different kinetics of plasma creatine absorption. However, muscle biopsies were not taken to determine Cr accumulation, and the authors concluded that these small differences in kinetics are unlikely to have any clinically relevant effects on muscle Cr elevation during periods of Cr loading. In the second study, Jager and colleagues [71] evaluated the effect of oral CPY supplementation on exercise performance in healthy young athletes in comparison to placebo and TCC. Results indicated that 4 weeks of supplementation with these Cr salts significantly improved performance during intermittent handgrip exercise of maximal intensity and that CPY might benefit endurance, due to enhanced aerobic metabolism. Combined, these studies are the first indication that the Cr salt CPY may have comparable effects to CM. However, very few of these investigations have been able to show clear advantages over CrM. For a more detailed review of this topic, peruse Jäger et al. [18].

Despite marketing claims, novel forms of oral Cr such as Cr phosphate [42, 72], Cr serum [26], *Kre-Alkalyn*® [73], Cr PEG [74, 75], and Cr ethyl ester [76] have failed to show any clear benefit or advantage over CrM. For example, creatine ethyl ester (CEE) has been purported to be a superior form of creatine in comparison to CM. To test this hypothesis [76], compared the effects of supplementing the diet with a placebo, CM, or CEE during 42 days of resistance training. Serum Cr, creatinine, and muscle total Cr content were assessed prior to and following 6, 27, and 48 days of supplementation and training. The researchers found that CEE supplementation promoted a very modest increase in muscle total Cr content, compared to the Cr accumulation shown in the CM group at days 6 and 27. In fact, study participants ingested twice the recommended dose of CEE, yet the CrM group resulted in significantly higher levels of serum Cr than the CEE group. Previous studies have shown that CEE degrades rather quickly to creatinine when exposed to low pH levels as would be found in the stomach [77, 78]. In the Spillane trial, serum creatinine levels were significantly increased in the CEE group after 6, 27, and 48 days of supplementation indicating less efficient uptake. These findings directly contradict claims that CEE is more effective in increasing muscle Cr stores.

PEG is a compound consisting of repeated chain ethylene oxide units. The water-soluble properties of PEGylation may improve absorption, half-life, and resistance to pH degradation of Cr. PEG Cr has been analyzed in two human trials, one utilizing 1.25 and 2.5 g doses of PEG compared to 5 g doses of CrM [74, 75]. Results of these studies showed that while PEG Cr might be effective, it does not provide a clear advantage or benefit compared to CrM. According to product claims *Kre-Alkalyn*® is "up to ten times more powerful than ordinary Creatine." However, the only study to examine this claim by Jagim et al. [73] demonstrated that neither manufacturers recommended doses of this buffered form of Cr (*Kre-Alkalyn*®) (1.5 $g \cdot day^{-1}$) or loading (20 $g \cdot day^{-1}$ for 7 days) and maintenance doses (5 $g \cdot day^{-1}$ for 21 days) promoted greater changes in muscle Cr content, body composition, strength, or anaerobic capacity than traditional supplementation with CrM (20 $g \cdot day^{-1}$ for 7 days, followed by a maintenance dose 5 $g \cdot day^{-1}$ for 21 days). Additionally there was no evidence that supplementing the diet with a buffered form of Cr resulted in fewer side effects than CrM. Collectively the current body of literature involving novel forms of Cr shows clearly that none are more effective than CrM at increasing muscle Cr concentrations. Other popular compounds such as HMβ and β-alanine assessed in combination with CrM did not assess muscle Cr concentrations in response to supplementation, and therefore their results are discussed elsewhere in this chapter.

To summarize this section, supplement combinations that have been shown to increase muscle Cr concentrations are presented in Table 9.1. CrM's ergogenic potential and capacity to enhance the bioenergetics of the phosphagen system are thought to reside in the extent of Cr accumulation within muscle. This has led to increased interest in combining CrM with compounds to improve the uptake and accumulation of Cr within muscle. However, when viewed in comparison to the large body of literature that demonstrates CrM's widespread use, safety, and performance-enhancing effects, a relatively undersized amount of work documents effective strategies and supplement combinations that may improve muscle Cr accumulation in response to supplementation. Probably due to an insulin-stimulating effect on the cellular Cr transporter, combining each dose of CrM with an insulin-stimulating CHO and PRO (~50 g of each or a total of 1 $g \cdot kg^{-1}$) appears to be a most effective strategy to improve Cr accumulation. The combination of PRO and CHO is particularly effective when smaller doses of these macronutrients are desired. The current crop of insulin-mimicking compounds such as D-pinitol ALA and Russian tarragon still has not demonstrated clear data on Cr accumulation in muscle to warrant research-based recommendations. While some of the findings on Cr salts (pyruvate in particular) are interesting, it is difficult to find evidence or a rational that warrants their use over CrM. Despite marketing claims, none of the novel forms of Cr on the market (Cr serum, Cr PEG, Cr ethyl ester, and buffered Cr) can demonstrate any clear benefit or advantage over CrM, and definitely none are able to demonstrate they promote better Cr accumulation within muscle.

9.3 Supplement Combinations to Promote Muscle Glycogen

Along with the phosphagen system, glycolysis and glycogenolysis are considered to be important energy contributors during prolonged and high-intensity exercise. For example, while the depletion of CHO is considered one of the primary causes of fatigue and poor performance during prolonged, strenuous exercise [82], muscle glycogen also fuels the regeneration of ATP during short-term, high-intensity (anaerobic) exercise. During a set of 12 maximum-effort repetitions, just over 82 % of ATP demands are estimated to be met by glycogenolysis [83]. A single bout of high-intensity resistance exercise characteristically results in a significant reduction in muscle glycogen of 30–40 % [84–86]. Conversely, the synthesis and restoration of muscle glycogen is affected not only by the extent of depletion but also by the type, duration, and intensity of the preceding exercise [15–17, 82, 87, 88]. The rapid restoration of muscle glycogen stores is a critical issue for all athletes who undertake training or competition sessions on the same or successive days. In general, the faster muscle glycogen stores can be replenished after exercise, the faster the recovery process and the greater the return of performance capacity [88].

However, when considering nutritional strategies that promote glycogen synthesis and restoration, it is important to remember that high glycogen values (excess of 200 mmol·kg wet muscle weight) can be achieved without a depletion phase [87] and with as little as 24–36 h of rest and high CHO intake ($10 \cdot kg \cdot day$) [89, 90]. Additionally, even the short-term high-CHO loading (~10–12 $g \cdot kg \cdot day$) protocols utilized may not suit all athletes' circumstances. In fact, promoting supercompensatory glycogen levels might only be of benefit to select endurance events such as time trials or where critically low (25 mmol·kg wet weight) muscle glycogen occurs [91, 92]. It is exciting to see the recent literature shifts from sports nutrition to a more pragmatic focus beyond traditional glycogen-loading diets, the generic grams per day and the often irrelevant macronutrient percentage recommendations, and addresses more contemporary issues such as rapid refueling techniques [93], fueling during restricted carb intake [94], and other strategies that may increase CHO availability [95–98].

Table 9.1 Supplement combinations and their effects on muscle creatine accumulation

Reference	Comparison	Assessment	Protocol	Main findings
Green et al. [59]	CrM + CHO compared to CrM only	Muscle [PCr and Cr] before and after supplementation, no exercise	5 g CrM or 5 g CrM+ 93 g CHO (glucose) 4 × · day^{-1}, 5 days	After 5 days, 60 % greater [PCr] from CrM + CHO (P < 0.01)
Robinson et al. [60]	High-CHO diet with CrM vs. high-CHO diet without CrM	Muscle [PCr and Cr], one-legged cycle exercise to exhaustion preceded supplementation	20 g CrM · day^{-1} 5 days	After 5 days, 23 % greater increase in muscle [total Cr] in exercised limb (P < 0.01)
Greenwood et al. [61]	CrM + CHO compared to CrM only and effervescent Cr	Whole-body Cr retention via 24-h urine samples for 4 days, 3 days of supplementation, no exercise	5 g CrM + 18 g CHO (glucose) 4 × · day^{-1}, or equivalent dose of CrM, 3 days	After 4 days, greater Cr retention from CrM + CHO compared to other groups (P < 0.05) (~% CrM retained 0, 60, 80, & 60 for P, CrM, CrM + CHO, & effervescent Cr, respectively)
Preen et al. [62]	CrM + CHO compared to CrM only and CrM + exercise (E)	Muscle [PCr and Cr] before and after 5 days of intervention, one group performed exercise	CrM: 20 g · day^{-1} CrM + CHO: 20 g · day^{1} + glucose 1 g · kg^{-1}, 2 × · day^{-1} CrM + E: 20 g · day^{-1} + 60 min repeated sprints daily	After 5 days, 9 % greater increase in [total Cr] from CrM + CHO (P < 0.05) (25 % vs. 16 % & 18 % for CrM + CHO vs. CrM & CrM + E, respectively)
Derave et al. [79]	CrM + PRO compared to CrM only and placebo (P)	Muscle [PCr and Cr] prior to and after 2-week right-leg immobilization followed by 6 weeks of right-leg resistance training	CrM: 15 g · day^{-1} during immobilization followed by 2.5 g · day^{-1} during rehabilitation CrM + PRO: CrM dose + 40 g protein and 6 g AA during training	After training, ~30 % increase from baseline in [total Cr] (right leg) in both CrM and CrM + PRO vs. P (P < 0.05)
Steenge et al. [43]	CrM + CHO (low & high dose) compared to CrM + CHO + PRO	Insulin and whole-body Cr retention values (24 h) before and after each supplement trial (all participants completed 4 trials)	CrM (4 × 5 g) +5 g CHO +50 g CHO, +93 g CHO or + PRO + CHO (50 g each)	After 24 h PRO + CHO provided similar insulin responses and [total Cr] accumulation values (~25 %) as high-dose CHO (P < 0.05)
Cribb et al. [63]	Compared CrM + CHO and CrM + PRO to CHO and PRO alone	muscle [PCr and Cr] before and after 11 weeks of resistance exercise	All groups: 1.5 g of supplement · kg · day^{-1} for 11 weeks CrM groups: 0.3 g · kg · day^{-1} 5 days followed by 0.01 g · kg · day^{-1} for 10 weeks	After 11 weeks, ~10 % increase from baseline, [total Cr] after 11 weeks in both CrM + CHO and CrM + PRO groups (P < 0.05)
Cribb et al. [80]	Compared PRO + CHO to CrM + PRO + CHO and PRO alone	Muscle [PCr and Cr] before and after 10 weeks of resistance exercise	All groups: 1.5 g of supplement · kg · day^{-1} for 11 weeks. CrM groups: 0.3 g · kg · day^{-1} 5 days followed by 0.01 g · kg · day^{-1} for 10 weeks	After 11 weeks, ~10 % increase from baseline, [total Cr] after 11 weeks in both CrM + CHO and CrM + PRO groups (P < 0.05)

(continued)

Table 9.1 (continued)

Reference	Comparison	Assessment	Protocol	Main findings
Cribb and Hayes [67]	Compared supplement timing, CrM + PRO + CHO before and after resistance exercise, to the same supplement at times not close to training	Muscle [PCr and Cr] assessed before and after 10 weeks of resistance exercise	Dose: 1.g supplement $\cdot$ kg^{-1} 2× $\cdot$ day^{-1} (CrM: 0.01 g $\cdot$ kg $\cdot^{-1}$) Taken immediately before and after workouts. Or twice a day 5 h outside workouts, 10 weeks	After 10 weeks, 14 % greater increase in [PCr] and 18 % greater increase in [total Cr] from supplement timing (PCr 16 % vs. 2 %; total Cr 25 % vs. 7 %, respectively) ($P < 0.05$)
Greenwood et al. [69]	Compared CrM+ D-pinitol high dose (HP) and low dose (LP) as well as pre-dosing (PreP) to CrM only and placebo (P)	Whole-body Cr retention via 24-h urine samples for 4 days, 3 days of supplementation, no exercise	CrM 4×5 g +2×0.5 g D-pinitol (LP) +4×0.5 g D-pinitol (HP) D-Pinitol 2×0.5 g D-pinitol 5 days prior to and during CrM (PreP)	After 4 days, whole-body Cr retention was greater in LP and PreP compared to HP, CrM only and P ($P < 0.05$) (% CrM retained 0 ± 0, 61 ± 15, 83 ± 5, 61 ± 22, and 78 ± 9 % for P, CM, LP, HP, and pre-P groups)
Burke et al. [73]	Compared ALA + CrM + CHO to CrM + CHO and CrM only	Muscle [PCr and Cr] assessed before and after 5 days of intervention	CrM: 20 g $\cdot$ day^{-1} +100 g $\cdot$ day^{-1} sucrose (CrM + CHO) +1000 mg $\cdot$ day^{-1} ALA (ALA + CrM + CHO)	After 5 days, greater increase in [PCr] and [total Cr] from ALA + CrM + CHO ($P < 0.05$) compared to CrM + CHO and CrM only (% increase for [PCr] 21, 0, & 0 %; [total Cr] 13.8, 2, & 4 % for ALA + CrM + CHO, CrM + CHO, and CrM, respectively) ($P < 0.05$)
Spillane et al. [57]	Compared maltodextrin placebo (PLA), CrM, and creatine ethyl ester (CEE)	Serum and muscle Cr assessed days 0, 6, 27, and 48 during a 4-day per week resistance-training program in young adult males	0.30 g/kg LBM for 5 days followed by ingestion at 0.075 g/kg LBM for 42 days. Note CEE dose was double the manufacturer's recommendation	Higher serum Cr concentrations in CrM ($p = 0.005$) compared to CEE Total muscle Cr content higher in CrM ($p = 0.026$) and CEE ($p = 0.041$) compared to PLA, CrM increased total muscle Cr levels at days 6 and 27. CEE only on day 27 Serum creatinine was greater in CEE compared to the PLA ($p = 0.001$) and CRT ($p = 0.001$) and increased at days 6, 27, and 48
Kerksick et al. [39]	Compared creatine + pinitol (CRP) or creatine monohydrate (CR)	Whole-body Cr retention via urine samples before during and after 4 weeks of resistance training	Loading phase (i.e., 20 g/day 1 for 5 days) before ingesting 5 g/day 1 the remaining 23 days	Creatine retention increased ($p < 0.001$) in both groups as a result of supplementation but was not different between groups ($p > 0.05$)

(continued)

Table 9.1 (continued)

Reference	Comparison	Assessment	Protocol	Main findings
Jagim et al. [40]	Compared CrM with KA (*Kre-Alkalyn)* low dose (KA-L) and higher dose (KA-H)	Muscle Cr content 0, 7, and 28 days during the participants' own resistance-training program	CrM 4 × 5 g/day for 7 days, maintenance (5 g/day for 21 days) KA manufacturer's recommended dose KA-L = 1.5 g/day for 28 days. KA-H = equivalent loading to CrM	No overall differences were detected except KA-L did not increase muscle free creatine content to the same degree as loading and maintenance doses of CrM (KA-L −1.1 ± 4.3, CrM 11.2 ± 4.3 mmol/kg DW, $p = 0.053$ KA-L 2.4 ± 8.5, CrM 24.6 ± 8.5 %, $p = 0.078$
Oliver et al. [81]	Compared RT extract or 500 mg placebo during 5 days of CrM loading	Muscle Cr content and whole-body daily Cr retention	Double-blind, randomized, and crossover manner, 500 mg of aqueous RT extract, or 500 mg placebo 30 min prior to ingesting 5 g of CrM twice per day for 5 days, then repeated after a 6-week washout period	Whole-body daily Cr retention increased in both groups. However, the addition of RT did not enhance whole-body Cr retention or muscle free Cr content

9.3.1 Before Exercise

More recent guidelines recommend that athletes undertake their activity and daily training sessions with high-CHO availability [95, 99]. This is based on clear evidence that strategies such as elevating pre-exercise muscle glycogen stores, consuming a pre-exercise CHO meal, or eating CHO during exercise increase endurance [93, 95] and performance [96, 99]. The concept of promoting CHO availability resides in the manipulation of the amount, type, and timing in the hours or days prior to and during the session and refueling recovery between sessions to provide athletes with practical recommendations. Choices that provide a high-CHO availability contain a comparatively high amount of energy and CHO, such as glucose (other sugars, polymers in sports drinks etc.). However, the extent of CHO availability is also often reflected in the degree of fiber and processing. In general, CHO choices toward the top of the list provide the most concentrated, easily assimilated source of fuel such as cereals and grain products. They are easily identified via packaging and often an extensive ingredient list. Conversely, CHO choices with low availability generally contain a proportionally higher fiber content (such as pulses and legumes) and/or a lower amount of energy and CHO (most vegetables). For a complete list and discussion on foods that promote CHO availability, refer to Cribb [98]. Athletes are often prescribed CHO recommendations in grams per day to meet goals in their training phases. An advantage of the high or low availability classification is the clear identification and prescription of carb choices to either promote or restrict CHO availability to suit individual needs and goals during each training phase. For example, the endurance athlete can make clear, confident selections based on their grams per day prescription to promote CHO availability in the days and hours leading up to and during sessions as well as strategic refueling after strenuous endurance-based activities to optimize glycogen synthesis rates, particularly if the next bout of exercise is less than 8 h away. Conversely, many strength athletes characteristically restrict CHO intake during intense training [100, 101].

One bout of resistance exercise can decrease muscle glycogen stores in the vicinity of 24–40 % [84–86], and extensive exercise-induced muscle damage can also affect glycogen uptake and synthesis [102]. CHO availability can affect work capacity, some anabolic and muscle-specific catabolic responses. The reader is recommended a more detailed discussion and application of CHO availability [98].

Pre-exercise meals and supplementation have been a considerable focus of exercise research because of its impact on substrate utilization [103–105]. However, the respective cases for high- or low-glycemic index pre-exercise meals to optimize performance appears to be equivocal [106, 107] and might be negligible, as the opportunity to consume CHO during exercise seems to nullify any glycemic characteristics of pre-exercise meals [108–110]. It is presumed that CHO immediately before and during exercise can provide an additional fuel source that may spare muscle glycogen, prevent low blood glucose concentrations, attenuate effort perception, and benefit the central nervous system as well as promote glycogen resynthesis during low-intensity periods [108–113]. Probably for these reasons, the investigation of CHO "fuel mixes" during exercise has received considerable attention.

9.3.2 During Exercise

Throughout the 1990s it was presumed that the oxidation (utilization) rate of exogenous CHO was a maximum of 60 g·h—larger amounts would likely not be metabolized and may cause gastrointestinal distress. However, most recent work suggests CHO intake rates can vary greatly among athletes, from 6 to 136 g·h, and variations at both ends of this scale can result in nausea and flatulence but also winning performances during ultra-endurance races [109]. Studies that have systematically tracked oxidation rates of various CHO sources and combinations now reveal that the rate limiting step in the oxidation of ingested CHO could be intestinal absorption, with limits on absorption of glucose in its various forms by the sodium-dependent glucose transporters (e.g., fructose via GLUT5 and glucose via SGLT1) [79, 114]. For example, limit on the absorption of glucose in its various forms via the sodium-dependent glucose transporter SGLT1 is ~1 g·min. When glucose is combined with fructose (a CHO with a different transporter), rates of ingested CHO can exceed 1.5 g·min. It appears that exogenous CHO oxidation to maintain power output when glycogen becomes depleted converges at a CHO ingestion rate of 80–90 g·h at least when glucose and fructose are co-ingested in a 2:1 ratio [97]. Generally, fluids/gels/bars that contain "multiple transporter CHOs" appear to be well tolerated [115, 116], promoting greater oxidation efficiency (less CHO remaining in the gastrointestinal tract) [79, 114–117] and delivering high rates of CHO [116, 118] and performance benefits when compared to glucose alone, particularly in activities lasting 3 or more hours [119, 120]. Based on this new information on CHO supplement combinations, new guidelines to promote individual experimentation with CHO intakes of up to 90 g·h in ultra-endurance sports have been proposed [93].

9.3.3 Post-exercise Refueling

Rapid recovery for subsequent performance is a prerequisite for effective training and competition, and this predominately relies upon the restoration of glycogen stores. Rapid restoration of glycogen stores is essential if exercise is required again within 24 h [95]. However, even for daily exercise, there is the real possibility that muscle glycogen would not be adequately replenished unless strategies are implemented. For example, pre-exercise muscle glycogen stores of endurance athletes are usually ~600 mm·kg·dry weight, and exhaustive exercise can deplete stores to 30–55 mm·kg dry weight [87, 121, 122]. Post-exercise glycogen synthesis rates can vary from ~5 to 58 mm·kg·dry weight·h [122–124] depending on the type and amount of fuel consumed. Therefore, maximum glycogen restoration could be achieved efficiently within 5–6 h or could take up to 48 h, depending upon the strategies (or the lack of) implemented. The process of

refueling does appear to be highly dependent on the provision of nutrients. For example, a delay in CHO intake post-exercise could result in a decrease in glycogen synthesis of up to 50 % [123]. Conversely, strategies that involve the consumption of rather high intakes (1.2 kg·h) report the highest rates for glycogen synthesis [93–95]. However, these amounts might not be practical for all athletes.

Combining a lower CHO intake with PRO supplements can assist with maximizing glycogen stores. Reported rates of muscle glycogen resynthesis across nine studies that have compared muscle glycogen storage over 2–6 h post-exercise with varied rates of CHO intake suggest that the addition of PRO to CHO intake (less than 1.2 g·kg·h) will enhance muscle glycogen synthesis [94]. CHO to PRO ratios of 4:1 have been suggested for refueling [93]. However, other ratios such as 2:1 or 3:1 may provide similar benefits, at least with regard to DOMS and markers of skeletal muscle damage [124]. In general, it appears that the addition of PRO to a CHO supplement will increase the rate of muscle glycogen storage during the hours immediately after exercise, particularly if the supplement contains a low to moderate amount of CHO. The combination of PRO and CHO may accelerate the rate of muscle glycogen storage possibly by activating glycogen synthesis by two different mechanisms. Firstly, this combination may raise plasma insulin levels beyond that typical of CHO alone, which may augment muscle glucose uptake and activate glycogen synthase via insulin-dependent and insulin-independent pathways [88]. Thus, these combinations have an additive effect on the activity of this enzyme. Glucose, sucrose, and glucose polymer supplements as well as high-CHO availability whole-food sources are an effective means of replenishing muscle glycogen. However, the type of PRO (or amino acids) that may be best to combine with CHO has received less attention. Studies that have reported a beneficial impact on muscle glycogen synthesis from the addition of PRO to a CHO supplement have utilized dairy sources [88, 125, 126] such as whey isolates [88, 127] and hydrolyzed PRO supplements in conjunction with insulin-promoting amino acids (AA) such as leucine and phenylalanine [128, 129]. In fact, studies that have examined this area directly suggests that insulin responses to PRO–CHO supplementation may be positively correlated with plasma concentrations of AA such as leucine, phenylalanine, and tyrosine [129]. Therefore, the concentration of certain AA within the supplement may underline its ability to stimulate insulin and, therefore, muscle glycogen restoration.

CrM, and more recently caffeine, has been documented as possible synergists that act with CHO to aid in glycogen synthesis rates [122]. In fact, Pedersen et al. [122] demonstrated the combination of CHO + caffeine (2 × 4 mg·kg) post-exercise can improve glycogen synthesis rates to a greater extent than CHO + PRO or CHO alone. In fact, the glycogen synthesis rates for this combination (~58 mmol·kg dry weight·h vs. 38 mmol·kg dry weight·h for CHO only) are one of the highest recorded responses for post-exercise CHO consumption [122]. Taylor et al. [130] recently utilized a similar post-exercise CHO + caffeine timing strategy and reported a significant improvement in a subsequent bout of high-intensity interval running [130]. However, the benefits need to be considered with associated side effects. Large doses of caffeine can produce nausea and disrupt sleep.

As discussed previously, supplementation with CrM promotes an ergogenic effect by enhancing PCr availability in muscle. However, another ergogenic effect from this supplement appears to be its positive impact on muscle glycogen storage. Seven studies have measured muscle glycogen levels in humans after CrM supplementation, and six have reported a stimulatory effect [53, 60, 131–134]. Robinson et al. [53] first showed that CrM supplementation in conjunction with a high-CHO diet for 5 days (after a bout of exhaustive exercise) resulted in 23 % greater increase in muscle glycogen as compared with a high-CHO diet without CrM. Nelson et al. [131] reported that loading with CrM for 5 days enhanced a subsequent 3 days muscle glycogen-loading protocol by 12 %. Op ‘t Eijnde et al. [132] demonstrated that supplementation with CrM (20 g daily) had no effect on muscle glycogen

stores during 2 weeks of leg immobilization. However, further administration (15 g daily) did enhance muscle glycogen levels (by 46 % greater than placebo) during 3 weeks of subsequent strength training. In a follow-up study that involved a similar protocol (and a 6-week training phase), these researchers reported that supplementation with PRO (46 g) combined with CrM augmented post-training muscle glycogen by 35 % greater than placebo (but not CrM alone) [133, 134]. Van Loon et al. [134] demonstrated that a 5-day CrM-loading phase augmented muscle glycogen by 14 % compared with no change in the placebo group. Furthermore, this study confirmed a significant correlation between changes in muscle Cr (mean increase of 32 %) and muscle glycogen during the loading phase. This substantiates other work [131–133] that suggests significant increase in muscle Cr is a prerequisite for enhanced muscle glycogen storage [28]. Supplementation with CrM + CHO or PRO during exercise increases muscle glucose transporter (GLUT-4) expression and glycogen storage [132, 133]. Treatment with CrM has also been shown to increase total body water including intracellular cell volume [135]. Changes in cell volume (cellular water content) have been shown to influence glycogen levels [136]. Therefore, the ability of CrM to influence GLUT-4 biogenesis and/or regulate cell volume may explain its beneficial impact on muscle glycogen storage. Overall, the findings of these studies suggest that increasing muscle Cr (by ~20 %) via supplementation ensures a beneficial impact on glycogen storage. However, for some athletes, careful consideration is needed when contemplating the addition of CrM. For example, loading with CrM characteristically results in a 1–3-kg gain in body weight (lean mass) [14, 20–22, 24, 25]. This added mass may offset any potential ergogenic benefit that might be achieved via boosting muscle glycogen stores. Therefore, in sports where any gain in body weight may disadvantage the athlete, the combination of PRO–CHO (without CrM) may be a more prudent choice to promote muscle glycogen. However, for all athletes, alongside more efficient glycogen restoration, another important advantage of PRO–CHO post-exercise supplementation is this combinations' well-documented effect on synthesis and muscle anabolism.

9.4 Supplement Combinations to Enhance Muscle Anabolism

Any favorable adaptive change in muscle must involve alterations in protein turnover. That is, the difference between rates of muscle protein synthesis (MPS) and muscle protein breakdown (MPB) determines net protein balance (NPB) [137]. A single bout of resistance exercise results in the acute stimulation of MPS 50–100 % above basal values which peaks within 3 h and remains elevated at a diminishing rate for up to 48 h post-exercise [138, 139]. NPB after resistance exercise remains negative, until nutrition, namely, a PRO source, is provided. The stimulation of MPS is the critical regulatory event in protein turnover that underlines changes in muscle mass [140]. The majority of acute-response investigations have shown that the consumption of amino acids/PRO close to resistance exercise results in the amplification of MPS, and the effect appears to be synergistic rather than simply additive [141, 142]. A CHO supplement (glucose, other sugars, and polymers) alone, before, during, or after resistance exercise, does not appear to alter the MPS [143] response, but it may reduce myofibrillar breakdown [144, 145] and circulating cortisol which can correspond with a greater increase in muscle fiber hypertrophy [146, 147]. Interestingly, the combination of a CHO supplement (such as glucose) with essential amino acids (EAA) (6–40 g), before or after resistance exercise, provides a synergistic effect on MPS and NPB that is much greater than either macronutrient alone [148–150]. In fact, when this combination is consumed 1 or 3 h after a single bout of resistance exercise, MPS rates were shown to increase up to 400 % above pre-exercise values, the highest value ever recorded [142]. While earlier investigations reported positive effects from amino acids, it is now clear that intact PRO supplements such as whey, casein, soy, and even

whole milk evoke an anabolic response that can be similar in magnitude to free form amino acids [151, 152]. These acute-response investigations paved the way to more recent work that has examined the interaction of PRO–CHO supplementation on the molecular events associated with the activation of MPS.

9.4.1 Supplement Timing

For instance, the mTOR complex and its downstream mRNA translational signaling proteins ($p70^{S6K}$, eIF-2B, and 4E-BP1) appear to be the focal molecular intersection point in the cascade that results in very high rates of MPS [153]. The EAAs [154] and particularly the branched-chain amino acid (BCAA) [155] stimulate MPS independently, directly via activation of this complex. Supplement timing with PRO–CHO ensures a higher activation of molecular events associated with increased MPS rates which is thought to underline improved adaptations from exercise, and these benefits are not exclusive to strength athletes [156–161]. For example, via the same molecular signaling pathway, PRO–CHO supplement timing stimulates a greater increase in MPS in other high-intensity anaerobic exercise, such as sprints [157]. This strategy also selectively stimulates a greater increase in myofibrillar MPS following prolonged cycling, and this increase appears to be mediated via the mTOR complex [153]. A higher activation of the mTOR signaling pathway, via supplement timing with PRO–CHO, not only modulates MPS but also upregulates glycogen synthesis [159] to improve recovery and subsequent exercise performance [160]. Ferguson-Stegall et al. [156, 160] reported that a PRO–CHO supplement (in the form of low-fat chocolate milk) alters the phosphorylation levels of this signaling cascade in a manner that accelerates muscle glycogen synthesis during recovery to improve performance in a subsequent bout of cycling exercise (see Sect. 8.1: Delicious Combination). Therefore, supplement timing with PRO–CHO, in close proximity to aerobic and anaerobic exercise training, results in the higher activation of the molecular signaling pathways that regulate muscle and glycogen synthesis. Additionally, strategies that promote and maintain muscle glycogen during exercise programs may provide the best chance of maximal activation of the signaling pathways that stimulate MPS during resistance exercise.

It is clear that the strategic intake of PRO–CHO before and/or after intense exercise not only augments MPS, most importantly it shifts net protein balance to a positive state. This anabolic response can be at least partly attributed to changes in the anabolic hormonal response pattern of insulin. This PRO–CHO-induced stimulation of insulin is important; it improves the anabolic response by increasing AA uptake and decreases the rate of muscle protein breakdown [142, 143, 145]. Despite over 15 years of investigations, the research on supplementation's ability to modulate anabolic hormones, such as growth hormone, IGF-1, and testosterone in a way that may lead to changes in strength and muscle mass, is at best equivocal [162–165]. More recent work suggests transient increases in endogenous anabolic hormones do not enhance fed-state anabolic signaling or MPS following resistance exercise and quite possibly have little to do with strength and hypertrophy outcomes [166].

The EAAs and particularly the BCAAs stimulate MPS independently, via a different pathway to insulin [159]. The BCAA leucine has a controlling influence over the activation, but not the duration, of MPS [167]. Increasing the leucine concentration of a PRO serving (to ~40 %) can increase resting MPS [168] and post-exercise [169] as a high rate of MPS from feeding is the underlying mechanism for changes in muscle mass [140]. This lead to a flurry of investigations that assessed the effects of adding leucine to PRO supplements in an attempt to augment MPS rates. However, several research groups have failed to achieve a greater elevation of MPS by adding leucine to a moderate dose of high-quality PRO (10–30 g) at rest [170] and post-exercise [171, 172]. Glynn et al. [170] reported no added benefit for resting human MPS in response to an optimal dose (10 g) of EAA that provided a higher concentration of leucine (3.5 g compared to 1.8 g). In fact, a low dose of whey PRO (6 g) with added

leucine or all other essential amino acids (to the equivalent of 25 g of whey PRO isolate) was not as effective as 25 g of whey PRO isolate alone at sustaining increased rates of MPS post-exercise [172]. These findings are important because they show that an EAA profile from high-quality PRO is sufficient for stimulating MPS in humans and additional leucine does not provide added benefit to MPS. Nevertheless, the ability of various PRO/AA supplement combinations to augment the anabolic response to exercise may well be population specific [173]. Combining PRO with leucine to optimize MPS and anabolism may be a good strategy for populations such as the elderly but also military where larger PRO servings (20 g or more) are difficult to incorporate into a feeding plan [174].

9.5 Combinations that Enhance Aerobic/Anaerobic Performance

Caffeine is a naturally occurring substance that is a widely consumed in a variety of forms. Caffeine produces multiple physiological effects throughout the body including increased catecholamine release and fat metabolism, resulting in glycogen sparing, increased intracellular Ca2+ release, inhibition of cAMP phosphodiesterase, and antagonism of adenosine receptors [175]. Several studies have demonstrated an improvement in exercise performance in submaximal endurance activities [81, 175–178], while its potential ergogenic effect in acute, high-intensity exercise is less clear in untrained individuals [175]. However, in a systematic review, studies using trained subjects and models specific to intermittent sports activity support the idea that caffeine is potentially ergogenic with anaerobic exercise [80]. Ephedrine was used as a CNS stimulant in China for centuries before its introduction to Western medicine in 1924 [179]. Ephedrine and its related alkaloids (mostly pseudoephedrine) are sympathomimetic agents which stimulate the sympathetic nervous system, increasing circulating catecholamines [180]. A number of studies have reported beneficial effects on exercise performance using ephedrine as the supplement [181, 182], whereas limited studies have reported benefit utilizing the related alkaloids such as pseudoephedrine [183, 184]. This is most likely due to ephedrine's direct adrenoceptor stimulating actions [185] and, therefore, is approximately 2.5-fold more potent than pseudoephedrine [183]. Though both caffeine and ephedrine have demonstrated independent ergogenic effects on exercise performance, research published from Doug Bell and Ira Jacob's lab at the Defense and Civil Institute of Environmental Medicine in Canada has reported in several instances that caffeine–ephedrine mixtures confer a greater ergogenic benefit than either drug alone [181, 186–189]. In a series of studies performed by Bell and Jacob [181, 186–188], enhancement of performance was observed during various exercise modalities: submaximal steady-state aerobic exercise [188], short- and long-distance running [186, 188], and maximal anaerobic cycling [187]. The caffeine–ephedrine mixture was consumed 1.5 to 2 h prior to exercise with a dosage range of 4–5 mg/kg for caffeine and 0.8–1 mg/kg for ephedrine [181, 186–188]. However, it should be noted that dosages above this were shown to illicit negative side effects such as vomiting and nausea during the exercise test. With this in mind, Bell and colleagues recommended using the lower dosage of 4 mg/kg and 0.8 mg/kg for caffeine and ephedrine, respectively. Importantly, the lower dosage still provided an ergogenic effect similar in magnitude to those reported previously using the higher doses [190].

Notwithstanding the independent effects from caffeine and ephedrine on metabolic and cardiovascular responses during exercise, no ergogenic effects on exercise performance were observed. However, when combined, exercise performance was significantly enhanced in a variety of exercise modalities. Researchers suggested that this is most likely due to ephedrine's effect on arousal (i.e., decreasing rating of perceived exertion during exercise), combined with caffeine's ability to enhance muscle metabolism [188, 189, 191]. Indeed Williams et al. [192] were also able to show increased alertness and enhancement of mood following ingestion of similar doses of

caffeine (300 mg) and ephedra (60 mg) 45 min prior to exercise testing. However, despite these improvements, caffeine and/or ephedra was unable to enhance muscle strength, muscle endurance, and peak anaerobic power. Given the beneficial effects of caffeine and ephedrine have predominately been observed in studies involving the Canadian military, it is clear that further research is needed to examine the practical application in recreational athletes and untrained individuals. However since 2006, all dietary supplements containing ephedrine alkaloids are illegal for sale in the United States [193]. Therefore, until ephedrine and ephedrine alkaloids are made legal again, very few studies if any are investigating the performance-enhancing effects of caffeine–ephedrine mixtures.

Recently, other ergogenic aids such as sodium bicarbonate (NaHCO3) and carbohydrate have also been used in combination with caffeine [194–196]. A recent systematic literature review examined the benefit of co-ingestion of caffeine and carbohydrate ingestion on endurance-exercise performance [197]. Criteria for inclusion were studies that used human subjects performing an endurance-exercise performance task and included both a carbohydrate and carbohydrate–caffeine condition. Based on effect size analysis, the authors concluded that co-ingestion of carbohydrate and caffeine provides a significant but small effect to improve endurance performance compared to carbohydrate alone. This was also confirmed in a recent study that showed that ingesting carbohydrate and caffeine 1 h before, prior to and during an intermittent sprint test (modified version of the Loughborough Intermittent Shuttle Test), was effective at transiently reducing fatigue and rating of perceived exertion while maintaining higher glucose levels at the final stages of the exercise test [198]. Conversely, co-ingestion of caffeine and carbohydrate was unable to improve high-intensity sprint cycling performance or reduce fatigue in active males. Interestingly, the combined caffeine and carbohydrate group demonstrated higher cortisol levels during the prolonged high-intensity intermittent exercise suggesting higher catabolism [196]. In contrast to the potential benefits of combining caffeine with carbohydrate, the combination of caffeine with sodium bicarbonate seems to provide no added benefit [194, 195]. Two recent studies used trained individuals to examine the combined effects of caffeine and sodium bicarbonate on high-intensity cycling performance and 2,000-m rowing performance [194, 195]. Despite independent benefits of supplementation, co-ingestion provided no greater advantage. Interestingly, while both studies used the same dosage of sodium bicarbonate (0.3 g/kg body mass), only one study demonstrated negative side effects [194].

The benefits of CrM to athletes are clear (Sect. 1.1). One proposed ergogenic benefit is the capacity of CrM to help maintain normal muscle pH levels during high-intensity exercise by consuming excess hydrogen ions during ATP resynthesis and thus possibly delaying fatigue (refer to Sidebar: the multifaceted role of the muscle PCr–Cr system in exercise metabolism). The intake of sodium bicarbonate ($NaHCO_3$) has also been shown to prevent exercise-induced perturbations in acid–base balance; this has resulted in enhanced performance [199–201]. Mero and colleagues [202] examined the buffering capacity of sodium bicarbonate in combination with CrM on consecutive maximal swims. In a double-blind crossover procedure, competitive male and female swimmers completed, in a randomized order, two different treatments (placebo and a combination of CrM and sodium bicarbonate). Thirty days of washout period was given between treatments. Both treatments consisted of placebo or CrM supplementation (20 g per day) for 6 days. In the morning of the seventh day, a placebo or sodium bicarbonate supplement (0.3 g per kg body weight) was taken 2 h prior to the warmup. Two maximal 100-m freestyle swims were performed with a passive recovery of 10 min in between. The first swim performances for both treatment groups were similar in time. However, the increase in time for the second swim performances was significantly less in the combination group compared to the placebo. Further, mean blood pH was higher in the combination group compared to the placebo group after supplementation on the test day. The data

indicated that simultaneous supplementation of CrM and sodium bicarbonate enhances the buffering capacity of the body and hence anaerobic performance [202]. In addition, using a similar CrM dosage but higher sodium bicarbonate dosage (0.3 g vs. 0.5 g per kg body weight), Barber and colleagues supported the benefits of co-ingestion of CrM and sodium bicarbonate on high-intensity, intermittent exercise in trained cyclists [203].

In summary, it is evident that when nutritional supplements with complimentary independent ergogenic effects are combined together, additional benefits can be attained. Caffeine–ephedrine, caffeine–carbohydrate, and CrM/sodium bicarbonate supplement mixtures have shown in research to provide an acute physiological response that enhances anaerobic and/or aerobic exercise. However, a number of limitations exist with both supplements. As mentioned, further research is needed to examine the practical application of caffeine–ephedrine combination in recreational athletes and untrained individuals, since most of the research has been performed in military soldiers. However, given the ban on selling ephedra products in the United States in 2006, it is unlikely that more research into the ergogenic potential of ephedra is unlikely. While sodium bicarbonate is a legal supplement, limited studies have examined its ergogenic effects on exercise performance when combined with CrM, and thus, further investigation is needed to confirm such observations.

Sidebar

Delicious Combination: The Efficacy of Low-Fat Chocolate Milk as a Post-exercise Carbohydrate–Protein Supplement

Lisa Ferguson-Stegall, Ph.D.

We examined the effects of a common and popular dairy beverage, low-fat chocolate milk, as a carbohydrate–protein supplement, and investigated its effects on recovery, as well as in adaptations to training [156, 160].

(continued)

We first investigated the effects of chocolate milk, compared to carbohydrate and placebo, on recovery from an acute exercise bout and subsequent cycling time trial performance [156]. Ten trained cyclists rode a 90-min glycogen depletion ride, followed by a 4-h recovery period in the laboratory. During this recovery time, the participants ingested chocolate milk, isocaloric carbohydrate, or placebo immediately post-exercise and again 2 h later. Muscle biopsies were taken to measure muscle glycogen resynthesis rates, as well as signaling protein activation states during recovery. After the 4-h recovery, the cyclists performed a 40-km time trial (TT) at race effort. We found that time trial performance was significantly faster when the subjects consumed the chocolate milk during recovery compared to the carbohydrate or the placebo supplements, although muscle glycogen restoration was not different between the chocolate milk and carbohydrate treatments. We also found that the proteins that control protein synthesis were activated to a greater extent after ingesting the chocolate milk beverage than the carbohydrate or placebo. Therefore, chocolate milk was shown to be a highly effective recovery supplement when ingested immediately and 2 h post-exercise [156]. From these results, we hypothesized that if chocolate milk were ingested post-exercise during an endurance training program, training adaptations would be significantly greater than if supplementing with carbohydrate only or nothing at all after each workout.

To test our hypothesis, we investigated the effects of consuming chocolate milk, isocaloric carbohydrate, or placebo after daily aerobic endurance sessions over a 4-week training program in healthy, but untrained subjects [160]. The average age was 22.0 ± 0.5 years, and average weight was 71.7 ± 2.4 kg. The average baseline

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VO_{2max} was 35.9 ± 1.9 ml/kg/min (absolute VO_{2max} = 2.6 ± 0.2 L/min). The participants were randomized into three groups: chocolate milk, carbohydrate, and placebo. The participants cycled at 75–80 % VO_{2max} for 60 min/day, 5 days/week for 4.5 weeks. Immediately upon completion of each cycling session, and again 1 h later, they ingested their supplemental beverage. The chocolate milk and carbohydrate beverages contained the same amount of energy and were matched for the small fat content. The placebo was artificially colored and flavored, but contained no calories. The beverages were prepared according to the body weights of the subjects, such that chocolate milk provided an average of 0.94 g carbohydrate, 0.31 g protein, and 0.17 g fat per kg body weight. The carbohydrate supplement provided an average of 1.25 g carbohydrate and 0.17 g fat per kg body weight. After 4.5 weeks of training, all three groups demonstrated significant increases in absolute and relative VO_{2max}. The average absolute VO_{2max} (L/min) increase for all subjects in the three treatment groups combined was 9.2 %. However, the most profound and exciting finding of this study was that the increase in both absolute and relative VO_{2max} was significantly greater in the chocolate milk group compared to carbohydrate and placebo groups (Fig. 9.2a, b). The average increase in absolute VO_{2max} for the chocolate milk group was 12.5 % higher than baseline levels, a twofold improvement over the increase found in the carbohydrate and placebo groups. Muscle oxidative capacity (measured by citrate synthase and succinate dehydrogenase activity, as well as PGC-1α content) and lactate threshold improved significantly in all treatment groups, with no differences found between treatments.

This suggests that the adaptations that lead to increased VO_{2max} in the chocolate milk group was cardiovascular rather than cellular in nature. We also found that the chocolate milk group experienced greater gains in lean tissue, along with greater reduction in fat mass after only 4.5 weeks of aerobic endurance training. Thus, the dairy treatment improved body composition compared to carbohydrate or placebo supplementation, which is a novel finding [160]. In summary, whether an individual is training for elite competition, or exercising regularly to improve fitness, body composition, and health, chocolate milk can be used as an effective—and delicious—post-exercise recovery beverage.

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9.6 Chronic Adaptations: Supplement Combinations that Promote Muscle Hypertrophy and Strength

In 1996, the formative work of Dr. Richard Kreider's research group rejuvenated a stale and benign topic by demonstrating that a CrM-containing supplement could significantly enhance strength and lean mass in resistance-trained individuals in less than a month. Utilizing 25 NCAA division IA football players, Kreider et al. [25] demonstrated that 28 days of supplementation with CrM–CHO (containing 99 $g \cdot day^{-1}$ glucose, 15.75 $g \cdot day^{-1}$ CrM) resulted greater ($P < 0.05$) gains in dual-energy x-ray absorptiometry (DEXA)-determined body mass and lean (fat-/bone-free) body mass (LBM) compared to an equivalent dose of CHO. Treatment with CrM–CHO also resulted in greater total bench press, squat, and power clean lifting volume and sprint performance [25]. This seminal work fueled a subsequent explosion of studies that examined the effects of various CrM-containing supplements on the chronic adaptations desired from resistance training. Burke et al. [57] assessed strength and LBM changes after 6 weeks of resistance exercise while ingesting a supplement

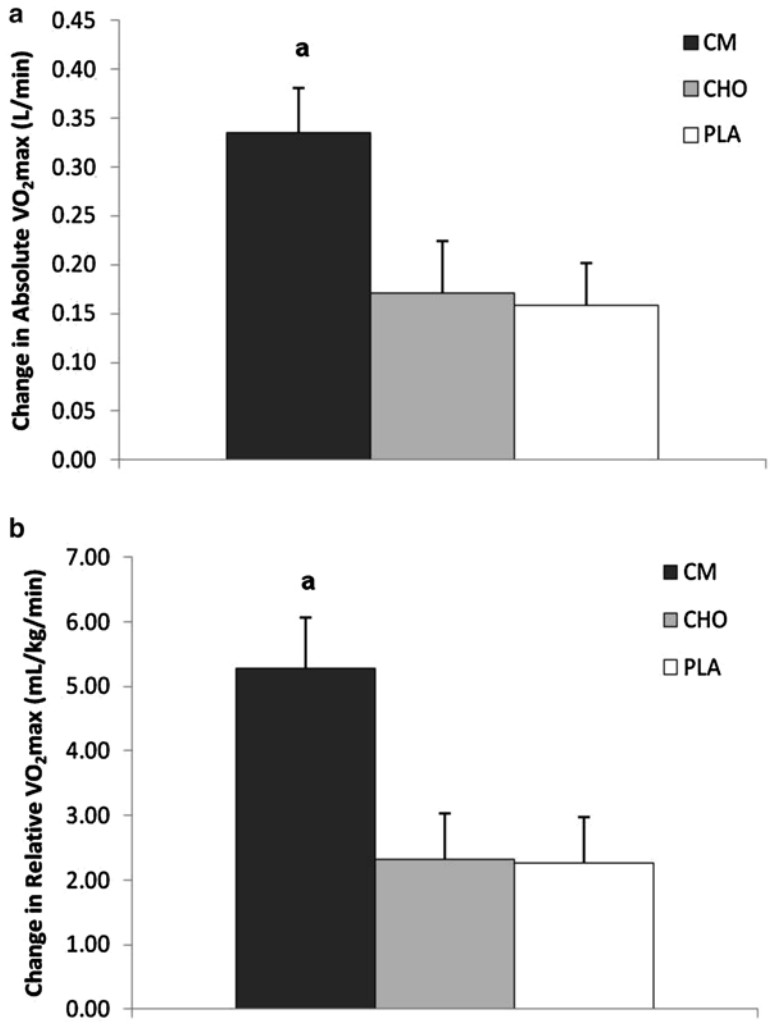

Fig. 9.2 VO_{2max} changes after 4.5 weeks of aerobic endurance training. (**a**) Change from baseline in absolute VO_{2max}. (**b**) Change from baseline in relative VO_{2max}. Values are mean ± SE. Significant treatment differences: *, CM vs. PLA and CHO ($P < 0.05$)

containing CrM and PRO (1.2 g whey · kg · day^{-1}, 0.1 g CrM · kg · day^{-1}, 6 weeks) in comparison to a similar dose of PRO (whey) or CHO (maltodextrin) (1.2 g · kg · day^{-1}). LBM increased to a greater extent in the CrM–PRO group compared to PRO or CHO alone. Bench press strength also increased to a greater extent in the CrM–PRO group compared to the PRO and CHO only groups, but all other strength/power measures increased to a similar extent [57]. The effectiveness of adding CrM to a PRO–CHO supplement on the development of strength and muscle mass was confirmed by another research group [56, 204]. Like Kreider et al. [24, 25] and Burke et al. [57], Cribb et al. [204] utilized experienced lifters to demonstrate a greater ($P < 0.05$) muscle hypertrophy response from the combination of CrM–PRO–CHO that was evident at three different levels of physiology. That is, compared to PRO–CHO and PRO alone (1.5 g · kg · day^{-1}), the CrM–PRO–CHO treatment demonstrated a greater gain in LBM, hypertrophy of the type-IIa and type-IIx fibers, and increase in contractile protein [204].

This research is particularly relevant as very few studies involving exercise and supplementation have confirmed improvements in body composition alongside hypertrophy responses at the cellular (i.e., fiber-specific hypertrophy) and subcellular level (i.e., contractile protein content) [56, 60, 204]. Definitely not all investigations support the hypothesis that a CrM-containing PRO–CHO supplement provides greater adaptations than supplementation with a similar amount of nitrogen and energy. However, it is interesting to note that often untrained populations have been involved [58, 205, 206]. While the influence of training status on the effects of supplementation is unknown, it has been speculated that trained individuals might experience more efficient muscle Cr uptake as exercise training is associated with improved insulin sensitivity [36]. Therefore, resistance-trained individuals may theoretically experience greater adaptations from supplementation [36].

9.6.1 Compounds of Potential

Aside from PROs and CHO, other compounds with purported ergogenic potential have been examined in combination with CrM during resistance training. However, in terms of absolute strength and body composition changes, the benefit of the supplement combination has seldom exceeded the results achieved from CrM treatment alone. For example, when compared with CrM only ($0.22\ g \cdot kg \cdot day^{-1}$), supplementation with a combination of pyruvate and CrM during 5 weeks of resistance training provided no greater benefit with regard to gains in body mass, LBM, 1RM strength, power output, and force development (vertical jump test) [207]. Likewise, studies that have examined the effects of combining CrM with magnesium [208], β-hydroxy-β-methylbutyrate (HMβ) [209, 210], or β-alanine [211, 212] have shown no greater ergogenic effect compared to treatment with CrM alone. This is somewhat surprising as recent years have seen a strong accumulation of research-based benefits with HMβ and β-alanine regarding muscle anabolism and ergogenics [213–216]. For example, Hoffman et al. [216] completed a 6-week training/supplementation study involving a CrM-, CrM+ β-alanine-, and a placebo-treated group. Both the CrM and CrM+ β-alanine groups demonstrated significantly better gains in 1RM strength and LBM than the placebo group, but no differences were detected between the two CrM-treated groups [216]. However, there were trends for better gains in LBM in the group given CrM+ β-alanine. Additionally, this group tended to show greater (average) training volumes for the bench press and squat exercises. If the study was of longer duration, it is possible that the greater amount of work completed by this group may have had an effect on strength development and lean tissue accruement. Recently Baier et al. [214] used 77 elderly men and women to report that HMβ (a leucine metabolite) in combination with L-arginine and L-lysine resulted in a 1.6 % increase in body cell mass (BIA) ($P = 0.002$) and lean mass (DEXA) by 1.2 % ($P = 0.05$) increase in lean body mass over a 1-year period [214], compared with no change in lean mass in a similar group of men and women receiving an isonitrogenous control supplement. Subjects weighing 68 kg or less were assigned a single dosage of 2 g of HMβ, 5 g of L-arginine, and 1.5 g of L-lysine per day. Those subjects weighing > 68 kg were assigned a single daily dosage of 3 g of HMβ, 7.5 g of L-arginine, and 2.25 g of L-lysine. The control group received a similar orange-tasting isonitrogenous and isocaloric drink consisting of a mixture of nonessential amino acids. Rates of whole-body protein flux, proteolysis, and protein synthesis were estimated using urinary ^{15}N-urea and ^{15}N-ammonia enrichments in a subgroup [214]. Lowery et al. [215] recently used a free acid form of HMβ (HMβ-FA) combined with ATP (400 g) during 12 weeks of structured resistance training. In a double-blind, placebo- and diet-controlled study, the researchers reported that the combination of HMβ-FA with ATP enhanced LBM, power, and strength ($p < 0.001$) in power-trained individuals. Moreover, during an overreaching phase of the trial, this supplement blunted a typical decrement in performance as evidenced by a further increase in strength during that period [215].

Based on the amount of research-based benefits recently published on HMβ and β-alanine's potential to augment muscle anabolism and performance, more research in combination with CrM on various population groups is warranted.

9.6.2 Industry Trends and Future Directions

Supplement timing, the strategic intake of PRO and/or AA with CHO close to resistance exercise, ensures a higher activation of molecular events associated with increased MPS and glycogen storage rates to improve recovery and adaptations. Of the many investigations that have examined strength and body composition from a nutrient intervention close to resistance exercise, a substantial number, but definitely not all, support the idea that strategic supplementation close to resistance exercise can enhance training adaptations, even when daily protein intake is adequate [98]. However, of these studies, less than a handful have addressed whether strategic intake close to resistance exercise offers clear advantages to other times outside the immediate hours surrounding a workout [60, 217, 218]. Of these three investigations, only two used resistance-trained individuals [60, 217] and only one has examined the effects of supplement timing at three levels of physiology—whole-body, cellular and subcellular [60]. Other differences included the type of nutrition, dosing protocol (training vs. non-training days), energy and macronutrient intake, as well as the resistance exercise program itself—each of these variables should be carefully considered in future resistance exercise training studies involving supplement timing.

The source of PRO acutely affects muscle amino acid uptake and net protein balance following resistance exercise. This appears to be related not only to amino acid composition but also to the pattern of amino acid delivery to peripheral tissues. For example, dairy milk PRO sources are shown to be more effective at supporting protein accretion than soy [219]. Whey is a collective term that encompasses a range of soluble fractions found in dairy milk. In supplement form, whey PRO is considered a "fast-absorbing" PRO based on studies that have shown consumption (20–30 g) instigates a rapid but transient increase in blood amino acid levels and stimulates a high rate of MPS [151, 152, 220]. On the other hand, casein (the other major dairy milk PRO) is more slowly absorbed from the gut and manifests a lower but sustained increase in blood amino acids for several hours [151, 152, 221]. These attributes suggest that the combination of whey and casein may be most beneficial in supporting muscle anabolism and increasing muscle mass during the course of an intense (high-overload) resistance-training program. In young, healthy adults, a blend of whey and casein (30 g) taken post-exercise has been shown to result in greater hypertrophy of the type I and II muscle fibers [222] and the greatest ($P<0.05$) increase in DEXA-determined LBM [223]. The whey PRO supplements used in these investigations are generally isolates (90 %+PRO) and concentrates (80 %+PRO). However, the degree of hydrolysis of the material (be it casein or whey) can affect absorption/digestion kinetics. While the supplement combination of whey and casein appears to be effective at promoting lean mass during resistance training, no studies have examined what type or ratio is most beneficial. Whether or not the addition of certain amino acids will optimize the effects of the supplement blend also remains unclear.

The combination of select amino acids with whole PRO supplements and CHO might be the best for the prolonged activation of MPS. For example, 10 years ago Borshiem et al. [150] reported that the combination of whey (17.5 g), free from AA (4.9 g), and CHO (77.4 g) stimulated net MPS to a greater extent than isoenergetic CHO supplement after resistance exercise. The authors also concluded that the addition of whole PRO to the AA-CHO supplement prolonged the anabolic response observed in previous studies with AA-CHO mixtures. This has inevitably led us to the newest trend in sports supplement research—the assessment of multi-ingredient performance supplements (MIPS). Now is in an era of MIPS proprietary blends containing intact PRO sources, amino acids, CrM,

β-alanine, vitamins, and root extracts purported to enhance the neuromuscular adaptations of resistance training [224–226]. While the data on the safety and efficiency on these products under the rigor of scientific investigation is always welcoming, it is important to identify if the intricate and often extensive formulation has been examined against one of the active (generic) ingredients listed such as CrM.

9.7 Combinations Shown to Enhance Anaerobic/Aerobic Exercise Performance

As previously mentioned in Sect. 6, oral β-alanine supplementation has shown to improve submaximal cycle ergometry performance and time to exhaustion [227], delay the onset of neuromuscular fatigue during incremental cycle ergometry [212], and/or increase the amount of work completed during high-intensity exercise (cycling to exhaustion at 110 % of estimated power maximum) [211]. Though carnosine, but more importantly β-alanine supplementation, may be an important physiological factor in determining high-intensity exercise performance, several studies suggest that it could also potentially enhance CrM's buffering capacity and thus provide additional ergogenic effects [211]. The potential synergistic effect of β-alanine and CrM supplementation was examined on various indices of cardiorespiratory endurance in healthy males [228]. Supplementation groups included CrM only (5.25 g), β-alanine only (1.6 g), CrM and β-alanine (5.25 g CrM, 1.6 g β-alanine plus 34 g of dextrose), and dextrose placebo. Following 28 days of supplementation, CrM and β-alanine independently showed improvements in two contributing factors (power output at ventilatory threshold and time to exhaustion) and one (power output at lactate threshold) of the physiological parameters measured, respectively. However when combined, supplementation resulted in improvements in 5 of the 8 physiological parameters measured (including percent VO_{2peak} associated with the lactate threshold and ventilatory threshold) during the incremental cycle ergometry test. While it is important to reiterate that the improvements were not significant when compared between groups, it was evident by a significant time effect within groups that the combination of CrM and β-alanine was greater at possibly delaying the onset of the fatigue and thus potentially enhancing endurance performance [228]. In contrast, using the same cohort of participants, Stout et al. [212] examined the onset of neuromuscular fatigue by using the physical working capacity at neuromuscular fatigue threshold test. Despite an independent benefit of β-alanine on delaying the onset of neuromuscular fatigue, there was not additive benefit of β-alanine and CrM supplementation. Similarly but in trained power/strength athletes, Hoffman and colleagues [216] failed to show any differences in strength (maximum bench press and squat) and power (Wingate anaerobic power test, 20-jump test) when CrM and β-alanine were supplemented together. However, CrM and β-alanine appeared to have a greater effect on lean tissue accruement and body fat composition compared to CrM alone. Taken together, despite the well-known independent buffering effects of β-alanine and CrM and some promising results when combining both supplements together, it is surprising that there have not been more investigations since 2006. Thus, further studies are clearly warranted to confirm the abovementioned effects of β-alanine and CrM supplementation on exercise performance and potential training adaptations.

Recently, the emergence of chronic β-alanine supplementation followed by acute sodium bicarbonate ingestion has gained popularity [229–236]. Intramuscular H^+ is buffered through the intracellular buffers (e.g., phosphates and carnosine), extracellular buffers (e.g., bicarbonate), and dynamic buffering system (i.e., the transport of H^+ outside the cells). As mentioned previously in Sects. 5 and 6, several investigations have shown increased intracellular and extracellular buffering capacity, achieved via acute or chronic sodium bicarbonate ingestion or chronic β-alanine supplementation, respectively, which can improve anaerobic exercise performance and

capacity. Given that both sodium bicarbonate and β-alanine exert their buffering effects in different compartments (i.e., outside and inside the muscle cells, respectively), it is conceivable that the combined use of these two supplements would have additive effects on high-intensity performance. Studies published in the past 10 years examining the additive benefits of β-alanine and sodium bicarbonate supplementation have been promising. Using similar supplementation protocols (4–6 weeks, 2–6.4 g per day of β-alanine + 200–500 mg of sodium bicarbonate), a number of studies have shown positive benefits (although not always statistically significant) in a variety of exercise performance modalities such as 2,000 m rowing performance [233], cycling capacity [231, 232], and high-intensity intermittent upper-body performance [236]. In contrast, others using similar exercise modalities failed to show any additive benefit [229, 235].

Specific combinations of amino acids—in particular branched-chain amino acids (leucine, isoleucine, valine), arginine, and glutamine—have been shown to improve indices of muscle function, damage, and recovery both during and following exercise in college track athletes (middle- and long-distance runners) [237, 238] and rugby players [239]. The amino acid mixture (% of total protein in grams) used for each study [237–239] consisted of L-glutamine (14 %), L-arginine (14 %), L-leucine, L-isoleucine, L-valine (total BCAA: 30 %), L-threonine, L-lysine, L-proline, L-methionine, L-histidine, L-phenylalanine, and L-tryptophan, with total protein varying from 2.2 to 7.2 g/day. Ohtani and colleagues [237] examined the effects of a daily dose of an amino acid mixture (mentioned above) on a middle- and long-distance runners engaging in sustained exercise for 2–3 h/day, 5 days/week for 6 months. During the 6-month period, subjects received three 1-month dosage treatments (2.2, 4.4, and 6.6 g/day), separated by a washout month between each trial. The 2.2 g/day dose was administered as a single dose at dinner; the 4.4 g/day dose was administered as two 2.2 g doses at breakfast and dinner; the 6.6 g/day dose was given as three 2.2 g doses, one at each daily meal. Results showed that the AA mixture at the daily dose of 6.6 g had the greatest effects, improving the self-assessment of the physical condition, reducing muscle damage, and enhancing hematopoiesis measures, which possibly suggests improved oxygen-handling capacity [237].

A similar study [239] examined the effects of the same AA mixture, but at a higher dosage (7.2 g/day), on rugby players for 3 months during a period of intensive physical training. Athletes maintained a regular training schedule with their teammates before, during, and after the 90-day trial period. The subjects were instructed to take a 3.6-g dose of the AA mixture after morning and evening meals every day for 90 days. Results from both studies [237, 239] suggest that the long-term administration of the AA mixture may increase the production of red blood cells, thereby perhaps enhancing the capacity of the blood to carry oxygen. Furthermore, these highly trained athletes reported that the long-term intake of the AA mixture produced a favorable effect on their physical fitness. In contrast to trained athletes, a recent study [240] demonstrated significant increases in treadmill time to exhaustion in healthy untrained women following 6 weeks of essential amino acid supplementation. The essential amino acid composition per 10 g consisted of L-isoleucine 1.483 g, L-leucine 1.964 g, L-valine 1.657 g, L-lysine 1.429 g, L-methionine 0.699 g, L-phenylalanine 1.289 g, L-threonine 1.111 g, and L-tryptophan 0.368 g. Subjects consumed on average 128 g of amino acids per week, or 18.3 g daily. It is clear from the results of the current study, taken together with the previous studies [237–239], that branched-chain amino acids when combined with other essential or nonessential amino acids have a beneficial effect during and following aerobic exercise performance. Although these results are interesting and provide practical application to most athletes when training or competing, a limitation to these studies is that the results were obtained in comparison to an isocaloric sugar (dextrin) placebo and not an equivalent dose of other amino acids or proteins. Thus, further research is needed to determine whether these specific amino acid combinations are more advantageous than regular protein supplements at improving indices of

muscle function, damage, and recovery during and following exercise.

In summary, CrM/β-alanine and the use of specific amino acid combinations have demonstrated in research to influence chronic adaptations that has enhanced exercise performance (predominantly aerobic exercise). More recently, β-alanine/sodium bicarbonate supplementation has demonstrated in research to improve anaerobic performance and capacity in trained and untrained individuals. However, similar to the combinations mentioned in Sect. 1.4, there are a number of limitations that also exist for these supplements. Firstly, very limited research has proven the beneficial effects of CrM/β-alanine supplementation on exercise performance. Therefore, until further research is conducted, we can only speculate as to whether combining CrM and β-alanine provides additional benefit compared to the independent effects from either supplement alone. Secondly, while the combination of specific amino acids such as branched-chain amino acids (leucine, isoleucine, valine), arginine and glutamine, has shown to improve exercise performance, further research is needed to determine whether these specific amino acid combinations are more advantageous than regular protein supplements as the results obtained to date are in comparison to an isocaloric sugar (dextrin) placebo and not an equivalent dose of other amino acids or proteins. Finally, while the additive benefits of chronic β-alanine supplementation followed by acute sodium bicarbonate ingestion may enhance the intracellular and extracellular buffering capacity and thus improve performance, further research is needed to confirm recent results as a number of studies have shown only minor, statistically nonsignificant effects.

9.8 Conclusion

The focus of this chapter was supplement combinations and dosing strategies that are effective at promoting either an acute physiological response that may improve/enhance exercise performance or influence chronic adaptations desired from training. The main conclusions are as follows:

- The capacity of CrM to augment the phosphocreatine system and provide an ergogenic or physiological benefit under a variety of conditions is well documented. The ability of CrM to enhance energetics and anabolism resides in the accumulation of Cr in the muscle cell. Variability with regard to dose–responses and muscle uptake among individuals has led to increasing interest in combinations that may improve muscle Cr accumulation in response to supplementation
- Probably due to an insulin-stimulating effect on the cellular Cr transporter, combining each dose of CrM (5–10 g) with insulin-stimulating CHO (20–50 g) with or without whey or other dairy isolates (up to 1.5 $g \cdot kg^{-1}$ day^{-1}) still appears to be the most effective strategy that promotes Cr accumulation within muscle. The combination of PRO and CHO is particularly effective when smaller doses of these macronutrients are desired. Taking a dose of CrM in a PRO–CHO supplement close to exercise may also promote effective Cr accumulation, glycogen replenishment, and adaptations from exercise.
- Insulin mimickers are compounds D-pinitol, α-linoleic acid (ALA), and herbals that may work like insulin to promote Cr uptake. However, to date all have failed to deliver clear evidence of their effectiveness to enhance muscle Cr accumulation, and none show any greater efficiency than that of PRO–CHO combinations to enhance muscle Cr content.
- Cr has been combined with different organic acids to form Cr salts with the intention of using acids that will create a synergistic effect or simply improve the properties. While several investigations have used Cr salts to demonstrate a performance-enhancing effect, very few of these investigations have been able to show clear advantages over CrM. Similarly, despite marketing claims, the research on novel Cr supplements such as phosphate, Cr serum, buffered Cr, Cr PEG, and Cr ethyl

ester has failed to show any clear benefit or advantage over CrM.

- The respective cases for high- or low-glycemic index pre-exercise meals to optimize performance appear to be equivocal. More recent guidelines recommend that athletes undertake their activity and daily training sessions with high-CHO availability. The concept of promoting carbohydrate (CHO) availability resides in the manipulation of the amount, type, and timing in the hours or days prior to and during the session and refueling recovery between sessions to provide athletes with practical recommendations
- The consumption of CHO fuel mixes before and during exercises has received considerable attention. When glucose is combined with fructose, a CHO with a different transporter, rates of ingested CHO can exceed previously determined oxidation rates. When glucose and fructose are co-ingested in a 2:1 ratio, in fluids, gels, and bars, these "multiple transporter" CHO fuel mixes appear to be well tolerated, promoting greater oxidation efficiency (less CHO remaining in the gastrointestinal tract) and performance benefits when compared to glucose alone, particularly in activities lasting 3 or more hours.
- The rapid restoration of muscle glycogen stores is a critical issue for all athletes who undertake training or competition sessions on the same or successive days. However, promoting supercompensatory glycogen levels might only be of benefit to very select endurance events. When considering nutritional combinations that promote glycogen synthesis and restoration, it is important to remember that high glycogen values can be achieved without a depletion phase and with as little as 24–36 h of rest and high CHO intake (10/kg/day). If short-term high-CHO loading (~10–12 g/kg/day) protocols do not suit all athletes' circumstances, combining a lower CHO intake with PRO can assist with maximizing glycogen stores. CHO to PRO ratios of 4:1 have been suggested for refueling. However, other ratios such as 2:1 or 3:1 may provide similar benefits.
- CrM and caffeine have been documented as possible synergists that act with CHO to aid in glycogen synthesis rates. In fact, the combination of CHO + caffeine (2 × 4 mg/kg) post-exercise provides the most rapid synthesis rates recorded. However, the benefits need to be considered with associated side effects. Large doses of caffeine can produce nausea and disrupt sleep. Loading with CrM is a well-documented strategy to boost muscle glycogen stores; however, where a gain in body weight may disadvantage the athlete, the combination of PRO–CHO (without CrM) may be a more prudent choice to promote muscle glycogen.
- The combination of select amino acids such as BCAAs with PRO and CHO might be the best for promoting anabolism and the adaptations desired from resistance exercise. For example, the combination of whey PRO, free from BCAAs and CHO, stimulates net muscle protein synthesis to a greater extent than isoenergetic CHO supplement after resistance exercise. While PRO supplements such as whey and casein appear to be effective at promoting lean mass during resistance training, no studies have examined what proportion of each is the most beneficial. The addition of an intact or whole PRO such as whey or casein to a AA-CHO supplement may prolong the anabolic response.
- Chronic adaptations that are desired from resistance training (i.e., increased strength, muscle hypertrophy, and/or lean body mass) appear to be enhanced by the combination of CrM with PRO or CHO (up to 1–5 $g \cdot kg \cdot day^{-1}$). The combination utilized may depend on individual requirements of the athlete. For instance, the additional CHO may be useful to some with high energy requirements. However, as PRO appears to provide similar benefits, the combination of CrM and PRO may be more suited when a high CHO intake (such as glucose) is not desired.
- Research-based benefits on HMβ or β-alanine's potential to augment muscle anabolism and performance are now apparent. However, under the rigor of scientific investigation, a

supplement combination or proprietary blend combining these with CrM is yet to provide any greater benefit than a group given CrM alone. Based on the amount of research-based benefits recently published on HMβ and β-alanine's potential to augment muscle anabolism and performance, more research in combination with CrM on various population groups is warranted

- The latest trend in sports supplement research is the assessment of multi-ingredient performance supplements (MIPS)—proprietary blends with various PRO sources, amino acids, CrM, beta-alanine, vitamins, and root extracts purported to enhance the neuromuscular adaptations of resistance training. While the data on the safety and efficiency on these products is always welcoming, it is important to identify if the intricate and often extensive formulation has been examined against one of the active (generic) ingredients listed such as CrM.

References

1. Balsom PD, Soderlund K, Ekblom B. Creatine in humans with special reference to creatine supplementation. Sports Med. 1994;18(4):268–80.
2. Greenhaff P. The nutritional biochemistry of creatine. J Nutr Biochem. 1997;8(11):610–8.
3. Walsh B, Tonkonogi M, Soderlund K, Hultman E, Saks V, Sahlin K. The role of phosphorylcreatine and creatine in the regulation of mitochondrial respiration in human skeletal muscle. J Physiol. 2001;537(Pt 3):971–8.
4. McConell GK, Shinewell J, Stephens TJ, Stathis CG, Canny BJ, Snow RJ. Creatine supplementation reduces muscle inosine monophosphate during endurance exercise in humans. Med Sci Sports Exerc. 2005;37(12):2054–61.
5. Wallimann T, Wyss M, Brdiczka D, Nicolay K, Eppenberger HM. Intracellular compartmentation, structure and function of creatine kinase isoenzymes in tissues with high and fluctuating energy demands: the 'phosphocreatine circuit' for cellular energy homeostasis. Biochem J. 1992;281(Pt 1):21–40.
6. Tesch PA, Thorsson A, Fujitsuka N. Creatine phosphate in fiber types of skeletal muscle before and after exhaustive exercise. J Appl Physiol. 1989;66(4):1756–9.
7. Greenhaff PL, Bodin K, Soderlund K, Hultman E. Effect of oral creatine supplementation on skeletal muscle phosphocreatine resynthesis. Am J Physiol. 1994;266(5 Pt 1):E725–30.
8. Bessman SP, Geiger PJ. Transport of energy in muscle: the phosphorylcreatine shuttle. Science. 1981;211(4481):448–52.
9. Hultman E, Greenhaff PL. Skeletal muscle energy metabolism and fatigue during intense exercise in man. Sci Prog. 1991;75(298 Pt 3–4):361–70.
10. Bogdanis GC, Nevill ME, Boobis LH, Lakomy HK, Nevill AM. Recovery of power output and muscle metabolites following 30 s of maximal sprint cycling in man. J Physiol. 1995;482(Pt 2):467–80.
11. Harris RC, Soderlund K, Hultman E. Elevation of creatine in resting and exercised muscle of normal subjects by creatine supplementation. Clin Sci. 1992;83(3):367–74.
12. Hultman E, Soderlund K, Timmons JA, Cederblad G, Greenhaff PL. Muscle creatine loading in men. J Appl Physiol. 1996;81(1):232–7.
13. Folin O, Denis W. Protein metabolism from the standpoint of blood and tissue analysis: seventh paper. An interpretation of creatine and creatinine in relation to animal metabolism. J Biol Chem. 1914;17:493–502.
14. Greenhaff PL, Casey A, Short AH, Harris R, Soderlund K, Hultman E. Influence of oral creatine supplementation of muscle torque during repeated bouts of maximal voluntary exercise in man. Clin Sci. 1993;84(5):565–71.
15. Bergstrom J, Hultman E. Muscle glycogen synthesis after exercise: an enhancing factor localized to the muscle cells in man. Nature. 1966;210(5033):309–10.
16. Bergstrom J, Hultman E. A study of the glycogen metabolism during exercise in man. Scand J Clin Lab Invest. 1967;19(3):218–28.
17. Hermansen L, Hultman E, Saltin B. Muscle glycogen during prolonged severe exercise. Acta Physiol Scand. 1967;71(2):129–39.
18. Jager R, Purpura M, Shao A, Inoue T, Kreider RB. Analysis of the efficacy, safety, and regulatory status of novel forms of creatine. Amino Acids. 2011;40(5):1369–83.
19. Deldicque L, Decombaz J, Zbinden Foncea H, Vuichoud J, Poortmans JR, Francaux M. Kinetics of creatine ingested as a food ingredient. Eur J Appl Physiol. 2008;102(2):133–43.
20. Birch R, Noble D, Greenhaff PL. The influence of dietary creatine supplementation on performance during repeated bouts of maximal isokinetic cycling in man. Eur J Appl Physiol Occup Physiol. 1994;69(3):268–76.
21. Casey A, Constantin-Teodosiu D, Howell S, Hultman E, Greenhaff PL. Creatine ingestion favorably affects performance and muscle metabolism during maximal exercise in humans. Am J Physiol. 1996;271(1 Pt 1):E31–7.

22. Earnest CP, Snell PG, Rodriguez R, Almada AL, Mitchell TL. The effect of creatine monohydrate ingestion on anaerobic power indices, muscular strength and body composition. Acta Physiol Scand. 1995;153(2):207–9.
23. Febbraio MA, Flanagan TR, Snow RJ, Zhao S, Carey MF. Effect of creatine supplementation on intramuscular TCr, metabolism and performance during intermittent, supramaximal exercise in humans. Acta Physiol Scand. 1995;155(4):387–95.
24. Kreider RB, Ferreira M, Wilson M, Grindstaff P, Plisk S, Reinardy J, et al. Effects of creatine supplementation on body composition, strength, and sprint performance. Med Sci Sports Exerc. 1998;30(1): 73–82.
25. Kreider RB, Klesges R, Harmon K, Grindstaff P, Ramsey L, Bullen D, et al. Effects of ingesting supplements designed to promote lean tissue accretion on body composition during resistance training. Int J Sports Nutr. 1996;6(3):234–46.
26. Kreider RB. Effects of creatine supplementation on performance and training adaptations. Mol Cell Biochem. 2003;244(1–2):89–94.
27. Poortmans JR, Francaux M. Adverse effects of creatine supplementation: fact or fiction? Sports Med. 2000;30(3):155–70.
28. Volek JS, Rawson ES. Scientific basis and practical aspects of creatine supplementation for athletes. Nutrition. 2004;20(7–8):609–14.
29. Snow RJ, Murphy RM. Factors influencing creatine loading into human skeletal muscle. Exerc Sports Sci Rev. 2003;31(3):154–8.
30. Persky AM, Brazeau GA, Hochhaus G. Pharmacokinetics of the dietary supplement creatine. Clin Pharmacokinet. 2003;42(6):557–74.
31. Persky AM, Brazeau GA. Clinical pharmacology of the dietary supplement creatine monohydrate. Pharmacol Rev. 2001;53(2):161–76.
32. Wyss M, Schulze A. Health implications of creatine: can oral creatine supplementation protect against neurological and atherosclerotic disease? Neuroscience. 2002;112(2):243–60.
33. Volek JSKW. Creatine supplementation: its effect on human muscular performance and body composition. J Strength Cond Res. 1996;10:198–203.
34. Casey A, Greenhaff PL. Does dietary creatine supplementation play a role in skeletal muscle metabolism and performance? Am J Physiol. 2000; 72(2 Suppl):607S–17.
35. Dempsey RL, Mazzone MF, Meurer LN. Does oral creatine supplementation improve strength? A meta-analysis. J Fam Pract. 2002;51(11):945–51.
36. Rawson ES, Volek JS. Effects of creatine supplementation and resistance training on muscle strength and weightlifting performance. J Strength Cond Res. 2003;17(4):822–31.
37. Kreider RBDW, Greenwood M, Parise G, Payne E, Tarnopolsky MA. Effects of creatine serum on muscle creatine and phosphagen levels. J Exerc Physiol Online. 2003;6(4):24–33.
38. Farquhar WB, Zambraski EJ. Effects of creatine use on the athlete's kidney. Curr Sports Med Rep. 2002;1(2):103–6.
39. Lemon PW. Dietary creatine supplementation and exercise performance: why inconsistent results? Can J Appl Physiol. 2002;27(6):663–81.
40. Steenge GR, Simpson EJ, Greenhaff PL. Protein- and carbohydrate-induced augmentation of whole body creatine retention in humans. J Appl Physiol. 2000;89(3):1165–71.
41. Saks VA, Dzhaliashvili IV, Konorev EA, Strumia E. Molecular and cellular aspects of the cardioprotective mechanism of phosphocreatine. Biokhimiia. 1992;57(12):1763–84.
42. Peeters BMLC, Mayhew JL. Effect of oral creatine monohydrate and creatine phosphate supplementation on maximal strength indices, body composition and blood pressure. J Strength Cond Res. 1998;13:3–9.
43. Guimbal C, Kilimann MW. A Na(+)-dependent creatine transporter in rabbit brain, muscle, heart, and kidney. cDNA cloning and functional expression. J Biol Chem. 1993;268(12):8418–21.
44. Haughland RBCD. Insulin effects on creatine transport in skeletal muscle. Proc Soc Exp Biol Med. 1975;148:1–4.
45. Odoom JE, Kemp GJ, Radda GK. The regulation of total creatine content in a myoblast cell line. Mol Cell Biochem. 1996;158(2):179–88.
46. Bennett SE, Bevington A, Walls J. Regulation of intracellular creatine in erythrocytes and myoblasts: influence of uraemia and inhibition of Na, K-ATPase. Cell Biochem Funct. 1994;12(2):99–106.
47. Gerber GB, Gerber G, Koszalka TR, Emmel VM. Creatine metabolism in vitamin E deficiency in the rat. Am J Physiol. 1962;202:453–60.
48. Vandenberghe K, Gillis N, Van Leemputte M, Van Hecke P, Vanstapel F, Hespel P. Caffeine counteracts the ergogenic action of muscle creatine loading. J Appl Physiol. 1996;80(2):452–7.
49. Loike JD, Somes M, Silverstein SC. Creatine uptake, metabolism, and efflux in human monocytes and macrophages. Am J Physiol. 1986;251(1 Pt 1): C128–35.
50. Moller A, Hamprecht B. Creatine transport in cultured cells of rat and mouse brain. J Neurochem. 1989;52(2):544–50.
51. Green AL, Simpson EJ, Littlewood JJ, Macdonald IA, Greenhaff PL. Carbohydrate ingestion augments creatine retention during creatine feeding in humans. Acta Physiol Scand. 1996;158(2):195–202.
52. Green AL, Hultman E, Macdonald IA, Sewell DA, Greenhaff PL. Carbohydrate ingestion augments skeletal muscle creatine accumulation during creatine supplementation in humans. Am J Physiol. 1996;271(5 Pt 1):E821–6.
53. Robinson TM, Sewell DA, Hultman E, Greenhaff PL. Role of submaximal exercise in promoting creatine and glycogen accumulation in human skeletal muscle. J Appl Physiol. 1999;87(2):598–604.

54. Greenwood M, Kreider RB, Earnest C, Rasmussen C, Almada A. Differences in creatine retention among three nutritional formulations of oral creatine supplements. J Exerc Physiol Online. 2003;6: 37–43.
55. Preen D, Dawson B, Goodman C, Beilby J, Ching S. Creatine supplementation: a comparison of loading and maintenance protocols on creatine uptake by human skeletal muscle. Int J Sports Nutr Exerc Metab. 2003;13(1):97–111.
56. Cribb PJ, Williams AD, Stathis CG, Carey MF, Hayes A. Effects of whey isolate, creatine, and resistance training on muscle hypertrophy. Med Sci Sports Exerc. 2007;39(2):298–307.
57. Burke DG, Chilibeck PD, Davidson KS, Candow DG, Farthing J, Smith-Palmer T. The effect of whey protein supplementation with and without creatine monohydrate combined with resistance training on lean tissue mass and muscle strength. Int J Sports Nutr Exerc Metab. 2001;11(3):349–64.
58. Tarnopolsky MA, Parise G, Yardley NJ, Ballantyne CS, Olatinji S, Phillips SM. Creatine-dextrose and protein-dextrose induce similar strength gains during training. Med Sci Sports Exerc. 2001;33(12): 2044–52.
59. Stout JEJ, Noonan D, Moore G, Cullen D. Effects of 8 weeks of creatine supplementation on exercise performance and fat-free weight in football players during training. Nutr Res. 1999;19(2):217–25.
60. Cribb PJ, Hayes A. Effects of supplement timing and resistance exercise on skeletal muscle hypertrophy. Med Sci Sports Exerc. 2006;38(11):1918–25.
61. Chilibeck PD, Stride D, Farthing JP, Burke DG. Effect of creatine ingestion after exercise on muscle thickness in males and females. Med Sci Sports Exerc. 2004;36(10):1781–8.
62. Greenwood MGLKR, Rasmussen C, Almada A, Earnest C. D-pinitol augments whole body creatine retention in man. J Exerc Physiol Online. 2001;4: 41–7.
63. Bates SH, Jones RB, Bailey CJ. Insulin-like effect of pinitol. Br J Pharmacol. 2000;130(8):1944–8.
64. Kerksick CM, Wilborn CD, Campbell WI, Harvey TM, Marcello BM, Roberts MD, et al. The effects of creatine monohydrate supplementation with and without D-pinitol on resistance training adaptations. J Strength Cond Res. 2009;23(9):2673–82.
65. Estrada DE, Ewart HS, Tsakiridis T, Volchuk A, Ramlal T, Tritschler H, et al. Stimulation of glucose uptake by the natural coenzyme alpha-lipoic acid/thioctic acid: participation of elements of the insulin signaling pathway. Diabetes. 1996;45(12): 1798–804.
66. Kishi Y, Schmelzer JD, Yao JK, Zollman PJ, Nickander KK, Tritschler HJ, et al. Alpha-lipoic acid: effect on glucose uptake, sorbitol pathway, and energy metabolism in experimental diabetic neuropathy. Diabetes. 1999;48(10):2045–51.
67. Burke DG, Chilibeck PD, Parise G, Tarnopolsky MA, Candow DG. Effect of alpha-lipoic acid combined with creatine monohydrate on human skeletal muscle creatine and phosphagen concentration. Int J Sports Nutr Exerc Metab. 2003;13(3):294–302.
68. Jäger RKI, Purpura M, Harris R, Ribnicky D, Pischel I. The effect of Russian tarragon (*Artemisia dracunculus* L.) on the plasma creatine concentration with creatine monohydrate administration. J Int Soc Sports Nutr. 2008;5 Suppl 1:4.
69. Oliver JM, Jagim AR, Pischel I, Jager R, Purpura M, Sanchez A, et al. Effects of short-term ingestion of russian tarragon prior to creatine monohydrate supplementation on whole body and muscle creatine retention and anaerobic sprint capacity: a preliminary investigation. J Int Soc Sports Nutr. 2014; 11(1):6.
70. Jager R, Harris RC, Purpura M, Francaux M. Comparison of new forms of creatine in raising plasma creatine levels. J Int Soc Sports Nutr. 2007;4:17.
71. Jager R, Metzger J, Lautmann K, Shushakov V, Purpura M, Geiss KR, et al. The effects of creatine pyruvate and creatine citrate on performance during high intensity exercise. J Int Soc Sports Nutr. 2008;5:4.
72. Eckerson JM, Stout JR, Moore GA, Stone NJ, Iwan KA, Gebauer AN, et al. Effect of creatine phosphate supplementation on anaerobic working capacity and body weight after two and six days of loading in men and women. J Strength Cond Res. 2005;19(4): 756–63.
73. Jagim AR, Oliver JM, Sanchez A, Galvan E, Fluckey J, Riechman S, et al. A buffered form of creatine does not promote greater changes in muscle creatine content, body composition, or training adaptations than creatine monohydrate. J Int Soc Sports Nutr. 2012;9(1):43.
74. Herda TJ, Beck TW, Ryan ED, Smith AE, Walter AA, Hartman MJ, et al. Effects of creatine monohydrate and polyethylene glycosylated creatine supplementation on muscular strength, endurance, and power output. J Strength Cond Res. 2009;23(3): 818–26.
75. Camic CL, Hendrix CR, Housh TJ, Zuniga JM, Mielke M, Johnson GO, et al. The effects of polyethylene glycosylated creatine supplementation on muscular strength and power. J Strength Cond Res. 2010;24(12):3343–51.
76. Spillane M, Schoch R, Cooke M, Harvey T, Greenwood M, Kreider R, et al. The effects of creatine ethyl ester supplementation combined with heavy resistance training on body composition, muscle performance, and serum and muscle creatine levels. J Int Soc Sports Nutr. 2009;6:6.
77. Giese MW, Lecher CS. Non-enzymatic cyclization of creatine ethyl ester to creatinine. Biochem Biophys Res Commun. 2009;388(2):252–5.
78. Katseres NS, Reading DW, Shayya L, Dicesare JC, Purser GH. Non-enzymatic hydrolysis of creatine ethyl ester. Biochem Biophys Res Commun. 2009; 386(2):363–7.

79. Jentjens RL, Moseley L, Waring RH, Harding LK, Jeukendrup AE. Oxidation of combined ingestion of glucose and fructose during exercise. J Appl Physiol. 2004;96(4):1277–84.
80. Astorino TA, Roberson DW. Efficacy of acute caffeine ingestion for short-term high-intensity exercise performance: a systematic review. J Strength Cond Res. 2010;24(1):257–65.
81. Astorino TA, Cottrell T, Lozano AT, Aburto-Pratt K, Duhon J. Increases in cycling performance in response to caffeine ingestion are repeatable. Nutr Res. 2012;32(2):78–84.
82. Jeukendrup AE. Nutrition for endurance sports: marathon, triathlon, and road cycling. J Sports Sci. 2011;29 Suppl 1:S91–9.
83. MacDougall JD, Ray S, Sale DG, McCartney N, Lee P, Garner S. Muscle substrate utilization and lactate production. Can J Appl Physiol. 1999;24(3):209–15.
84. Robergs RA, Pearson DR, Costill DL, Fink WJ, Pascoe DD, Benedict MA, et al. Muscle glycogenolysis during differing intensities of weight-resistance exercise. J Appl Physiol. 1991;70(4):1700–6.
85. Tesch PAP-SL, Yström L, Castro M, Dudley G. Skeletal muscle glycogen loss evoked by resistance exercise. J Strength Cond Res. 1998;12(2):67–73.
86. Haff GG, Koch AJ, Potteiger JA, Kuphal KE, Magee LM, Green SB, et al. Carbohydrate supplementation attenuates muscle glycogen loss during acute bouts of resistance exercise. Int J Sports Nutr Exerc Metab. 2000;10(3):326–39.
87. Sherman WM, Brodowicz G, Wright DA, Allen WK, Simonsen J, Dernbach A. Effects of 4 h preexercise carbohydrate feedings on cycling performance. Med Sci Sports Exerc. 1989;21(5):598–604.
88. Ivy JL, Goforth Jr HW, Damon BM, McCauley TR, Parsons EC, Price TB. Early postexercise muscle glycogen recovery is enhanced with a carbohydrate-protein supplement. J Appl Physiol. 2002;93(4):1337–44.
89. Fairchild TJ, Fletcher S, Steele P, Goodman C, Dawson B, Fournier PA. Rapid carbohydrate loading after a short bout of near maximal-intensity exercise. Med Sci Sports Exerc. 2002;34(6):980–6.
90. Bussau VA, Fairchild TJ, Rao A, Steele P, Fournier PA. Carbohydrate loading in human muscle: an improved 1 day protocol. Eur J Appl Physiol. 2002;87(3):290–5.
91. Hawley JA, Schabort EJ, Noakes TD, Dennis SC. Carbohydrate-loading and exercise performance. An update. Sports Med. 1997;24(2):73–81.
92. Burke LM, Hawley JA, Schabort EJ, St Clair Gibson A, Mujika I, Noakes TD. Carbohydrate loading failed to improve 100-km cycling performance in a placebo-controlled trial. J Appl Physiol. 2000;88(4):1284–90.
93. Burke LM, Hawley JA, Wong SH, Jeukendrup AE. Carbohydrates for training and competition. J Sports Sci. 2011;29 Suppl 1:S17–27.
94. Betts JA, Williams C. Short-term recovery from prolonged exercise: exploring the potential for protein ingestion to accentuate the benefits of carbohydrate supplements. Sports Med. 2010;40(11):941–59.
95. Burke LM. Fueling strategies to optimize performance: training high or training low? Scand J Med Sci Sports. 2010;20 Suppl 2:48–58.
96. Cox GR, Clark SA, Cox AJ, Halson SL, Hargreaves M, Hawley JA, et al. Daily training with high carbohydrate availability increases exogenous carbohydrate oxidation during endurance cycling. J Appl Physiol. 2010;109(1):126–34.
97. Jeukendrup AE. Carbohydrate intake during exercise and performance. Nutrition. 2004;20(7–8):669–77.
98. Smith-Ryan AEAJ. Sport nutrition & performance enhancing supplements. Linus Books; 2013.
99. Rodriguez NR, DiMarco NM, Langley S, American Dietetic Association, Dietitians of Canada, American College of Sports Medicine, et al. Position of the American Dietetic Association, Dietitians of Canada, and the American College of Sports Medicine: nutrition and athletic performance. J Am Diet Assoc. 2009;109(3):509–27.
100. Slater G, Phillips SM. Nutrition guidelines for strength sports: sprinting, weightlifting, throwing events, and bodybuilding. J Sports Sci. 2011;29 Suppl 1:S67–77.
101. Helms ER, Aragon AA, Fitschen PJ. Evidence-based recommendations for natural bodybuilding contest preparation: nutrition and supplementation. J Int Soc Sports Nutr. 2014;11:20.
102. Zehnder M, Muelli M, Buchli R, Kuehne G, Boutellier U. Further glycogen decrease during early recovery after eccentric exercise despite a high carbohydrate intake. Eur J Nutr. 2004;43(3):148–59.
103. Coyle EF. Substrate utilization during exercise in active people. Am J Clin Nutr. 1995;61(4 Suppl):968S–79.
104. Foster C, Costill DL, Fink WJ. Effects of preexercise feedings on endurance performance. Med Sci Sports. 1979;11(1):1–5.
105. Chryssanthopoulos C, Williams C. Pre-exercise carbohydrate meal and endurance running capacity when carbohydrates are ingested during exercise. Int J Sports Med. 1997;18(7):543–8.
106. Moore LJ, Midgley AW, Thurlow S, Thomas G, Mc Naughton LR. Effect of the glycaemic index of a pre-exercise meal on metabolism and cycling time trial performance. J Sci Med Sports. 2010;13(1):182–8.
107. Donaldson CM, Perry TL, Rose MC. Glycemic index and endurance performance. Int J Sports Nutr Exerc Metab. 2010;20(2):154–65.
108. Karelis AD, Smith JW, Passe DH, Peronnet F. Carbohydrate administration and exercise performance: what are the potential mechanisms involved? Sports Med. 2010;40(9):747–63.
109. Pfeiffer B, Stellingwerff T, Hodgson AB, Randell R, Pottgen K, Res P, et al. Nutritional intake and gastrointestinal problems during competitive endurance events. Med Sci Sports Exerc. 2012;44(2):344–51.

110. Burke LM, Claassen A, Hawley JA, Noakes TD. Carbohydrate intake during prolonged cycling minimizes effect of glycemic index of preexercise meal. J Appl Physiol. 1998;85(6):2220–6.
111. Chen YJ, Wong SH, Chan CO, Wong CK, Lam CW, Siu PM. Effects of glycemic index meal and CHO-electrolyte drink on cytokine response and run performance in endurance athletes. J Sci Med Sports. 2009;12(6):697–703.
112. Wong SH, Chan OW, Chen YJ, Hu HL, Lam CW, Chung PK. Effect of preexercise glycemic-index meal on running when CHO-electrolyte solution is consumed during exercise. Int J Sports Nutr Exerc Metab. 2009;19(3):222–42.
113. Phillips SM, Sproule J, Turner AP. Carbohydrate ingestion during team games exercise: current knowledge and areas for future investigation. Sports Med. 2011;41(7):559–85.
114. Jentjens RL, Underwood K, Achten J, Currell K, Mann CH, Jeukendrup AE. Exogenous carbohydrate oxidation rates are elevated after combined ingestion of glucose and fructose during exercise in the heat. J Appl Physiol. 2006;100(3):807–16.
115. Pfeiffer B, Cotterill A, Grathwohl D, Stellingwerff T, Jeukendrup AE. The effect of carbohydrate gels on gastrointestinal tolerance during a 16-km run. Int J Sports Nutr Exerc Metab. 2009;19(5):485–503.
116. Pfeiffer B, Stellingwerff T, Zaltas E, Jeukendrup AE. Oxidation of solid versus liquid CHO sources during exercise. Med Sci Sports Exerc. 2010;42(11): 2030–7.
117. Rowlands DS, Thorburn MS, Thorp RM, Broadbent S, Shi X. Effect of graded fructose coingestion with maltodextrin on exogenous 14C-fructose and 13C-glucose oxidation efficiency and high-intensity cycling performance. J Appl Physiol. 2008;104(6): 1709–19.
118. Pfeiffer B, Stellingwerff T, Zaltas E, Hodgson AB, Jeukendrup AE. Carbohydrate oxidation from a drink during running compared with cycling exercise. Med Sci Sports Exerc. 2011;43(2):327–34.
119. Currell K, Jeukendrup AE. Superior endurance performance with ingestion of multiple transportable carbohydrates. Med Sci Sports Exerc. 2008;40(2): 275–81.
120. Triplett D, Doyle JA, Rupp JC, Benardot D. An isocaloric glucose-fructose beverage's effect on simulated 100-km cycling performance compared with a glucose-only beverage. Int J Sports Nutr Exerc Metab. 2010;20(2):122–31.
121. Piehl Aulin K, Soderlund K, Hultman E. Muscle glycogen resynthesis rate in humans after supplementation of drinks containing carbohydrates with low and high molecular masses. Eur J Appl Physiol. 2000;81(4):346–51.
122. Pedersen DJ, Lessard SJ, Coffey VG, Churchley EG, Wootton AM, Ng T, et al. High rates of muscle glycogen resynthesis after exhaustive exercise when carbohydrate is coingested with caffeine. J Appl Physiol. 2008;105(1):7–13.
123. Ivy JL, Katz AL, Cutler CL, Sherman WM, Coyle EF. Muscle glycogen synthesis after exercise: effect of time of carbohydrate ingestion. J Appl Physiol. 1988;64(4):1480–5.
124. Samadi A, Gaeini AA, Kordi MR, Rahimi M, Rahnama N, Bambaeichi E. Effect of various ratios of carbohydrate-protein supplementation on resistance exercise-induced muscle damage. J Sports Med Phys Fitness. 2012;52(2):151–7.
125. Zawadzki KM, Yaspelkis 3rd BB, Ivy JL. Carbohydrate-protein complex increases the rate of muscle glycogen storage after exercise. J Appl Physiol. 1992;72(5):1854–9.
126. Williams M, Raven PB, Fogt DL, Ivy JL. Effects of recovery beverages on glycogen restoration and endurance exercise performance. J Strength Cond Res. 2003;17(1):12–9.
127. Berardi JM, Price TB, Noreen EE, Lemon PW. Postexercise muscle glycogen recovery enhanced with a carbohydrate-protein supplement. Med Sci Sports Exerc. 2006;38(6):1106–13.
128. van Loon LJ, Saris WH, Kruijshoop M, Wagenmakers AJ. Maximizing postexercise muscle glycogen synthesis: carbohydrate supplementation and the application of amino acid or protein hydrolysate mixtures. Am J Clin Nutr. 2000;72(1):106–11.
129. van Loon LJ, Saris WH, Verhagen H, Wagenmakers AJ. Plasma insulin responses after ingestion of different amino acid or protein mixtures with carbohydrate. Am J Clin Nutr. 2000;72(1):96–105.
130. Taylor C, Higham D, Close GL, Morton JP. The effect of adding caffeine to postexercise carbohydrate feeding on subsequent high-intensity interval-running capacity compared with carbohydrate alone. Int J Sports Nutr Exerc Metab. 2011;21(5):410–6.
131. Nelson AG, Arnall DA, Kokkonen J, Day R, Evans J. Muscle glycogen supercompensation is enhanced by prior creatine supplementation. Med Sci Sports Exerc. 2001;33(7):1096–100.
132. Op 't Eijnde B, Urso B, Richter EA, Greenhaff PL, Hespel P. Effect of oral creatine supplementation on human muscle GLUT4 protein content after immobilization. Diabetes. 2001;50(1):18–23.
133. Derave W, Eijnde BO, Verbessem P, Ramaekers M, Van Leemputte M, Richter EA, et al. Combined creatine and protein supplementation in conjunction with resistance training promotes muscle GLUT-4 content and glucose tolerance in humans. J Appl Physiol. 2003;94(5):1910–6.
134. van Loon LJ, Murphy R, Oosterlaar AM, Cameron-Smith D, Hargreaves M, Wagenmakers AJ, et al. Creatine supplementation increases glycogen storage but not GLUT-4 expression in human skeletal muscle. Clin Sci. 2004;106(1):99–106.
135. Francaux M, Poortmans JR. Effects of training and creatine supplement on muscle strength and body mass. Eur J Appl Physiol Occup Physiol. 1999;80(2):165–8.
136. Low SY, Rennie MJ, Taylor PM. Modulation of glycogen synthesis in rat skeletal muscle by changes in cell volume. J Physiol. 1996;495(Pt 2):299–303.

137. Rasmussen BB, Phillips SM. Contractile and nutritional regulation of human muscle growth. Exerc Sports Sci Rev. 2003;31(3):127–31.
138. Phillips SM, Tipton KD, Aarsland A, Wolf SE, Wolfe RR. Mixed muscle protein synthesis and breakdown after resistance exercise in humans. Am J Physiol. 1997;273(1 Pt 1):E99–107.
139. Yarasheski KE, Pak-Loduca J, Hasten DL, Obert KA, Brown MB, Sinacore DR. Resistance exercise training increases mixed muscle protein synthesis rate in frail women and men ≥76 yr old. Am J Physiol. 1999;277(1 Pt 1):E118–25.
140. Rennie MJ, Wackerhage H, Spangenburg EE, Booth FW. Control of the size of the human muscle mass. Annu Rev Physiol. 2004;66:799–828.
141. Moore DR, Tang JE, Burd NA, Rerecich T, Tarnopolsky MA, Phillips SM. Differential stimulation of myofibrillar and sarcoplasmic protein synthesis with protein ingestion at rest and after resistance exercise. J Physiol. 2009;587(Pt 4):897–904.
142. Rasmussen BB, Tipton KD, Miller SL, Wolf SE, Wolfe RR. An oral essential amino acid-carbohydrate supplement enhances muscle protein anabolism after resistance exercise. J Appl Physiol. 2000;88(2):386–92.
143. Borsheim E, Cree MG, Tipton KD, Elliott TA, Aarsland A, Wolfe RR. Effect of carbohydrate intake on net muscle protein synthesis during recovery from resistance exercise. J Appl Physiol. 2004;96(2):674–8.
144. Staples AW, Burd NA, West DW, Currie KD, Atherton PJ, Moore DR, et al. Carbohydrate does not augment exercise-induced protein accretion versus protein alone. Med Sci Sports Exerc. 2011;43(7):1154–61.
145. Roy BD, Tarnopolsky MA, MacDougall JD, Fowles J, Yarasheski KE. Effect of glucose supplement timing on protein metabolism after resistance training. J Appl Physiol. 1997;82(6):1882–8.
146. Baty JJ, Hwang H, Ding Z, Bernard JR, Wang B, Kwon B, et al. The effect of a carbohydrate and protein supplement on resistance exercise performance, hormonal response, and muscle damage. J Strength Cond Res. 2007;21(2):321–9.
147. Tarpenning KM, Wiswell RA, Hawkins SA, Marcell TJ. Influence of weight training exercise and modification of hormonal response on skeletal muscle growth. J Sci Med Sports. 2001;4(4):431–46.
148. Tipton KD, Rasmussen BB, Miller SL, Wolf SE, Owens-Stovall SK, Petrini BE, et al. Timing of amino acid-carbohydrate ingestion alters anabolic response of muscle to resistance exercise. Am J Physiol Endocrinol Metab. 2001;281(2):E197–206.
149. Miller SL, Tipton KD, Chinkes DL, Wolf SE, Wolfe RR. Independent and combined effects of amino acids and glucose after resistance exercise. Med Sci Sports Exerc. 2003;35(3):449–55.
150. Borsheim E, Aarsland A, Wolfe RR. Effect of an amino acid, protein, and carbohydrate mixture on net muscle protein balance after resistance exercise. Int J Sports Nutr Exerc Metab. 2004;14(3):255–71.
151. Elliot TA, Cree MG, Sanford AP, Wolfe RR, Tipton KD. Milk ingestion stimulates net muscle protein synthesis following resistance exercise. Med Sci Sports Exerc. 2006;38(4):667–74.
152. Tipton KD. Role of protein and hydrolysates before exercise. Int J Sports Nutr Exerc Metab. 2007;17(Suppl):S77–86.
153. Moore DR, Atherton PJ, Rennie MJ, Tarnopolsky MA, Phillips SM. Resistance exercise enhances mTOR and MAPK signalling in human muscle over that seen at rest after bolus protein ingestion. Acta Physiol. 2011;201(3):365–72.
154. Dickinson JM, Fry CS, Drummond MJ, Gundermann DM, Walker DK, Glynn EL, et al. Mammalian target of rapamycin complex 1 activation is required for the stimulation of human skeletal muscle protein synthesis by essential amino acids. J Nutr. 2011;141(5):856–62.
155. Karlsson HK, Nilsson PA, Nilsson J, Chibalin AV, Zierath JR, Blomstrand E. Branched-chain amino acids increase p70S6k phosphorylation in human skeletal muscle after resistance exercise. Am J Physiol Endocrinol Metab. 2004;287(1):E1–7.
156. Ferguson-Stegall L, McCleave EL, Ding Z, Doerner 3rd PG, Wang B, Liao YH, et al. Postexercise carbohydrate-protein supplementation improves subsequent exercise performance and intracellular signaling for protein synthesis. J Strength Cond Res. 2011;25(5):1210–24.
157. Coffey VG, Moore DR, Burd NA, Rerecich T, Stellingwerff T, Garnham AP, et al. Nutrient provision increases signalling and protein synthesis in human skeletal muscle after repeated sprints. Eur J Appl Physiol. 2011;111(7):1473–83.
158. Breen L, Philp A, Witard OC, Jackman SR, Selby A, Smith K, et al. The influence of carbohydrate-protein co-ingestion following endurance exercise on myofibrillar and mitochondrial protein synthesis. J Physiol. 2011;589(Pt 16):4011–25.
159. Ivy JL, Ding Z, Hwang H, Cialdella-Kam LC, Morrison PJ. Post exercise carbohydrate-protein supplementation: phosphorylation of muscle proteins involved in glycogen synthesis and protein translation. Amino Acids. 2008;35(1):89–97.
160. Ferguson-Stegall L, McCleave E, Ding Z, Doerner Iii PG, Liu Y, Wang B, et al. Aerobic exercise training adaptations are increased by postexercise carbohydrate-protein supplementation. J Nutr Metab. 2011;2011:623182.
161. Creer A, Gallagher P, Slivka D, Jemiolo B, Fink W, Trappe S. Influence of muscle glycogen availability on ERK1/2 and Akt signaling after resistance exercise in human skeletal muscle. J Appl Physiol. 2005;99(3):950–6.
162. Kraemer WJ, Volek JS, Bush JA, Putukian M, Sebastianelli WJ. Hormonal responses to consecutive days of heavy-resistance exercise with or without nutritional supplementation. J Appl Physiol. 1998;85(4):1544–55.
163. Williams AG, Ismail AN, Sharma A, Jones DA. Effects of resistance exercise volume and nutritional

supplementation on anabolic and catabolic hormones. Eur J Appl Physiol. 2002;86(4):315–21.
164. Willoughby DF, Stout J, Wilborn C, Taylor L, Kerksick C, editor. Effects of heavy resistance training and proprietary whey Casein Leucine protein supplementation on serum and skeletal muscle IGF-1 levels and IGF-1 and MGF mRNA expression. Int Soc Sports Nutr; 2005.
165. Kraemer WJ, Spiering BA, Volek JS, Ratamess NA, Sharman MJ, Rubin MR, et al. Androgenic responses to resistance exercise: effects of feeding and L-carnitine. Med Sci Sports Exerc. 2006;38(7):1288–96.
166. West DW, Phillips SM. Associations of exercise-induced hormone profiles and gains in strength and hypertrophy in a large cohort after weight training. Eur J Appl Physiol. 2012;112(7):2693–702.
167. Norton LE, Wilson GJ, Layman DK, Moulton CJ, Garlick PJ. Leucine content of dietary proteins is a determinant of postprandial skeletal muscle protein synthesis in adult rats. Nutr Metab. 2012;9(1):67.
168. Katsanos CS, Kobayashi H, Sheffield-Moore M, Aarsland A, Wolfe RR. A high proportion of leucine is required for optimal stimulation of the rate of muscle protein synthesis by essential amino acids in the elderly. Am J Physiol Endocrinol Metab. 2006;291(2):E381–7.
169. Pasiakos SM, McClung HL, McClung JP, Margolis LM, Andersen NE, Cloutier GJ, et al. Leucine-enriched essential amino acid supplementation during moderate steady state exercise enhances postexercise muscle protein synthesis. Am J Clin Nutr. 2011;94(3):809–18.
170. Glynn EL, Fry CS, Drummond MJ, Timmerman KL, Dhanani S, Volpi E, et al. Excess leucine intake enhances muscle anabolic signaling but not net protein anabolism in young men and women. J Nutr. 2010;140(11):1970–6.
171. Tipton KD, Elliott TA, Ferrando AA, Aarsland AA, Wolfe RR. Stimulation of muscle anabolism by resistance exercise and ingestion of leucine plus protein. Appl Physiol Nutr Metab. 2009;34(2):151–61.
172. Churchward-Venne TA, Burd NA, Mitchell CJ, West DW, Philp A, Marcotte GR, et al. Supplementation of a suboptimal protein dose with leucine or essential amino acids: effects on myofibrillar protein synthesis at rest and following resistance exercise in men. J Physiol. 2012;590(Pt 11):2751–65.
173. Yang Y, Breen L, Burd NA, Hector AJ, Churchward-Venne TA, Josse AR, et al. Resistance exercise enhances myofibrillar protein synthesis with graded intakes of whey protein in older men. Br J Nutr. 2012;108(10):1780–8.
174. Churchward-Venne TA, Breen L, Di Donato DM, Hector AJ, Mitchell CJ, Moore DR, et al. Leucine supplementation of a low-protein mixed macronutrient beverage enhances myofibrillar protein synthesis in young men: a double-blind, randomized trial. Am J Clin Nutr. 2014;99(2):276–86.
175. Keisler BD, Armsey 2nd TD. Caffeine as an ergogenic aid. Curr Sports Med Rep. 2006;5(4):215–9.
176. Greer F, McLean C, Graham TE. Caffeine, performance, and metabolism during repeated Wingate exercise tests. J Appl Physiol. 1998;85(4):1502–8.
177. Greer F, Friars D, Graham TE. Comparison of caffeine and theophylline ingestion: exercise metabolism and endurance. J Appl Physiol. 2000;89(5):1837–44.
178. Desbrow B, Biddulph C, Devlin B, Grant GD, Anoopkumar-Dukie S, Leveritt MD. The effects of different doses of caffeine on endurance cycling time trial performance. J Sports Sci. 2012;30(2):115–20.
179. Homsi J, Walsh D, Nelson KA. Psychostimulants in supportive care. Support Care Cancer. 2000;8(5):385–97.
180. Hoffman BB. Adrenoreceptor-activating and other sympathomimetic drugs. In: Katzung BG, editor. Basic and clinical pharmacology. 8th ed. New York: The McGraw Hill Companies, Inc; 2001. p. 120–37.
181. Bell DG, Jacobs I, Ellerington K. Effect of caffeine and ephedrine ingestion on anaerobic exercise performance. Med Sci Sports Exerc. 2001;33(8):1399–403.
182. Jacobs I, Pasternak H, Bell DG. Effects of ephedrine, caffeine, and their combination on muscular endurance. Med Sci Sports Exerc. 2003;35(6):987–94.
183. Gillies H, Derman WE, Noakes TD, Smith P, Evans A, Gabriels G. Pseudoephedrine is without ergogenic effects during prolonged exercise. J Appl Physiol. 1996;81(6):2611–7.
184. Hodges AN, Lynn BM, Bula JE, Donaldson MG, Dagenais MO, McKenzie DC. Effects of pseudoephedrine on maximal cycling power and submaximal cycling efficiency. Med Sci Sports Exerc. 2003;35(8):1316–9.
185. Dulloo AG. Ephedrine, xanthines and prostaglandin-inhibitors: actions and interactions in the stimulation of thermogenesis. Int J Obes Relat Metab Disord. 1993;17 Suppl 1:S35–40.
186. Bell DG, Jacobs I. Combined caffeine and ephedrine ingestion improves run times of Canadian Forces Warrior Test. Aviat Space Environ Med. 1999;70(4):325–9.
187. Bell DG, Jacobs I, Zamecnik J. Effects of caffeine, ephedrine and their combination on time to exhaustion during high-intensity exercise. Eur J Appl Physiol Occup Physiol. 1998;77(5):427–33.
188. Bell DG, McLellan TM, Sabiston CM. Effect of ingesting caffeine and ephedrine on 10-km run performance. Med Sci Sports Exerc. 2002;34(2):344–9.
189. Graham TE. Caffeine, coffee and ephedrine: impact on exercise performance and metabolism. Can J Appl Physiol. 2001;26:Suppl:S103–19.
190. Bell DG, Jacobs I, McLellan TM, Zamecnik J. Reducing the dose of combined caffeine and ephedrine preserves the ergogenic effect. Aviat Space Environ Med. 2000;71(4):415–9.
191. Magkos F, Kavouras SA. Caffeine and ephedrine: physiological, metabolic and performance-enhancing effects. Sports Med. 2004;34(13):871–89.

192. Williams AD, Cribb PJ, Cooke MB, Hayes A. The effect of ephedra and caffeine on maximal strength and power in resistance-trained athletes. J Strength Cond Res. 2008;22(2):464–70.
193. Bicopoulos D, editor. AusDI: drug information for the healthcare professional. 2nd ed. Castle Hill: Pharmaceutical Care Information Services; 2002.
194. Carr AJ, Gore CJ, Dawson B. Induced alkalosis and caffeine supplementation: effects on 2,000-m rowing performance. Int J Sports Nutr Exerc Metab. 2011;21(5):357–64.
195. Kilding AE, Overton C, Gleave J. Effects of caffeine, sodium bicarbonate, and their combined ingestion on high-intensity cycling performance. Int J Sports Nutr Exerc Metab. 2012;22(3):175–83.
196. Lee CL, Cheng CF, Lee CJ, Kuo YH, Chang WD. Co-ingestion of caffeine and carbohydrate after meal does not improve performance at high-intensity intermittent sprints with short recovery times. Eur J Appl Physiol. 2014;114(7):1533–43.
197. Conger SA, Warren GL, Hardy MA, Millard-Stafford ML. Does caffeine added to carbohydrate provide additional ergogenic benefit for endurance? Int J Sports Nutr Exerc Metab. 2011;21(1):71–84.
198. Cooper R, Naclerio F, Allgrove J, Larumbe-Zabala E. Effects of a carbohydrate and caffeine gel on intermittent sprint performance in recreationally trained males. Eur J Sports Sci. 2014;14(4):353–61.
199. Douroudos II, Fatouros IG, Gourgoulis V, Jamurtas AZ, Tsitsios T, Hatzinikolaou A, et al. Dose-related effects of prolonged NaHCO3 ingestion during high-intensity exercise. Med Sci Sports Exerc. 2006;38(10):1746–53.
200. Mc Naughton L, Thompson D. Acute versus chronic sodium bicarbonate ingestion and anaerobic work and power output. J Sports Med Phys Fitness. 2001;41(4):456–62.
201. McNaughton L, Backx K, Palmer G, Strange N. Effects of chronic bicarbonate ingestion on the performance of high-intensity work. Eur J Appl Physiol Occup Physiol. 1999;80(4):333–6.
202. Mero AA, Keskinen KL, Malvela MT, Sallinen JM. Combined creatine and sodium bicarbonate supplementation enhances interval swimming. J Strength Cond Res. 2004;18(2):306–10.
203. Barber JJ, McDermott AY, McGaughey KJ, Olmstead JD, Hagobian TA. Effects of combined creatine and sodium bicarbonate supplementation on repeated sprint performance in trained men. J Strength Cond Res. 2013;27(1):252–8.
204. Cribb PJ, Williams AD, Hayes A. A creatine-protein-carbohydrate supplement enhances responses to resistance training. Med Sci Sports Exerc. 2007; 39(11):1960–8.
205. Chromiak JA, Smedley B, Carpenter W, Brown R, Koh YS, Lamberth JG, et al. Effect of a 10-week strength training program and recovery drink on body composition, muscular strength and endurance, and anaerobic power and capacity. Nutrition. 2004; 20(5):420–7.
206. Villanueva MG, He J, Schroeder ET. Periodized resistance training with and without supplementation improve body composition and performance in older men. Eur J Appl Physiol. 2014;114(5):891–905.
207. Stone MH, Sanborn K, Smith LL, O'Bryant HS, Hoke T, Utter AC, et al. Effects of in-season (5 weeks) creatine and pyruvate supplementation on anaerobic performance and body composition in American football players. Int J Sports Nutr. 1999;9(2):146–65.
208. Selsby JT, DiSilvestro RA, Devor ST. Mg2+−creatine chelate and a low-dose creatine supplementation regimen improve exercise performance. J Strength Cond Res. 2004;18(2):311–5.
209. Jowko E, Ostaszewski P, Jank M, Sacharuk J, Zieniewicz A, Wilczak J, et al. Creatine and beta-hydroxy-beta-methylbutyrate (HMB) additively increase lean body mass and muscle strength during a weight-training program. Nutrition. 2001;17(7–8):558–66.
210. Crowe MJ, O'Connor DM, Lukins JE. The effects of beta-hydroxy-beta-methylbutyrate (HMB) and HMB/creatine supplementation on indices of health in highly trained athletes. Int J Sports Nutr Exerc Metab. 2003;13(2):184–97.
211. Hill CA, Harris R, Kim HJ, Boobis L, Sale C, Wise JA, editors. The effect of beta-alanine and creatine monohydrate supplementation on muscle composition and exercise performance. Am Coll Sports Med. 2005;37(5):S348 (Medicine and Science in Sports and Exercise).
212. Stout JR, Cramer JT, Mielke M, O'Kroy J, Torok DJ, Zoeller RF. Effects of twenty-eight days of beta-alanine and creatine monohydrate supplementation on the physical working capacity at neuromuscular fatigue threshold. J Strength Cond Res. 2006; 20(4):928–31.
213. Wilson JM, Fitschen PJ, Campbell B, Wilson GJ, Zanchi N, Taylor L, et al. International society of sports nutrition position stand: beta-hydroxy-beta-methylbutyrate (HMB). J Int Soc Sports Nutr. 2013;10(1):6.
214. Baier S, Johannsen D, Abumrad N, Rathmacher JA, Nissen S, Flakoll P. Year-long changes in protein metabolism in elderly men and women supplemented with a nutrition cocktail of beta-hydroxy-beta-methylbutyrate (HMB), L-arginine, and L-lysine. JPEN J Parenter Enteral Nutr. 2009;33(1):71–82.
215. Lowery RP, Joy JM, Rathmacher JA, Baier SM, Fuller J, Jr, Shelley MC, 2nd, et al. Interaction of beta-hydroxy-beta-methylbutyrate free acid (HMB-FA) and adenosine triphosphate (ATP) on muscle mass, strength, and power in resistance trained individuals. J Strength Cond Res. 2014.
216. Hoffman J, Ratamess N, Kang J, Mangine G, Faigenbaum A, Stout J. Effect of creatine and beta-alanine supplementation on performance and endocrine responses in strength/power athletes. Int J Sports Nutr Exerc Metab. 2006;16(4):430–46.

217. Hoffman JR, Ratamess NA, Tranchina CP, Rashti SL, Kang J, Faigenbaum AD. Effect of protein-supplement timing on strength, power, and body-composition changes in resistance-trained men. Int J Sports Nutr Exerc Metab. 2009;19(2):172–85.
218. Burk A, Timpmann S, Medijainen L, Vahi M, Oopik V. Time-divided ingestion pattern of casein-based protein supplement stimulates an increase in fat-free body mass during resistance training in young untrained men. Nutr Res. 2009;29(6):405–13.
219. Phillips SM, Hartman JW, Wilkinson SB. Dietary protein to support anabolism with resistance exercise in young men. J Am Coll Nutr. 2005;24(2):134S–9.
220. Tang JE, Manolakos JJ, Kujbida GW, Lysecki PJ, Moore DR, Phillips SM. Minimal whey protein with carbohydrate stimulates muscle protein synthesis following resistance exercise in trained young men. Appl Physiol Nutr Metab. 2007;32(6):1132–8.
221. Res PT, Groen B, Pennings B, Beelen M, Wallis GA, Gijsen AP, et al. Protein ingestion before sleep improves postexercise overnight recovery. Med Sci Sports Exerc. 2012;44(8):1560–9.
222. Andersen LL, Tufekovic G, Zebis MK, Crameri RM, Verlaan G, Kjaer M, et al. The effect of resistance training combined with timed ingestion of protein on muscle fiber size and muscle strength. Metab Clin Exp. 2005;54(2):151–6.
223. Kerksick CM, Rasmussen CJ, Lancaster SL, Magu B, Smith P, Melton C, et al. The effects of protein and amino acid supplementation on performance and training adaptations during ten weeks of resistance training. J Strength Cond Res. 2006;20(3):643–53.
224. Ormsbee MJ, Mandler WK, Thomas DD, Ward EG, Kinsey AW, Simonavice E, et al. The effects of six weeks of supplementation with multi-ingredient performance supplements and resistance training on anabolic hormones, body composition, strength, and power in resistance-trained men. J Int Soc Sports Nutr. 2012;9(1):49.
225. Ormsbee MJ, Thomas DD, Mandler WK, Ward EG, Kinsey AW, Panton LB, et al. The effects of pre- and post-exercise consumption of multi-ingredient performance supplements on cardiovascular health and body fat in trained men after six weeks of resistance training: a stratified, randomized, double-blind study. Nutr Metab. 2013;10(1):39.
226. Lowery RP, Joy JM, Dudeck JE, Oliveira de Souza E, McCleary SA, Wells S, et al. Effects of 8 weeks of Xpand(R) 2X pre workout supplementation on skeletal muscle hypertrophy, lean body mass, and strength in resistance trained males. J Int Soc Sports Nutr. 2013;10(1):44.
227. Stout JR, Cramer JT, Zoeller RF, Torok D, Costa P, Hoffman JR, et al. Effects of beta-alanine supplementation on the onset of neuromuscular fatigue and ventilatory threshold in women. Amino Acids. 2007;32(3):381–6.
228. Zoeller RF, Stout JR, O'Kroy JA, Torok DJ, Mielke M. Effects of 28 days of beta-alanine and creatine monohydrate supplementation on aerobic power, ventilatory and lactate thresholds, and time to exhaustion. Amino Acids. 2007;33(3):505–10.
229. Mero AA, Hirvonen P, Saarela J, Hulmi JJ, Hoffman JR, Stout JR. Effect of sodium bicarbonate and beta-alanine supplementation on maximal sprint swimming. J Int Soc Sports Nutr. 2013;10(1):52.
230. Bellinger PM, Howe ST, Shing CM, Fell JW. Effect of combined beta-alanine and sodium bicarbonate supplementation on cycling performance. Med Sci Sports Exerc. 2012;44(8):1545–51.
231. Sale C, Saunders B, Hudson S, Wise JA, Harris RC, Sunderland CD. Effect of beta-alanine plus sodium bicarbonate on high-intensity cycling capacity. Med Sci Sports Exerc. 2011;43(10):1972–8.
232. Saunders B, Sale C, Harris RC, Sunderland C. Effect of sodium bicarbonate and Beta-alanine on repeated sprints during intermittent exercise performed in hypoxia. Int J Sports Nutr Exerc Metab. 2014; 24(2):196–205.
233. Hobson RM, Harris RC, Martin D, Smith P, Macklin B, Gualano B, et al. Effect of beta-alanine with and without sodium bicarbonate on 2,000-m rowing performance. Int J Sports Nutr Exerc Metab. 2013;23(5):480–7.
234. de Salles PV, Roschel H, de Jesus F, Sale C, Harris RC, Solis MY, et al. The ergogenic effect of beta-alanine combined with sodium bicarbonate on high-intensity swimming performance. Appl Physiol Nutr Metab. 2013;38(5):525–32.
235. Ducker KJ, Dawson B, Wallman KE. Effect of beta alanine and sodium bicarbonate supplementation on repeated-sprint performance. J Strength Cond Res. 2013;27(12):3450–60.
236. Tobias G, Benatti FB, de Salles PV, Roschel H, Gualano B, Sale C, et al. Additive effects of beta-alanine and sodium bicarbonate on upper-body intermittent performance. Amino Acids. 2013; 45(2):309–17.
237. Ohtani M, Maruyama K, Suzuki S, Sugita M, Kobayashi K. Changes in hematological parameters of athletes after receiving daily dose of a mixture of 12 amino acids for one month during the middle- and long-distance running training. Biosci Biotechnol Biochem. 2001;65(2):348–55.
238. Ohtani M, Sugita M, Maruyama K. Amino acid mixture improves training efficiency in athletes. J Nutr. 2006;136(2):538S–43.
239. Ohtani M, Maruyama K, Sugita M, Kobayashi K. Amino acid supplementation affects hematological and biochemical parameters in elite rugby players. Biosci Biotechnol Biochem. 2001;65(9):1970–6.
240. Antonio J, Sanders MS, Ehler LA, Uelmen J, Raether JB, Stout JR. Effects of exercise training and amino-acid supplementation on body composition and physical performance in untrained women. Nutrition. 2000;16(11–12):1043–6.

Nutritional Supplements for Strength and Power Athletes

10

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Abstract

Over the last decade, research involving nutritional supplementation and sport performance has increased substantially. Strength and power athletes have specific needs to optimize their performance. Nutritional supplementation cannot be viewed as a replacement for a balanced diet, but an important addition to it. However, diet and supplementation are neither mutually exclusive nor does one depend on the other. Strength and power athletes have four general areas of supplementation needs. First strength athletes need supplements that have a direct effect on performance. The second areas of supplements are those that promote recovery. The third group is the supplements that enhance immune function. The last group of supplements is those that provide energy or have a direct effect on the workout. This chapter will review the key supplements needed to optimize performance and training of the strength athlete.

Keywords

Strength • Power • Hypertrophy • Recovery • Performance

10.1 Introduction

The supplement industry is a multibillion-dollar-a-year industry. There are new and more innovative supplements that are released on daily basis. The problem that exists is that there is very little supporting evidence in many cases. Thus, we have to determine what is and what a superior sport supplement is not.

To stay on the cutting edge of nutritional supplementation, we must identify what supplements have been shown to be effective and safe when used properly. Many of the leading experts in the field have identified and separated many leading supplements into categories that range from safe and effective to those that have harmful side effects or no supporting literature. To try disseminating all of the information that is

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available, we have to ask three simple questions in regard to the specific supplement: Is there a sound scientific rationale? Is there any scientific evidence that the rationale may affect health or exercise? Is it legal and safe? While this text has covered many of the supplements out there, it is almost impossible to cover them all. This chapter will cover supplements that have strong evidence that they are safe, effective, and legal.

The two main components to becoming an advanced strength and power athlete are intense training and superior nutrition. While we can never devalue the importance of a balanced diet, nutrition supplementation can provide the impetus for huge gains. Nutrition is by far more difficult to take care of than the training. You can have an excellent day from the training standpoint by simply putting in the time. Nutrition involves a 24 h a day 7 days a week commitment. Nutritional supplementation is an area where a strength athlete can really separate themselves from the crowd. Strength and power athletes have many needs from a nutritional stand point. It would be detrimental to assume that the only supplements that strength athletes need are those that promote protein synthesis (discussed later). The demands of a strength athlete are very high, and the body must be put in an advantageous environment to make the appropriate adaptations. Nutrition habits might make the difference between being able to withstand the pounding and physical abuse that a strength athlete endures and succumbing to the rapid onset of fatigue. Without providing the proper fuel to the body, it will not be able to operate at maximal ability. This is the main reason why nutrition is such an important part of becoming the best that you can be.

The supplement needs of strength athletes can be broken down into four general categories. First, strength athletes need supplements that have a direct effect on performance. These supplements will have direct effect on protein synthesis, hormonal adaptations, or proven effects on strength, power, or hypertrophy. Second, there are supplements that have been categorized to promote recovery. Strength athletes have demanding schedules and intense workloads; their bodies need optimal recovery. These supplements will enhance recovery and support adaptation. Third, there are supplements touted as an effective immune function option. These supplements will go hand in hand with those that promote recovery. Heavy and rigorous strength training can have negative effects on immune function. Thus, it is necessary to make sure that strength athlete's nutritional standards are high. Finally, a fourth group, are supplements that provide energy or have a direct effect on the workout. These supplements create the optimal environment for adaptation to rigorous training regimens. It is important to note that in many cases, these supplements overlap into many categories. However, it would be redundant to list them more than once. Taking the commitment and perfecting these habits will make a drastic improvement in performance, which will no doubt translate into success on the field.

10.2 Review of Literature

Supplements that enhance strength, power, or hypertrophy directly

10.2.1 Creatine

Creatine has dominated the supplement market for over a decade. Creatine has been researched more than any other nutritional supplement on the market today. Creatine is a nitrogenous organic compound obtained predominantly from the ingestion of meat or fish and is also synthesized endogenously in the kidney, liver, and pancreas [1, 2]. Creatine is a naturally occurring amino acid that is derived from the amino acids glycine, arginine, and methionine. When creatine enters the muscle cell, it accepts a high-energy phosphate and forms phosphocreatine (PC). PC is the storage form of high-energy phosphate, which is used by the skeletal muscle cell to rapidly regenerate adenosine triphosphate (ATP) during bouts of maximal muscular contraction [3]. The conversion of ATP into adenosine diphosphate (ADP) and a phosphate group generates the

energy needed by the muscles during short-term, high-intensity exercise. PC availability in the muscles is vitally important in energy production since ATP is unable to be stored in excessive amounts within the muscle and is rapidly depleted during bouts of exhaustive exercise. Oral creatine monohydrate supplementation has been reported to increase muscle creatine and phosphocreatine (PC) content by 15–40 %, enhance the cellular bioenergetics of the phosphagen system, improve the shuttling of high-energy phosphates between the mitochondria and cytosol via the creatine phosphate shuttle, and enhance the activity of various metabolic pathways [4].

While creatine research has now branched into its effects on cancer [5] and various delivery methods, strength and power athletes are only concerned about creatine's amazing results in athletics. Scientific studies indicate that creatine supplementation is an effective and safe nutritional strategy to promote gains in strength and muscle mass during resistance training [6–10]. Creatine has become one of the most popular nutritional supplements for resistance-trained athletes and body builders. In fact, creatine could be the most research nutritional supplement in the last decade. A recent periodical search yielded over 1,000 hits for creatine in sport and performance.

As previously noted, the energy for all-out maximal effort exercise lasting up to 10 s is primarily derived from limited stores of adenosine triphosphate (ATP) in the muscle. Creatine, when present in the muscle in sufficient amounts, donates a phosphate group to ADP, and it rapidly retransforms to ATP that is immediately available to the muscle to be used as fuel for exercise. During explosive exercise, the phosphate from PC stored in the muscle is also cleaved off to provide energy for resynthesis of ATP. This allows the ATP pool to be turned over several dozen times during an all-out maximal effort exercise bout lasting up to 10 s. Theoretically, the more creatine consumed, the more energy for brief high-intensity activity. However, it does appear that creatine supplementation has an upper limit. Once creatine stores are saturated, then excess creatine is not beneficial. Thus, more recent research has based creatine supplementation on body weight or more specifically lean body mass. Creatine could be extremely advantageous to strength athletes given its ability to promote strength gains during training. Studies indicate that creatine supplementation during training can increase gains in one repetition maximum (1RM) strength and power. Peeters et al. [11] investigated the effect of creatine monohydrate (CrM) and creatine phosphate (CrP) supplementation on strength, body composition, and blood pressure over a 6-week period. Strength tests performed were the one repetition maximum (1RM) bench press, 1RM leg press, and maximal repetitions on the seated preacher bar curl with a fixed amount of weight. Subjects were divided into three groups matched for strength: placebo (Pl), CrM, and CrP. All subjects were provided a standardized strength training regimen and ingested a loading dosage of 20 g per day for the first 3 days of the study, followed by a maintenance dose of 10 g per day for the remainder of the 6-week supplementation period. Significant differences were noted between the Pl group and the two Cr groups for changes in lean body mass, body weight, and 1RM bench press. These results suggest that oral creatine supplementation will result in greater strength and fat-free mass development. Eckerson et al. [12] also studied the effects of 2 and 5 days of creatine loading on anaerobic working capacity (AWC) using the critical power (CP) test in women. Ten physically active women randomly received two treatments separated by a 5-week washout period: (A) 18 g dextrose as placebo (PL) or (B) 5.0 g Cr + 18 g dextrose taken four times per day for 5 days. The PL resulted in no significant changes in AWC following supplementation; however, creatine increased AWC by 22.1 % after 5 days of loading ($p < 0.05$). These results suggest that creatine supplementation is effective for increasing AWC in women following 5 days of loading without an associated increase in BW. A study by Volek et al. [10] was undertaken to investigate the influence of oral supplementation with creatine monohydrate on muscular performance during repeated sets of high-intensity resistance exercise. Fourteen active men were randomly assigned in a double-blind

fashion to either a creatine group or a placebo group. Both groups performed a bench press exercise protocol and a jump squat exercise protocol on three different occasions separated by 6 days. Creatine supplementation resulted in a significant improvement in peak power output during all 5 sets of jump squats and a significant improvement in repetitions during all 5 sets of bench presses. A significant increase in body mass of 1.4 kg was observed after creatine ingestion. One week of creatine supplementation (25 g/day) enhances muscular performance during repeated sets of bench press and jump squat exercise. Kreider et al. [13] conducted a study where 25 NCAA division IA football players were matched-paired and assigned to supplement their diet for 28 days during resistance/agility training with creatine. Subjects performed a maximal repetition test on the isotonic bench press, squat, and power clean; and subjects performed a cycle ergometer sprint test. Gains in bench press lifting volume; the sum of bench press, squat, and power clean lifting volume; and total work performed during the first five 6-s sprints were significantly greater in the creatine group. The addition of the creatine supplement promoted greater gains in fat-/bone-free mass, isotonic lifting volume, and sprint performance during intense resistance/agility training. While this is only a few studies that have been reviewed, there are dozens of studies that have shown an increase in strength and power and high-intensity performance.

Over the course of a competitive season, athletes tend to lose lean mass due to factors such as the increase stress on the body, alterations in resistance-training programs, eating habits, etc. Maintenance of muscle mass is the typical goal of strength coaches during the competitive season. Investigations with creatine supplementation on high-intensity intermittent exercise have typically been proven effective to increase performance and build muscle mass, suggesting that athletes who ingest creatine would gain ergogenic benefits from supplementation. To test the effects of creatine to negate oxidative stress, Claudino and colleagues [14] researched recruited elite handball players to participate in a 28-day training and supplementation period. If not in the control group, participants either ingested 5 g of creatine monohydrate or maltodextrin a day over the course of the study in a double-blind manner. The strength training was programmed into four stages: familiarization, hypertrophy, strength, and peak. At the conclusion of the study, there was an increase in body mass for both groups (creatine: percent change = +0.8; ES = +0.1 and placebo: percent change = +2.2 %; ES = +0.1, main time effect $p = 0.06$), but results were not significantly different between groups ($p = 0.7$). All subjects experienced a decrease in jumping performance. With this in mind, the athletes ingesting creatine exhibited an attenuated reduction in muscular power when compared to the placebo group [14].

Thirty-two anaerobically strength-trained men were put through four experimental testing sessions, consisting of either a 5 k run continuously at anaerobic threshold velocity or intermittently (1:1 min at vVO_{2max}) followed by a leg or bench press 1RM test and repetitions to failure, to determine the ergogenic benefits of creatine on concurrent exercise [15]. With de Salles Painelli leading the investigation, the subjects were given 20 g a day for 7 days preloading, followed by 5 g per day of creatine or placebo during the study. The supplementation of creatine was able to maintain leg press strength during the muscular endurance test when compared to the control group which decreased in leg press endurance ($p = 0.05$). Muscular endurance testing on the bench press was increased with the supplementation of creatine after both aerobic training sessions. This research would suggest that creatine supplementation may negate the effects of concurrent exercise, allowing athletes to increase work capacity without interfering with strength and muscular hypertrophy [15].

While daily supplementation of creatine has been proven effective in increasing muscle fiber size, augmenting gain in lean mass, and strength, time of supplementation has more often than not been shown to be most beneficial to net muscle protein synthesis pre-workout. Pre-supplementation of creatine has been challenged by a study of Dr. Jose Antonio and Victoria Ciccone who found greater gains in

body composition and strength in those who ingested creatine immediately after their workout. Nineteen recreational resistance-trained males participated in the 4-week study where they either ingested 5 g of creatine before their workout or 5 g after the completion of their workout completing four workouts a week. Body composition and bench press 1RM were the dependent variables, and results found a significant time effect for both fat-free mass ($p = 0.001$) and bench press 1RM ($p < 0.001$). Magnitude inferences were used to determine the potential benefit of either pre- or post-workout ingestion. The inferences revealed that post-supplementation was possibly for gains in fat-free mass (post, 2.0 ± 1.2; pre, 0.4 ± 2.2) and losses in fat-free mass (post, -1.2 ± 1.6; pre, -0.01 ± 2.0) as well as likely beneficial for increases in 1RM bench press (post, 7.6 ± 6.2; pre, 6.6 ± 8.2) [16].

High-intensity exercise leads to an accumulation of hydrogen atoms (acid) and carbon dioxide in the body. This can lead to a decrease of performance, unless the acidity is buffered out. A proven effective acid buffer is sodium bicarbonate, more commonly known as baking soda. The bicarbonate ions bonds with the H+ and CO2 to bring the body back to a homeostatic state. Recently combination of creatine and sodium bicarbonate has been investigated to determine if a synergistic effect between the two supplements can allow for a higher training volume with an augmented response in protein synthesis. Barber and colleagues put 13 trained males through a supplementation period of either a placebo (Pl; 20 g maltodextrin + 0.5 g·kg (−1) maltodextrin), creatine (Cr; 20 g + 0.5 g·kg (−1) maltodextrin), or creatine plus sodium bicarbonate (Cr + Sb; 20 g + 0.5 g·kg (−1) sodium bicarbonate). The subjects underwent six 10-s Wingate sprint tests on a cycle ergometer with a minute rest between sprints. The peak power for sprints 4–6 was significantly lower than sprint 1, in both the placebo and creatine groups. Interestingly, those who ingested creatine plus sodium bicarbonate only saw a significant decrease in power for sprint 6, when compared to the baseline sprint. Suggesting that a co-supplementation of both creatine and sodium bicarbonate can help maintain power and force in high-intensity exercise [17].

10.2.2 Protein and Amino Acids

It has long been believed that excess protein intake was necessary for optimal muscle growth in response to strength training. First, we must understand that skeletal muscle growth is possible only when muscle protein synthesis exceeds muscle protein breakdown. The body is in a continuous state of protein turnover; as old proteins are destroyed or degraded, new ones are being synthesized. Thus, when synthesis of contractile proteins is occurring at a faster rate than degradation, the net result is a positive protein balance or more specifically myofibrillar hypertrophy. Knowing this, we understand that we need protein or the building blocks of those proteins, amino acids (AA), available to ensure that we are in a positive balance. However, the only problem is that we really do not store amino acids in our body, but draw available amino acids from the amino acid pool. The amino acid pool is a mixture of amino acids available in the cell derived from dietary sources or the degradation of protein. A protein balance is achieved when the dietary intake is balanced by the excretion of urea wastes. Amino acids enter this pool by three ways. Amino acids enter during digestion of protein in the diet, when body protein decomposes, and when carbon sources and NH_3 synthesize the nonessential amino acids. In addition, the body attempts to maintain a pattern of constancy in the free AA pool and in the rate of protein turnover. As previously noted amino acids are not actually stored but are in constant turnover. The AA pool exists to provide individual AAs for protein synthesis and oxidation, and it is replenished only by protein breakdown or AA's entering the body from the diet. Thus, the free amino acid pool provides the link between dietary protein and body protein in that both dietary protein and body protein feeds into the free pool. Effects of dietary protein intake play a vital role on AA pools. Not only does the amount of dietary protein intake play a role but also the type of protein or amino acid as well as the frequency of ingestion.

It is clear from a physiological perspective that we cannot properly build muscle without sufficient protein intake. Research has clearly defined

a vital role of protein and AA supplementation in the development of skeletal muscle. It is interesting to note that previous studies have concluded that acute protein synthesis following resistance training is similar in fed [18] and fasted [19, 20] subjects. Only the rate of turnover changes slightly, but still remains in a negative balance. However, studies have found that with dietary protein or amino acid supplementation, muscle protein synthesis rate is increased. Biolo et al. [21] evaluated the interactions between resistance training and amino acid supplementation and the corresponding effects on protein kinetics. Six untrained men acted as subjects in this study. Each participant was infused with a mixed (phenylalanine, leucine, lysine, alanine, glutamine) amino acid solution. Baseline and post-resistance-training (5×10 sets of leg press and 4×8 sets of nautilus squat, leg curl, and leg extension) samples were taken. The results revealed increased protein synthesis and no change in protein degradation. Tipton and colleagues [22] investigated the effects of orally administered amino acids (40 g CHO (placebo solution), 40 g mixed amino acids (EAA+NEAA), or 40 g essential amino acids (EAA only+arginine)) on postexercise net protein synthesis. They also sought to determine whether there would be a difference in the anabolic effect of amino acid supplementation if they used a mixed amino acid source or essential amino acids alone. The findings of this study indicated that postexercise amino acid supplementation elicits a positive protein balance as compared to the negative balance seen with resistance training alone. The Tipton study also concluded that supplementation with the essential amino acids alone is equivalent to that of a mixed amino acid supplement. Although research has concluded that postexercise amino acid supplementation has positive effect on protein synthesis, amino acid supplementation is not always an option. Thus, Esmark et al. [23] investigated the timing of protein intake after exercise on muscle hypertrophy and strength. This study used a milk and soy protein supplement (containing 10 g protein (from skimmed milk and soybean), 7 g carbohydrate, and 3.3 g lipid) instead of an amino acid mixture. Although protein synthesis was not calculated in this study, measurements of hypertrophy were made. As previously noted, muscular hypertrophy is the result of net protein synthesis. The results of the Esmark study indicated that skeletal muscle hypertrophy was significantly increased after resistance training when a protein supplement was taken. The findings also suggested that when the supplement was taken immediately after the training versus 2 h later, the hypertrophic response was greater. In the most recent study by Tipton and colleagues [24], they evaluated the effects of casein and whey protein ingestion on protein balance after resistance training. Twenty-three subjects consumed one of three drinks 1 h after a bout of leg extensions. Subjects consumed either placebo, 20 g of casein protein, or 20 g of whey protein. The results indicated that ingestion of whey or casein protein after a bout of resistance exercise increases net muscle protein synthesis. In a review by Rennie and colleagues [25], they concluded that there is no doubt that increasing amino acid concentrations by intravenous infusion, meal feeding, or ingestion of free amino acids increases muscle protein synthesis. They also concluded that in the postexercise period, increased availability of amino acids enhances muscle protein synthesis. These studies have clearly identified that amino acid or protein supplementation enhances protein synthesis and suppresses degradation, resulting in net protein synthesis.

Another possibility of AA supplementation is to supplement the branched chain amino acids (BCAAs). The BCAAs are made up of leucine, isoleucine, and valine. BCAAs are the only AAs that are used exclusively for the synthesis of tissue protein and not for other hormones; thus, their value is paramount. The BCAAs cannot be broken down in the liver like the other AAs. Liver does not contain the branched amino acid aminotransferase enzyme, which other tissues like the muscle do. These amino acids are unique in that their amino group can be removed to form a-ketoglutarate to make branched chain keto acids plus the amino acid glutamate. The amino group on glutamate is transferred to pyruvate regenerating a-ketoglutarate to form alanine and glutamine. Elevated levels of BCAA in the free

pool contribute various metabolic pathways, producing many intermediates that could be important to cellular metabolism. Given that BCAAs are involved in the synthesis of glutamine, they may play an important role for strength and power athletes. Glutamine (which will be discussed later in detail) has a beneficial effect on recovery. This is important given the rigor of the training regimens of strength athletes.

Therefore, it is clear from these studies and others that protein or AA supplementation does enhance the physiological adaptations of resistance training. A recent review by Kersick and Leutholtz [26] had the following conclusions as a synopsis of the current literature on protein and AA supplementation. First, ingestion of amino acids after resistance exercise has been shown at many different time points in several studies to stimulate increases in muscle protein synthesis, cause minimal changes in protein breakdown, and increase overall protein balance. Kersick also concluded that intact proteins or combinations of them that are commonly used in popular protein supplements appear to elicit similar increases in protein balance after resistance training as compared to other studies using free amino acids.

Whey protein isolate has been known for augmenting protein synthesis postexercise, but in 2010, it was also proven beneficial in attenuating the negative effects of isometric and isokinetic forces in untrained individuals [27]. Seventeen males volunteered and ingested 1.5 g/kg.bw/day (totaling to ~30 g per day) of either a whey protein isolate or carbohydrate for 14 days. During the course of the study, the participants completed a unilateral isokinetic knee flexion and isokinetic/isometric knee extension on each leg via the Cybex Testing and Rehabilitation System of four sets of 10 repetitions at 120 % of maximum voluntary contraction. Along with assessments of strength, plasma creatine kinase, and lactate dehydrogenase, markers of muscle damage were determined 24-h postexercise as well as 2, 3, 4, 7, 10, and 14 days following the testing session. The researchers Cooke, Rybalka, Stathis, Cribb, and Hayes concluded that isometric knee extension strength was significantly higher, following whey protein supplementation 3 and 7 days into recovery versus those on carbohydrate supplementation. During the recovery period, participants who were taking whey protein supplementations experienced a lower lactate dehydrogenase level during recovery [27].

Along with whey, casein is also a popular form of protein, both are extracted from milk proteins, but the method of absorption and bioavailability make these two protein sources very different. To test the effect of whey and casein on protein synthesis, Wilborn and colleagues put NCAA DIII female basketball players through an 8-week offseason undulating periodized training program 4 days per week, and they ingested either 24 g of whey protein or 24 g of casein protein 30 min prior and immediately after each training session. Variables tested on the athletes were body composition, 1RM on bench press as well as leg press, muscular endurance, and skill testing. Both experimental groups had a decrease in body fat with those on whey protein experiencing a higher loss in percent body fat (whey protein, -2.0 ± 1.1 %; casein protein, -1.0 ± 1.6 %; $p > 0.001$). Both groups had an increase in lean body mass (WP, -1.3 ± 1.2 kg; CP, 1.4 ± 1.0 kg; $p > 0.001$) as well as a decrease in fat mass. The athletes who ingested whey protein lost 1.3 ± 1.2 kg of fat mass, while the casein protein group lost 0.6 ± 1.4 kg of body weight from fat. Although there was no significant difference between the groups, all of the athletes experienced an increase in strength, eluding to protein's ability to elicit strength gain from resistance training. For power and agility, there were no significant differences between groups. In spite of the study revealing a difference in performance markers or body composition between whey and casein, Wilborn did prove the ability of females to elicit increase in muscle mass and decrease in fat mass from protein supplementation, allowing for an increase in strength and performance [28].

For active individuals who want to activate protein synthesis after exercise, the recommended intake of protein is 1.4–2.0 g/kg.bw/day, higher than the Dietary Reference Intakes (DRI) which is about 0.8 g/kg.bw/day. If a higher protein diet along with resistance training can help augment muscle growth, would a very high-protein

diet elicit an even higher response in lean body mass? This question was answered by Dr. Jose Antonio, who recruited 30 resistance-trained males to ingest either their typical daily intake of protein or 4.4 g/kg.bw/day [29]. This diet was maintained for 8 weeks, and body composition, dietary food logs, and training volume were measured over the course of the study. At the conclusion of the study, it was determined that the high-protein subjects consumed on average 307 ± 69 g of protein compared to the control group who ingested roughly 138 ± 42 g of protein. Even though the high-protein subjects did experience a significant increase in protein ingestion, there were no significant differences in the changes of body composition between the groups. The high-protein group did not experience a significant increase in lean body mass from taking in excess protein. The conclusion of the study suggests that having a hypocaloric diet as well as consuming five times the recommended protein intake did not augment an increase in protein proliferation [29].

10.2.3 Carnosine/β-Alanine

Carnosine is a dipeptide comprised of the amino acids histidine and β-alanine naturally occurring in the brain, cardiac muscle, kidney, stomach, and in large amounts in skeletal muscles. Carnosine has been widely studied for its effects on improved wound healing, antioxidant activity, and its anti-aging properties. Carnosine is found in high concentrations in skeletal muscle, primarily the type II muscle fibers. These are the fast-twitch muscle fibers used in explosive movements like weight training and sprinting. In fact, it has also been concluded that carnosine levels are found in higher concentrations in athletes whose performance demands serious anaerobic output.

Carnosine contributes to buffering of H+, thus attenuating a drop in pH associated with anaerobic metabolism. Carnosine is very effective at buffering the hydrogen ions responsible for producing the ill effects of lactic acid. Carnosine is believed to be one of the primary muscle-buffering substances available in skeletal muscle. In theory, if carnosine could attenuate the drop in pH noted with high-intensity exercise, then one could possibly exercise longer. However, carnosine is rapidly degraded into β-alanine and histidine as soon as it enters the blood through the activity of the enzyme, carnosinase. As such, there is no advantage to using direct carnosine supplementation. Thus, β-alanine is believed to be the answer to increasing carnosine in skeletal muscle. β-Alanine is an amino acid that is not involved in structural proteins and functions to combine with another amino acid, histidine, to form carnosine. However, the synthesis is under some kind of limited control. Using a supplemental form of β-alanine can significantly increase the synthesis. Histidine is already present in abundance within skeletal muscles, so it is β-alanine that acts as the rate-limiting factor in carnosine conversion. Recent studies conducted by Dr. Roger Harris [30] have demonstrated that taking β-alanine orally is effective at increasing carnosine levels. An individual that takes β-alanine orally on a regular basis can expect to increase their muscle's synthesis of carnosine by up to 64 %. This study also showed that your body only creates a certain amount of carnosine. This does increase as you work out, but it does eventually plateau. At this point, the only way to increase your body's production of carnosine is to take β-alanine orally. A recent study [31] supplemented men with β-alanine for 10 weeks. Muscle carnosine was significantly increased by +58.8 % and +80.1 % after 4- and 10-week β-alanine supplementation. Carnosine, initially 1.71 times higher in type IIa fibers, increased equally in both type I and IIa fibers, with no increase observed in control subjects.

Researchers including Roger Harris and Jeff Stout have begun to do extensive research in the area of β-alanine supplementation for strength athletes. Stout et al. [32] recently conducted a study that examined the effects of β-alanine supplementation on physical working capacity at fatigue threshold (PWCFT) in untrained young men. The results revealed a significantly greater increase in PWCFT of 9 % over placebo. The findings suggest that β-alanine supplementation for 28 days may delay the onset of neuromuscular fatigue. Another study by Stout [33] examined

the effects of 28 days of β-alanine supplementation on the physical working capacity at fatigue threshold, ventilatory threshold, maximal oxygen consumption, and time-to-exhaustion in women. Results of this study indicated that β-alanine supplementation delays the onset of neuromuscular fatigue and the ventilatory threshold at submaximal workloads and increases in total time to exhaustion during maximal cycle ergometry performance. Stout concluded that β-alanine supplementation appears to improve submaximal cycle ergometry performance and total time to exhaustion in young women, perhaps as a result of an increased buffering capacity due to elevated muscle carnosine concentrations.

In the last 2 years, there have been several studies that have investigated the effects of supplementing both creatine and β-alanine together. This proposed benefit would increase work capacity and decrease time to fatigue. Hoffman [34] studied the effects of creatine and creatine plus β-alanine on strength, power, body composition, and endocrine changes examined during a 10-week resistance-training program in collegiate football players. Results of this study demonstrated that creatine plus β-alanine was effective at enhancing strength performance. Creatine plus β-alanine supplementation also appeared to have a greater effect on lean tissue accruement and body fat composition than creatine alone. Stout [32] also investigated the effects of β-alanine and creatine on the onset of fatigue. Stout found that while β-alanine was effective at reducing fatigue, creatine did not have an additive effect.

The most recent studies that document the effectiveness of β-alanine are just now being published. There are many studies that have recently been completed that are yet to be published. However, there appears to be enough research currently to evaluate its effectiveness. It appears that not only does β-alanine appear to increase muscle carnosine levels, but those changes appear to translate into performance benefits. Due to the relationship with carnosine, the investigation of the ergogenic effects of beta-alanine and its ability to delay neuromuscular fatigue has rapidly increased in recent years. While some of the research is still conflicting, beta-alanine has been shown to be an effective performance-enhancing supplement within the research literature. For example, in a study measuring the effectiveness of beta-alanine on work capacity at heart rate threshold, researchers found that a 28-day supplementation of beta-alanine was potentially able to increase heart rate training threshold [35]. Beta-alanine's ability to enhance high interval training has been the focus of a majority of research. In a study using 50 recreationally trained men, there was no difference in anaerobic running capacity between those taking the supplementation and the subjects who were participating in the intermittent running alone [35]. Similar results were found using cycle ergometer HITT training and beta-alanine on increasing VO_{2peak} [36]. The study covered 6 weeks with participants performing interval training 3 times per week while taking the supplement. At the conclusion of the study, the supplementation of beta-alanine was not conducive to an increase in VO_{2peak} [36]. To test the buffering effects of increased carnosine via beta-alanine supplementation during severe exercise, Gross and colleagues administered supplementation of beta-alanine pre- and post-severe cycling intervals [37]. It was determined that supplementation had beneficial effect on sever exercise metabolism, allowing participants to experience an increased aerobic energy metabolism. Also those on beta-alanine supplementation experienced a reduced lactate accumulation, leading support to the buffering benefits of increased carnosine stores [37]. Several recent studies have investigated the synergistic effect of beta-alanine with the buffering capabilities of sodium bicarbonate on maximal cardiovascular sprints. The current research concludes that a co-supplementation may be effective in negating the metabolic effects of sprint interval work [38, 39]. It has been proposed that athletes who are considered highly trained may experience a less ergogenic response than those in a deconditioned state. In 2014, de Salles Painelli and colleagues conducted a study testing this theory. Over the course of 4 weeks, trained participants as well as non-trained individuals were given either beta-alanine or placebo. The study revealed that both trained and non-trained individuals are capable of gaining ergogenic benefits from beta-alanine [40].

10.3 Arginine/ Alpha-Ketoglutarate

Arginine is one of the amino acids produced in the human body by the digestion or hydrolysis of proteins. Arginine can also be produced synthetically. Because it is produced in the body, it is referred to as nonessential, meaning that no food or supplements are necessary for humans to ingest. Arginine compounds can be used in treating people with liver dysfunction due to its role in promoting liver regeneration.

The amino acid arginine has several roles in the body, such as assisting in wound healing, helping remove excess ammonia from the body, stimulating immune function, and promoting secretion of several hormones, including glucagon, insulin, and growth hormone. NO_2 is a compound produced from the amino acid arginine that elicits arteriole vasodilation and assists in nutrient transport/recovery in muscles. This has been proposed to cause a perpetual muscle pump in users as well as condone gains in muscle.

Campbell and colleagues [40] evaluated the pharmacokinetics, safety, and efficacy of arginine α-ketoglutarate (AAKG) in trained adult men. Subjects participated in two studies that employed a randomized, double-blind, controlled design. In study 1, 10 healthy men fasted for 8 h and then ingested 4 g of timed-release or non-timed-release AAKG. Blood samples were taken for 8 h after AAKG ingestion to assess the pharmacokinetic profile of L-arginine. After 1 week, the alternative supplement was ingested. In study 2, which was placebo controlled, 35 resistance-trained adult men were randomly assigned to ingest 4 g of AAKG (three times a day) or placebo. Participants performed 4 days of periodized resistance training per week for 8 weeks. At 0, 4, and 8 weeks of supplementation, the following tests were performed: clinical blood markers, one repetition maximum bench press, isokinetic quadriceps muscle endurance, anaerobic power, aerobic capacity, total body water, body composition, and psychometric parameter tests. In study 1, significant differences were observed in plasma arginine levels in subjects taking non-timed-release and timed-release AAKG. In study 2, significant differences were observed in the AAKG group for 1RM bench press, Wingate peak power, blood glucose, and plasma arginine. No significant differences were observed between groups in body composition, total body water, isokinetic quadriceps muscle endurance, and aerobic capacity. AAKG supplementation appeared to be safe and well tolerated and positively influenced 1RM bench press and Wingate peak power performance. A study conducted by Elam et al. [41], combining weight training with either arginine and ornithine or placebo, found that the amino acid combination produced decreases in body fat, resulted in higher total strength and lean body mass, and reduced evidence of tissue breakdown after only 5 weeks.

It is well documented that the infusion of arginine stimulated growth hormone secretion from the anterior pituitary [42–44]. This increase in growth hormone secretion from arginine infusion has been attributed to the suppression of endogenous somatostatin secretion. However, other studies done in human trials have not had positive results. Janet Walberg-Rankin [45] studied the effects of arginine on growth hormone (GH) and influence on body composition and muscle function. Male weight trainers were divided into three groups, including control (Con), arginine (Arg), and placebo (Pla), and given a similar resistance exercise prescription. Subjects in the Pla and Arg group demonstrated a significant decrease in peak torque for the biceps and quadriceps. Neither supplement acutely affected serum GH or arginine over 90 min after ingestion. There was no significant difference between groups in nitrogen balance. Thus, the supplement had no influence on weight loss, fat or lean tissue loss, muscle function, or overall GH status.

At very high intakes (approximately 250 mg per 2.2 lb of body weight), the amino acid, arginine, has increased growth hormone levels [46], an effect that has interested body builders due to the role of growth hormone in stimulating muscle growth. However, at lower amounts recommended by some manufacturers (5 g taken 30 min before exercise), arginine failed to increase growth hormone release and may even have impaired the release of growth hormone in

younger adults [47]. High amounts of arginine do not appear to raise levels of insulin [48], another anabolic bodybuilding hormone. More modest amounts of a combination of these amino acids have not had measurable effects on any anabolic hormone levels during exercise.

While it is obvious that there are conflicting results in the literature, it is important to discuss arginine as a nutritional supplement. Arginine or NO_2 has been one of the hottest supplements over the last few years. There are tons of anecdotal evidence suggesting that arginine is a powerful modulator of strength and performance; however, the current literature is not decisive.

10.3.1 Aromatase Inhibitors

The never-ending pursuit of bigger muscles, by athletes and bodybuilders, leads to the creation of new and innovative supplements to compliment vigorous training. Over the last 20 years, research in the area of sport nutrition has confirmed the benefit of supplements such as creatine, BCAAs, and whey protein. However, the most potent and anabolic agent is naturally occurring testosterone. Testosterone is a hormone naturally produced by the body. The Anabolic effect of testosterone includes promotion of the protein biosynthesis. It accelerates muscle buildup, increases the formation of red blood cells, speeds up regeneration, and speeds up recovery time after injuries or illness. It also stimulates the entire metabolism, which results in the burning of body fat. Studies by Bhasin et al. [49–52] and Sinh-Hikim et al. [53, 54] have shown that testosterone at supraphysiological levels increases muscle size and strength. Thus, many supplement companies have sought to create ways to increase naturally occurring levels of testosterone. Over the last decade, many supplements such as prohormones, testosterone derivatives, and now aromatase inhibitors have flooded the market with promises of "testosterone" like gains in strength and lean mass. The newest of these supplements are aromatase inhibitors (AIs). Although AIs are not new themselves, they are relatively new to the fitness community. Aromatase is an enzyme involved in the production of estrogen that acts by catalyzing the conversion of testosterone (an androgen) to estradiol (an estrogen) [55].

AIs have been used in an "athletic" setting for many years. However, their use was only thought to be beneficial to individuals using steroids. Steroids that aromatize heavily are responsible for extreme elevations in estrogen. Higher than normal estrogen levels can lead to several physiological problems. Thus, aromatase inhibitors have been used to prevent the testosterone conversion and limit the negative effects of aromatase. Recently the idea has been proposed that AIs may present an advantageous option for individuals not on steroids. Zmuda et al. [56] investigated the effects of an aromatase inhibitor in 14 male subjects. Researchers found that serum testosterone levels increased during all three drug treatments, whereas estradiol level increased only with testosterone alone, demonstrating that the aromatase inhibitor effectively inhibited testosterone aromatization. Leder [57] investigated the ability of the orally administered aromatase inhibitor, anastrozole, to increase endogenous testosterone production in 37 elderly men with screening serum testosterone levels less than 350 ng/dl. The findings of this study demonstrate that aromatase inhibition increases serum bioavailable and total testosterone levels to the youthful normal range in older men with mild hypogonadism. Serum estradiol levels decrease modestly but remain within the normal male range. Furthermore research has investigated eugonadal boys that were given the aromatase inhibitors exemestane [58] and anastrozole [59]; there was a comparable suppression of estradiol with a parallel increase in testosterone and free testosterone concentrations.

Now that science has determined, in fact, that AIs do increase testosterone levels, a new wave of AIs have hit the market. Traditionally AIs are obtained by prescription. However, many nutritional supplements are now available that claim to inhibit aromatase. A study on an over-the-counter AI was recently completed [60]. This study examined the blood hormone responses over a 3-week cycle of 600 mg per day of AI. The study used six normal men aged 32–40, and in

addition to tracking changes in sex hormone levels, it also looked at common indicators of toxicity. Total testosterone levels rose by an average of 188 %, while free testosterone levels rose by an average of 226 % over the course of 3 weeks. A nonsignificant decrease in estradiol was also seen. Furthermore, Numazawa and colleagues [61, 62] have shown that androst-4-ene-3,6,17-trione (the active ingredient in 6-OXO™) irreversibly binds to the aromatase enzyme thereby causing a halt in estradiol production.

A recent study conducted at Baylor University examined the effects a newly marketed aromatase inhibitor on body composition and changes in serum hormone levels [63]. All subjects were considered experienced weight lifters with a minimum of 1 year of experience. The 16 participants were equally divided, matched by age and body weight, and then assigned an 8-week supplementation protocol consisting of the oral ingestion of either 4 capsules/day (72 mg/day of hydroxyandrost-4-ene-6,17-dioxo-3-THP ether and 3,17-diketo-androst-1,4,6-triene) at bed time or 4 capsules/day of placebo (72 mg maltodextrin) at bed time. Total body mass and body composition, as well as venous blood samples were determined at week 0 and after weeks 4, 8, and 11. Results indicated significant changes in both free and total testosterone. Total endogenous testosterone, free testosterone, and dihydrotestosterone (DHT) increased by an average of 300, 600, and 630 % from baseline, respectively, in 8 weeks. While there were significant increases in testosterone and DHT, there were no significant changes in estradiol, estrone, estriol, or a variety of serum and urinary clinical safety markers. Therefore, these increases in testosterone and no change in estrogen would lead us to believe that the aromatase enzyme was apparently inhibited by the supplement. Furthermore, body fat significantly decreased 1 % in the active group with 1.5 lb decrease in fat mass. At the end of 8 weeks of supplementation, subjects had a 3-week washout period. After 3 weeks of washout, testosterone and estrogen levels had returned to normal baseline levels. The results of this study also concluded that there were no significant changes in any clinical safety markers, particularly those indicative of hepatic and renal function. The results of this study suggest that over-the-counter aromatase inhibitors can increase endogenous levels of testosterone without adversely affecting clinical safety markers.

The results of this study have concluded that aromatase inhibition can increase fat-free mass by increasing the endogenous levels of testosterone. Years of research on aromatase inhibitors have helped breast cancer patients and menopause and andropause sufferers. Results of the years of research have concluded that aromatase inhibitors can decrease estrogen and increase testosterone. This might lead us to believe that there is some benefit to resistance-trained athletes in using these products.

10.3.2 ZMA

The biological importance of magnesium and zinc is revealed by the various metabolic processes in which these elements regulate biological function. Zinc and Magnesium are two minerals that are used in a number of metabolic processes and hormonal regulation. Zinc is an essential trace element involved in a range of vital biochemical processes and is required for the activity of more than 300 enzymes. Zinc-containing enzymes participate in many components of macronutrient metabolism, particularly cell replication. Zinc deficiencies have been shown to be higher in athletes and/or individuals who recreationally train [64–66]. Singh et al. [65, 66] investigated blood (plasma) levels of zinc, and other trace minerals were determined in 66 men before and after a 5-day period of sustained physical and psychological stress. Singh found that zinc levels decreased by 33 %.

These zinc deficiencies may also contribute to impaired immune function and decreased performance [64, 67–69]. A 2004 review by Gleeson et al. [70] concluded both heavy exercise and nutrition exert separate influences on immune function; these influences appear to be stronger when exercise stress and poor nutrition act synergistically. Dietary deficiencies of energy, protein, and specific micronutrients are associated with

depressed immune function and increased susceptibility to infection.

Magnesium is an essential element in human nutrition; it is the cofactor in enzymes of carbohydrate metabolism. Magnesium, a ubiquitous element that plays a fundamental role in many cellular reactions, is involved in more than 300 enzymatic reactions in which food is metabolized and new products are formed. Some important examples include glycolysis, fat and protein metabolism, adenosine triphosphate synthesis, and second messenger system. Magnesium also serves as a physiological regulator of membrane stability and in neuromuscular, cardiovascular, immune, and hormonal function. Magnesium has also been shown to diminish the hormone cortisol [71]. Cortisol has been shown to be detrimental to strength gains and muscle mass. A 1984 [72] study that found 14 days of magnesium supplementation decreased cortisol. Another study [73] in 1998 found similar results, concluding that magnesium supplementation reduced the stress response without affecting competitive potential.

Magnesium supplementation has been reported to improve adaptations to exercise, specifically resistance training [69, 74, 75]. Therefore, supplementation of zinc and magnesium may enhance immune function, the hormone testosterone, increase strength, and diminish the effects of cortisol, thus having a benefit to resistance-training athletes.

A 2000 study [76] found significant changes in hormones (testosterone, IGF-1) and muscle strength when athletes supplemented with a zinc and magnesium supplement.

Zinc and magnesium supplementation has been reported to have positive effects on resistance-training athletes [74, 76, 77]. Subsequently decreases in zinc and magnesium have been associated with loss of strength and muscle mass. However, athletes have been reported to have lower levels of zinc and magnesium possibly due to increased sweating while training or inadequate intake in their diets [65, 66, 78–80]. A 2000 study was conducted on collegiate football players during 8 weeks of spring practice. The purpose of this study was to assess the effect of a novel Zn, Mg, and vitamin B6 formulation (ZMA) on anabolic hormones and muscle function. Twenty-seven subjects successfully followed the nightly supplement regimen over the course of the study and completed the testing sessions. The results of ZMA supplementation on anabolic hormone profile in football players pre-post spring football practice indicates that the ZMA group had increased concentrations of total testosterone, free testosterone, and IGF-I compared to plateaus or drops in the placebo group. Significant increases in isokinetic torque and power measurements were also seen. The ZMA group increases were significantly different than the placebo group. Wilborn et al. [81] examined whether supplementing the diet with a commercial supplement containing zinc magnesium aspartate (ZMA) during training affects zinc and magnesium status, anabolic and catabolic hormone profiles, and/or training adaptations. Forty-two resistance-trained males were matched according to fat-free mass and randomly assigned to ingest in a double-blind manner either a dextrose placebo (P) or ZMA 30–60 min prior to going to sleep during 8 weeks of standardized resistance training. Subjects completed testing sessions at 0, 4, and 8 weeks that included body composition assessment, 1RM and muscular endurance tests on the bench and leg press, a Wingate anaerobic power test, and blood analysis to assess anabolic/catabolic status as well as markers of health. Results indicated that ZMA supplementation nonsignificantly increased serum zinc levels by 11–17 % ($p = 0.12$). However, no significant differences were observed between groups in anabolic or catabolic hormone status, body composition, 1RM bench press and leg press, upper or lower body muscular endurance, or cycling anaerobic capacity.

ZMA supplementation has become a popular nutritional practice among resistance-trained athletes. Preliminary research findings have indicated that training decreases zinc and magnesium availability leading to reductions in testosterone and strength. Zinc and magnesium supplementation have been suggested as a means to maintain zinc and magnesium status and thereby improve training adaptations. However, there is still some discrepancy in the literature.

10.4 Supplements that Promote Recovery

10.4.1 Glutamine

Glutamine is classified as a nonessential amino acid since it can be readily synthesized by various tissues such as the skeletal muscles, liver, and adipose tissue [82]. Glutamine contributes a large amount of amino acids to the free pool as discussed earlier. However, when the need for glutamine is high, the body may not be able to synthesize it at a fast enough rate to replenish depletion, hence the possible need for supplementation. In fact, glutamine is the most abundant amino acid in the body, representing about 60 % of the amino acid pool in muscles. In a healthy person, the concentration of glutamine in the blood is 3–4 times greater than all other amino acids. Research has shown glutamine to contribute to the prevention of muscle breakdown [83], increase in growth hormone, protein synthesis, improved intestinal health, decrease in the risk of overtraining, and improved immune system function. During catabolic conditions in the body, glutamine content is decreased, and during anabolic states, glutamine levels are high [84]. Recent reports have shown that plasma glutamine levels decrease acutely after single sessions of high-intensity running [85] and after more extended periods of intensive running training [86]. Glutamine is also believed to play a large role in the enhancement of the immune system. Intense physical training may have a negative effect on the immune system by causing a transient suppression of the entire system. The demands on muscle and other organs are so high during intense physical training that the immune system may suffer from a lack of glutamine that temporarily affects its function [87]. It has been suggested that since skeletal muscle is the major tissue involved in glutamine production, that skeletal muscle must thus play a vital role in the process of glutamine utilization in the immune cells. It has been shown that lymphocytes and macrophages utilize glutamine as an energy source at a rate similar to that of glucose. These cells of the immune system have high levels of glutaminase, which is a key enzyme in catabolism of glutamine. High rates of glycolysis (using glucose) and glutaminolysis (using glutamine) provide powerful supplies of energy for these cells. In addition, glutamine provides nitrogen for the synthesis of nucleotides, which are needed for new DNA and RNA during cell multiplication of lymphocytes and for mRNA synthesis and DNA repair in macrophages. A decrease in the blood glutamine concentration may reduce the maximum rate of lymphocyte cell production. In addition, a decrease in glutamine concentration may limit the level of phagocytosis and the rate of cytokine production by macrophage. Since blood glutamine levels decline after heavy exercise, it is possible that exercise-induced immunosuppression will be caused in part by a glutamine deficiency. A study by Rohde investigated the influence of glutamine supplementation on exercise-induced immune system changes for 3 bouts of bicycle ergometer exercise [88]. Oral glutamine supplementation abolished the decrease in plasma glutamine concentration postexercise without influencing any of the immune system parameters.

Physiologic improvement in sports only occurs during the rest period following hard training. This adaptation is in response to maximal loading of the cardiovascular and muscular systems. During recovery periods, these systems build to greater levels to compensate for the stress that you have applied. Proper nutrition and rest are essential in preventing an overtraining effect. Individuals suffering from overtraining also are more susceptible to disease and infections as a result of lowered immunity. One of the results of overtraining is that each day the amount of muscle glutamine gets a little lower. Eventually, the muscle goes below the critical amount of glutamine needed to sustain an anabolic state, and they revert into a long-term catabolic state. This may be due to the role of glutamine as a primary source of fuel for the cells of the immune system, particularly lymphocytes, macrophages, and killer cells. Thus, glutamine supplementation may enhance performance and adaptation in strength and power athletes.

10.4.2 HMB

β-Hydroxy-β-methylbutyric acid, or HMB, is a metabolite of the essential amino acid leucine. HMB is thought to play a role in the regulation of protein breakdown in the body. HMB helps slow down proteolysis, which is the natural process of breaking down muscle that occurs especially after strenuous activity. It appears that HMB supplementation has a protective effect on muscle and may help the body get a head start on the recovery process by minimizing the amount of protein degradation after exercise. HMB allows the body to stay in an anabolic state longer and this allows the body to build more muscle. The theory began that taking supplemental HMB could possibly slow the breakdown of protein in the body, thus increasing muscle mass and strength.

The body synthesizes a small amount of HMB from α-ketoisocaproate as a by-product of leucine metabolism. Theoretically, increasing availability of HMB would minimize protein degradation. In support of this theory, a number of animal studies have reported that adding HMB to the diet enhanced growth rates in pigs [89], increased muscle mass and decreased body fat in steers [90], improved several markers of immune function in chickens [91, 92], and decreased markers of catabolism during training in race horses [93]. Based on these findings, it has been hypothesized that HMB supplementation during training in humans may inhibit protein degradation leading to greater gains in strength and muscle mass.

Several studies have evaluated the effects of HMB supplementation on strength and body composition alterations during training in untrained subjects initiating training and in well-trained athletes. Nissen [94] studied the effects of dietary supplementation with the leucine metabolite HMB. HMB significantly decreased the exercise-induced rise in muscle proteolysis as measured by urine 3-methylhistidine during 2 weeks of exercise. Fat-free mass was significantly increased in HMB-supplemented subjects compared with the control group. They concluded that supplementation with HMB can partly prevent exercise-induced proteolysis and/or muscle damage and result in larger gains in muscle function associated with resistance training. Another study by Knitter [95] investigated HMB supplementation on muscle damage as a result of intense endurance exercise. Creatine phosphokinase and lactate dehydrogenase (LDH) activities were measured before and after a prolonged run to assess muscle damage. The placebo-supplemented group exhibited a significantly greater increase in creatine phosphokinase activity after a prolonged run than did the HMB-supplemented group. In addition, LDH activity was significantly lower with HMB supplementation compared with the placebo group. These findings support the hypothesis that HMB supplementation helps prevent exercise-induced muscle damage. Vukovich and coworkers [96] reported that HMB supplementation (3 g/day for 8 weeks during resistance training) significantly increased muscle mass, reduced fat mass, and promoted greater gains in upper and lower extremity 1RM strength in a group of elderly men and women initiating training. Likewise, Panton and colleagues [97] reported that HMB supplementation during 8 weeks of resistance training increased functional ability to get up, walk, and sit down in a group of elderly subjects. More recently, Gallagher and associates [98] evaluated the effects of HMB supplementation (0.38 and 0.76 mg/kg/day) during 8 weeks of resistance training in previously untrained men. The researchers reported that HMB supplementation promoted significantly less muscle creatine kinase excretion and greater gains in muscle mass (in the 0.38 mg/kg/day group only) than subjects taking a placebo. Collectively, these findings support contentions that HMB supplementation may lessen catabolism leading to greater gains in strength and muscle mass. Kreider et al. [99] conducted a study on experienced resistance-trained athletes. Athletes were supplemented with HMB for 28 days during training. Results revealed that although trends were observed, HMB supplementation did not significantly affect markers of muscle degradation, muscle mass, or strength. These findings suggest that HMB supplementation does not appear to significantly affect strength

and/or muscle mass in well-trained subjects. As with most supplements, there are some conflicting results. However, there does appear to be sound scientific rationale that HMB supplementation may affect catabolism.

Previous research has focused on hydroxy-beta-methylbutyrate, and it has been proven to increase lean body mass as well as strength. In the most recent years, HMB has been created in a free acid form to help increase bioavailability. Pioneering research has found that the free acid form of HMB has been able to approximately double the plasma levels after administration of the supplement [100]. It has also been found that HMB-FA, has a 25 % greater uptake in the body, allowing for improved utilization. In a 12-week study, Wilson investigated the benefits of HMB-FA supplementation on skeletal muscle hypertrophy, body composition, strength, stress hormones, and testosterone in resistance-trained males [101]. Subjects were prescribed an undulating training period for 8 weeks, followed by a 2-week overreaching cycle, and ended the study with a 2-week training volume taper. During the 12 weeks, subjects were administered 3 g per day of either HMB-FA or a placebo taken in 1 g dosages: 30 min prior to working out, before lunch, and prior to supper. Results of the study presented a significant increase in strength variables, with the HMB-FA group experiencing a 25 % increase in strength for squat, 12 % for bench press, and 16 % for deadlift compared to a 5, 3, and 9 % increase, respectively, for the placebo group. The supplementation groups also experienced a significant decrease in body fat (−5.4 ± 1.6 kg) when compared to the placebo group (−1.7 ± 2.7 kg). Hydroxy-beta-methylbutyrate free acid suppressed an elevation in creatine kinase during the overreaching period, leading to musculo-protective benefits of HMB-FA supplementation [101].

In an almost identical study, HMB-FA was tested with the addition of adenosine triphosphate. Supplementation of ATP would help maintain performance as well as increase volume during highly fatiguing contractions. When paired with the increased speed in muscle regeneration from HMB-FA, the potential for an individual to train at a higher workload while minimizing the stress and recovery time needed between workouts may exist. Lowery and associates tested this supplementation protocol in a triple-blind-manner, 3 g of HMB-FA, 400 mg of ATP, and 3 g of HMB-FA/400 mg ATP, over the course of 12 weeks. Strength training followed an 8-week periodized program, leading into a 2-week overreaching cycle, and concluding with a 2-week taper. Individuals ingesting HMB-FA + ATP experienced a significant increase in lean body mass 8.5 ± 0.08 kg (12.7 %) as well as an increase in strength in by 23.5 %. Those taking HMB-FA increase lean body mass by 7.4 ± 0.4 kg, subjects ingesting ATP increase lean body mass by 4.4 ± 0.4 kg, and the placebo group experienced a 2.1 ± 0.5 kg increase. During the overreaching cycle, participants who were ingesting HMB-FA only had a decrease in strength by .5 %, whereas those on the placebo declined in strength by −4.5 %. Interestingly, the HMB-FA/ATP subjects were not negatively affected by the overreaching cycle, but actually gained strength (+1.2 %). The conclusion of this study suggests that HMB-FA and ATP are capable of increasing strength as well as increasing body composition. The combination of HMB-FA with ATP can provide a synergistic effect of increased lean body mass as well as strength [102].

A majority of research has measured the benefits of HMB-FA on strength training, because of HMB-FA being a metabolite to leucine the trigger for muscle growth. Aerobically, HMB-FA could potentially lend its benefits of an increased recovery time and attenuating muscle damage properties in high interval training. In 2013 a study was conducted to test the effects of HMB-FA supplementation paired with HIIT and its effects on maximal oxygen consumption, ventilatory threshold, respiratory compensation point, and time to exhaustion [103]. Twenty-six male and female participants were divided into either a placebo + HIIT or HMB-FA + HIIT, with an additional control group of eight people. Subjects completed 12 HIIT exercises on a cycle ergometer. Those not in the control group ingested 3 g of either HMB-FA or placebo during the study. Results indicated a significant difference ($p = 0.003$) in VO_{2peak} with HMB-FA having

a greater increase in VO_{2peak} values than the control ($p=0.001$) or the placebo group ($p=0.032$), whereas no difference was found between the control group and the placebo + HIIT group ($p=0.09$). For both peak power and time to exhaustion, there were significant differences between across groups ($p=0.013$ and $p=0.002$, respectively). While no significant difference was experienced between the HMB-FA and the placebo + HIIT, both groups had a greater increase than the control group for both peak power and time to exhaustion. Robinson and Stout found that pairing supplementation of HMB-FA with HIIT training can lead to increase in VO_{2max} performance than HIIT training alone.

10.4.3 Antioxidants

Oxidative stress is the steady-state level of oxidative damage in a cell, tissue, or organ caused by free radicals or the reactive oxygen species (ROS). Reactive oxygen species, such as free radicals and peroxides, represent a class of molecules that are derived from the metabolism of oxygen and exist inherently in all aerobic organisms. Free radicals are simply electrons that are no longer attached to atoms. There are many different sources by which the reactive oxygen species are generated. Most reactive oxygen species come from the endogenous sources as by-products of normal and essential metabolic reactions, such as energy generation from mitochondria. The level of oxidative stress is determined by the balance between the rate at which oxidative damage is induced and the rate at which it is efficiently repaired and removed. Free radicals interact with other molecules within cells. This can cause oxidative damage to proteins, membranes, and genes. Physical exercise induces oxidative stress and tissue damage. Although a basal level of reactive oxygen species (ROS) is required to drive redox signaling and numerous physiologic processes, excess ROS during exercise may have adverse implications on health and performance. High-intensity resistance training has also been shown to increase free radical production. Antioxidant nutrients may be helpful in that regard. Additionally the overtraining effect can induce increases in ROS.

To combat the effects of oxidative stress, antioxidants can be taken. Antioxidants block the process of oxidation by neutralizing free radicals. That is why there is a constant need to replenish our antioxidant resources. Antioxidants from our diet appear to be of great importance in controlling damage by free radicals. Each nutrient is unique in terms of its structure and antioxidant function.

Vitamin E is actually a generic term that refers to all entities that exhibit biological activity of the isomer tocopherol. Alpha-tocopherol, the most widely available isomer, has the highest biopotency or strongest effect in the body. Because it is fat-soluble, alpha-tocopherol is in a unique position to safeguard cell membranes, largely composed of fatty acids, from damage by free radicals. Vitamin E is an important intramembrane antioxidant and membrane stabilizer. Vitamin E supplementation has been advocated for athletes in the hope of improving performance, minimizing exercise-induced muscle damage, and maximizing recovery. Meydani et al. [104] reported that vitamin E-treated subjects had a decrease in oxidative stress over 12 days following eccentric exercise (downhill running). Cannon et al. [105] concluded that supplementation of vitamin E for 48 days reduced the amount of creatine kinase leakage in young and old men during recovery from downhill running bouts. In subsequent studies, Rokitski et al. [106] concluded that supplementation of vitamin E for 5 months decreases creatine kinase leakage in aerobic cyclists. These studies indicate that vitamin E supplementation can help reduce muscle damage caused by free radical damage. Hartmann et al. [107] noted that DNA damage could occur in white blood cells after exercise. These researchers concluded that a 2,400 mg dose of vitamin E resulted in decreased damage to the DNA of white blood cells in exercised individuals.

Vitamin C, also known as ascorbic acid, is a water-soluble vitamin. As such, it scavenges free radicals that are in an aqueous environment inside cells. Vitamin C works synergistically with vitamin E to destroy free radicals. Vitamin C is

used in numerous metabolic processes in the body. Theoretically, it could benefit exercise performance by improving metabolism during exercise. Ascorbic acid also may reduce the occurrence of upper respiratory tract infections brought about by intense training [108]. Other associations for ascorbic acid involve a role in the synthesis of collagen, which is necessary for strong cartilage, tendon, and bone. Certain hormones such as adrenaline and neurotransmitters need ascorbic acid. Ascorbic acid also aids in the absorption of iron and helps in the formation of red blood cells that carry oxygen to the muscle tissues.

Vitamin C does appear control reactive oxidant species formed during exercise. If not controlled, these species have the ability to react with cell membranes and damage them. In 1992, Kaminski et al. [109] examined the relationship between vitamin C given to 19 subjects for 3 days before exercise and seven after and the muscle damage induced by two bouts of eccentric exercise. The authors concluded that vitamin C reduced muscle damage [109]. Vitamin C is also important to a host of numerous other functions within the body.

Vitamins C and E are not the only antioxidants; in fact, vitamin A has antioxidant properties. Coenzyme Q10 (CoQ10 or ubiquinone), which is essential to energy production, can also protect the body from destructive free radicals. In addition, uric acid, a product of DNA metabolism, has become increasingly recognized as an important antioxidant. Additionally, substances in plants called phytochemicals are being investigated for their antioxidant activity and health-promoting potential.

In a crossover study to test the benefit of antioxidant supplementation on oxidative stress during exercise, Ackerman et al. [110] gave 13 resistance-trained males either a placebo or an antioxidant drink before performing a hypertrophic training session. Each of the participants completed six sets with 10 repetitions at 70 % of a predicted 1RM on back squat. After the completion of the first testing session, subjects returned for a subsequent testing session to intake the other dose of either placebo or supplement. During the placebo trial, subjects experienced a significant decrease in concentric mean power. Training volume for the antioxidant supplement was significantly higher (6,746 ± 5.9 W) than the placebo group (6,493 ± 17.1 W). Growth hormone was measured after each of the training sessions and determined that plasma concentrations were significantly less after consumption of the antioxidant supplement (6.65 ± 1.84 vs. 16.08 ± 2.78 ng#×2,219;ml^{-1}; $p < 0.05$, ES'r = 0.89). For this investigation, an ingestion of antioxidants was effective in improving contractile work in the muscle, suggesting that there may be an ergogenic benefit from antioxidant supplementation during intensive resistance training.

A fat-soluble, vitamin-like substance, CoQ10, plays a vital role in ATP production in the mitochondria. During oxidative phosphorylation, 96 % of all ATP produced involves coenzyme Q10; with this in mind, supplementation could potentially provide ergogenic as well as antioxidant benefits during exercise. Using highly trained German athletes, Alf headed a study to investigate CoQ10's influence on the lactate threshold [111]. Over the course of the 6-week study, 100 subjects both ingested 300 mg of ubiquinol or placebo and performed three (week 0, week 3, week 6) maximal power output tests on a cycle ergometer to measure lactate threshold. After data analysis, the study showed a significant increase in physical performance for both groups. Those on the placebo increased .30 ± 0.18 W/kg bw or +8.5 % (±5.7) when compared to baseline. The ubiquinol group increased performance levels 11 % from 3.70 W/kg bw to 4.08 W/kg bw. When compared, there was a significant difference in the maximal power produced between the CoQ10 group versus the placebo. Although more research needs to be completed to confirm these benefits, this study shows that ingesting additional ubiquinol has a potentially beneficial ergogenic effect on exercise performance.

To test the effects of Glycine Propionyl-l-Carnitine (GlycoCarn®) and three other pre-workout nutrient supplements, 19 resistance-trained males were recruited for a 6-week supplement study [112]. Over the course of the study, subjects participated in six testing sessions 1 week apart, where each subject's body composition, 1RM bench press, upper body muscular endurance, blood markers of oxidative stress, and skeletal

muscle oxygen saturation was tested. In a crossover design, each participant performed the testing session under a different supplemental condition each time (placebo, GlycoCarn®, or one of the three dietary supplements). At the conclusion of the study, none of the supplements were effective in improving performance or blood markers.

10.5 Supplements that Enhance Immune Function

10.5.1 Vitamins and Minerals

Immunosuppression in athletes involved in heavy training may increase the athlete's exposure to pathogens and provide optimal conditions for illness and injury. Heavy prolonged exercise is associated with numerous hormonal and biochemical changes, many of which potentially have detrimental effects on immune function. Furthermore, improper nutrition can compound the negative influence of heavy exertion on the immune system. For optimal nutrition, one must consume the adequate amount of nutrients. Nutrients are defined as the chemicals taken into the body that are used to produce energy, provide building blocks for new molecules, or function in other chemical reactions. Essential nutrients are the nutrients that must come from the food we ingest because our body cannot make them or is unable to make the required amount of them. Other nutrients can be synthesized from the ingested nutrients. Athletes are not clinically immune deficient; it is possible that the combined effects of small changes in several immune parameters may compromise resistance to minor illnesses [112]. Strategies to prevent immune deficiencies in athletes include avoiding overtraining, providing adequate rest and recovery during the training, and ensuring adequate nutrition. In a review by Gleeson [70], it was concluded that strenuous prolonged exertion and heavy training are associated with depressed immune function. Furthermore, improper nutrition can compound the negative influence of heavy exertion on immune system decrements.

Unlike the macronutrients, the body requires only small amounts of vitamins and minerals. They do not supply any caloric needs, nor do they produce energy. Vitamins are organic compounds that have many important roles for normal functioning, growth, and maintenance of the body. They also help extract energy from the macronutrients. Vitamins are classified into two categories: fat-soluble and water-soluble. Fat-soluble vitamins are vitamins A, D, E, and K. The eight B vitamins and vitamin C make up the water-soluble vitamins. Each vitamin plays a major role in several body functions and may cause health problems if lead to a deficiency. Vitamins can be found in just about every food, but the way foods are stored, processed, and cooked often lead to the loss of vitamins [113]. Minerals are elemental atoms, which are not destroyed by heat, light, or pH changes. There are seven major minerals including sodium, potassium, chloride, calcium, phosphorus, magnesium, and iron. Each mineral has a specific role, from components of hormones and enzymes to structural function. Significant deficits would lead to severe problems and illnesses. Both plants and animals are good sources of minerals; some examples would include whole grains, vegetables, milk, meats, and fruit [114]. Although it is impossible to counter the effects of all of the factors that contribute to exercise-induced immunosuppression, it has been shown to be possible to minimize the effects of many factors.

10.5.2 CLA

Conjugated linoleic acids are essential fatty acids that have been reported to possess significant health benefits in animals [115, 116]. CLA is a naturally occurring fatty acid primarily found in beef and dairy fats. Research has indicated that CLA may possess a number of health- and performance-enhancing benefits. There are some data suggesting that CLA supplementation may modestly promote fat loss and/or increases in lean mass [117–120]. CLA has been marketed as a supplement that may promote health as well as provide ergogenic value to athletes. Although most research on CLA has been conducted on animals, there have been a number of recent studies that provide greater insight on how CLA may be beneficial to enhance health and performance

in humans. CLA feedings in animals have been shown to lessen markers of catabolism [121], enhance the immune system [122, 123], and increase bone mineral content [124, 125]. A 2005 [126] study investigated the effect of dietary CLA supplementation on the immune system and plasma lipids and glucose of healthy human volunteers. Subjects were given 3 g (6 × 500 mg capsules) of CLA per day for 12 weeks. A 12-week washout period followed the intervention period. Levels of plasma IgA and IgM were increased, while plasma IgE levels were decreased. CLA supplementation also decreased the levels of the proinflammatory cytokines, TNF-alpha, and IL-1beta, but increased the levels of the anti-inflammatory cytokine, IL-10. This study showed that CLA could beneficially affect immune function in healthy human volunteers. Another study [127] done in animals was undertaken to investigate the growth performance and immune responses when supplemented with conjugated linoleic acid (CLA). There were no significant differences in growth performance among treatments; however, the results indicated dietary CLA supplementation could enhance the immune response.

CLA has also shown other potential performance benefits. CLA supplementation has been reported to decrease markers of catabolism. This may help athletes tolerate higher training volumes leading to greater gains in strength and/or fat-free mass over time. Lowery and coworkers [118] investigated the effects of CLA supplementation (7.2 g/day) during 6 weeks of resistance training in novice body builders. The researchers reported that CLA supplementation significantly increased arm mass, body mass, and gains in leg press strength. This study provides evidence that CLA supplementation during training may affect training adaptations. Thom and colleagues [117] evaluated the effects of CLA supplementation on body composition alterations in 20 healthy male and female subjects. Results revealed no significant changes in body weight. However, subjects ingesting CLA experienced a significant decrease in body fat (−4.3 %). Kreider et al. [128] evaluated the effects of ingesting 9.2 g/day of CLA for 30 days on body composition, bone density, strength, and markers of catabolism in experienced resistance-trained athletes [129, 130]. Results revealed that CLA supplementation did not affect body mass, fat mass, or fat-free mass. However, statistical trends were observed, indicating that CLA may have lessened markers of catabolism, promoted greater gains in strength, increased bone density, and enhanced immune status. Consequently, results tended to support the theoretical value of CLA supplementation.

Beuker and colleagues [131] evaluated the effects of CLA supplementation during training on body composition, blood lipids, and cycling power output. The authors reported that CLA supplementation increased the efficacy of power output as well as decreased plasma cholesterol by approximately 15 %. These findings provide additional support that CLA supplementation may affect training adaptations and lipid profiles.

CLA appears to have many benefits for the strength athlete. While there are conflicting results, it appears that there is plenty of supporting evidence as to the efficacy of CLA supplementation.

10.6 Supplements that Provide Energy and Enhanced Workouts

10.6.1 Carbohydrate

Carbohydrate serves as the primary fuel for moderate- to high-intensity exercise. The amount of carbohydrate that can be stored in the liver and muscle, however, is limited, and it takes time to replenish carbohydrate stores. When significant amounts of carbohydrate are depleted, it may be difficult to fully replenish carbohydrate levels within 1 day. Consequently, when athletes train once or twice per day over a period of days, carbohydrate levels may gradually decline, leading to fatigue, poor performance, and/or overtraining [132, 133]. Therefore, it is imperative that active individuals and athletes consume enough carbohydrate in their diet in order to maintain carbohydrate availability. In addition, different types of carbohydrate may provide some advantages over others when consumed prior to, during, and/or following exercise.

There is substantial evidence suggesting that the performance of resistance-training exercises can elicit a significant decrement in glycogen stores resulting in decreased performance. Robergs et al. [134] demonstrated that subjects performing six sets of leg extensions at 35 and 70 % of 1RM had a decrease in muscle glycogen by 38 and 39 %, respectively. In a study by Tesch et al. [135], nine bodybuilders completed five sets each of front squats, back squats, leg presses, and leg extensions to fatigue, comprising 30 min of exercise. Biopsies of muscle samples were obtained from the vastus lateralis before and immediately after exercise. Muscle glycogen concentration was 26 % lower postexercise. Data from Essen-Gustavsson and Tesch [136] with nine bodybuilders performing the same exercise regimen revealed a 28 % decrement in muscle glycogen content as well as a 30 % decrease in muscle triglyceride content.

Currently some scientific evidence suggests that carbohydrate supplementation prior to and during high-volume resistance training results in the maintenance of muscle glycogen concentration, which potentially could result in the maintenance or increase of performance during a training bout. One of the most important nutritional strategies to follow exercise is to ingest adequate amounts of carbohydrate and protein. Research indicates that athletes who ingest 1.5 g/kg of carbohydrate within 2 h after exercise experience a greater rate of muscle glycogen resynthesis [137]. In a study by Haff et al. [138], six resistance-trained men ingested a 250 g carbohydrate supplement or placebo during a morning training session, rested for 4 h, and then performed a second session consisting of multiple sets of light-intensity squats (55 % 1RM) to exhaustion. During the second training session, the number of sets and repetitions performed was markedly higher with the carbohydrate consumption, and subjects were able to exercise for 30 min longer. The authors concluded that athletes engaging in multiple exercise sessions per day would receive a performance advantage with carbohydrate ingestion via maintenance of intramuscular glycogen stores, due to greater glycogen resynthesis during recovery.

As discussed earlier, amino acids have a positive effect on protein synthesis. It has been hypothesized that carbohydrate and amino acid supplementation together would result in greater gains. Bird et al. [139] investigated chronic alteration of the acute hormonal response associated with liquid carbohydrate (CHO) and/or essential amino acid (EAA) ingestion on hormonal and muscular adaptations following resistance training. Thirty-two untrained young men performed 12 weeks of resistance training twice a week. EAA and CHO ingestion attenuated 3-methylhistidine excretion 48 h following the exercise bout. CHO+EAA resulted in a 26 % decrease, while PLA displayed a 52 % increase. In addition muscle cross-sectional area increased across groups for type I, IIa, and IIb fibers, with CHO+EAA displaying the greatest gains in cross-sectional area relative to PLA. These data indicate that CHO+EAA ingestion enhances muscle anabolism following resistance training to a greater extent than either CHO or EAA consumed independently.

Based on the current scientific literature, it may be advisable for athletes who are performing high-volume resistance training to ingest carbohydrate supplements before, during, and immediately after resistance training.

10.6.2 Caffeine

Caffeine is one of the most widely used stimulants in the world. It occurs naturally in the foods and beverages such as coffee, tea, soft drinks, chocolate, and cocoa. The average caffeine consumption in the United States is approximately 200 mg or equivalent to 2 cups of coffee a day. Ten percent of the population ingests more than 1,000 mg per day. Caffeine is also added to several over-the-counter medicines such as some weight-loss products, pain medicines, and cold remedies. Caffeine acts as a stimulant on the central nervous system, which causes the heart rate and blood pressure to increase.

Most of the research with caffeine and exercise has indicated an improvement in time to exhaustion and improved work output in comparison to

control during aerobic exercise [140–144]. Ivy and colleagues [144] demonstrated an improved work output of 7.4 % with individuals ingesting caffeine when compared to the control group during aerobic cycling bouts. In contrast to several other studies that mainly addressed the ergogenic effects of caffeine in trained individuals, Graham and Spriet [143] showed that the same ergogenic effects of caffeine could be seen on untrained, caffeine-naive subjects. Several studies indicate that the ergogenic effects of caffeine were best seen when regulated for body weight, with the recommendation for enhancing endurance performance at 80–85 % VO_{2max} in trained athletes at 9 mg/kg [145–147].

However, caffeine has not had the same results in short-term exercise. Doherty et al. [148] assessed the effects of caffeine ingestion on both aerobic and anaerobic exercise. The results showed that the participants experienced a greater improvement in endurance exercise than that of graded or short-term exercise. In a related study also conducted by Doherty [149], the participants performed a 1-min all-out effort on a cycle ergometer. The results suggest that high-intensity cycling performance can be increased via an increase in mean power output, following moderate caffeine ingestion (5 mg/kg). In a study conducted by Collomp and colleagues [150], the effect of 5 mg/kg caffeine ingestion on the Wingate Anaerobic Test was assessed. The results showed that caffeine administration did not significantly change either maximal anaerobic capacity or power. However, there was a significant increase in both catecholamine and blood lactate levels compared to the placebo trials. Another study [151] was conducted to determine the effect of caffeine on time to exhaustion and on associated metabolic and circulatory measures. Eight male subjects ingested either caffeine (5 mg/kg body weight) or a placebo 1 h prior to exercise at 85–90 % of maximum workload. Subjects were encouraged to complete three 30-min intermittent cycling periods at 70 rpm with 5 min rest between each. The exercise was terminated when the subject failed to complete three 30-min periods or failed to maintain 70 rpm for at least 15 s consecutively. Serum-free fatty acids, glycerol, blood glucose, lactate, perceived exertion, heart rate, and O2 cost were measured. The time to exhaustion was significantly longer during the caffeine trial than during the placebo trial. Serum-free fatty acid levels were significantly different between trials. The decline in blood glucose levels was significantly less during the caffeine trial than during the placebo trial. There were no significant differences between trials for the other measures. It was concluded that caffeine increases time to exhaustion when trained subjects cycled intermittently at high levels of intensity.

While there are conflicting results on the effects of caffeine and performance, there does appear to be benefit. Not only has caffeine demonstrated its capabilities in enhancing performance directly, it has the potential to have profound effects indirectly. Like other stimulants, caffeine has been advertised and sold as a way to stimulate energy expenditure and possibly result in weight by stimulating both lipolysis and energy expenditure [152]. A recent study found that coffee ingestion (200 mg of caffeine) resulted in a 7 % increase in energy expenditure for 3 h following ingestion [153]. Recent research on the effects of caffeine continues to support its role in increasing energy expenditure. Another study found that caffeine alone increased energy expenditure by 13 % while doubling lipid turnover, and these effects suggested to be mediated through the sympathetic nervous system [152]. It is clear that there is great potential for caffeine as an ergogenic aid.

10.6.3 Summary/Practical Applications

Efficient sport nutrition is a multifaceted and complex endeavor. With a premium being placed on performance, the strength athlete needs to use every capable tool to perfect his/her performance. Pinnacle nutrition has to include a proper balance of carbohydrates, proteins, fats, water, vitamins, and minerals. However, the strength athlete has the benefit of nutrition science to optimize training. While there is no replacement for a balanced diet, sport supplements can assist in development. There are three supplements that have substantial scientific support for their effectiveness (Table 10.1). Creatine supplementation has been commonplace in sports for many years. There is

Table 10.1 Supplements for strength and power athletes

Nutrient	Theoretical ergogenic value	Summary of research findings/ recommendations
Creatine	Creatine is a naturally occurring amino acid that is derived from the amino acids glycine, arginine, and methionine. When creatine enters the muscle cell, it accepts a high-energy phosphate and forms phosphocreatine (PC). PC is the storage form of high-energy phosphate, which is used by the skeletal muscle cell to rapidly regenerate adenosine triphosphate (ATP) during bouts of maximal muscular contraction	Creatine has been proven to increase strength, muscle mass, and sprint performance. Research supports the use of creatine in increase strength, lean body mass, power, sprint performance, and recovery. No clinical side effects are supported in the literature
Protein	Protein is the main component of muscles, organs, and hormones. The cells of muscles, tendons, and ligaments are maintained, repaired, and enhanced with protein. Skeletal muscle growth is possible only when muscle protein synthesis exceeds muscle protein breakdown; thus, adequate dietary protein is essential	Research has defined a vital role of protein development of muscle mass and hormonal regulation. Post-workout protein supplementation has shown increases in protein synthesis and muscle mass
Amino acids	Amino acids are organic compounds that combine to form proteins. When proteins are degraded, amino acids are left. The human body requires a number of amino acids to facilitate skeletal muscle growth and repair, as well as hormonal development that is necessary for adaptations to stress	Amino acid supplementation has extensive research suggesting that pre- and post-workout AA supplementation can increase protein synthesis and slow degradation
β-Alanine	β-Alanine is an amino acid that is not involved in structural proteins and functions to combine with another amino acid, histidine, to form carnosine. Carnosine is believed to be one of the primary muscle-buffering substances available in skeletal muscle. In theory if carnosine could attenuate the drop in pH noted with high-intensity exercise, then one could possibly exercise longer	β-Alanine supplementation appears to improve submaximal cycle ergometry performance and total time to exhaustion. There appears to be enough research currently to evaluate its effectiveness, and it appears that not only does β-alanine appear to increase muscle carnosine levels, but those changes appear to translate into performance benefits
Arginine	Arginine is an amino acid that has numerous functions in the body. It is used to make compounds in the body such as nitric oxide, creatine, glutamate, and proline and can be converted to glucose and glycogen if needed. In large doses, arginine also stimulates the release of hormones growth hormone and prolactin. Arginine has also been suggested to assist in wound healing, help remove excess ammonia from the body, and stimulate immune function	There are some conflicting results in the research regarding arginine. However, there is some evidence that arginine supplementation can increase strength, muscle mass, and growth hormone levels
Aromatase inhibitors	Aromatase is an enzyme involved in the production of estrogen that acts by catalyzing the conversion of testosterone (an androgen) to estradiol (an estrogen). Aromatase inhibitors are believed to inhibit the conversion of testosterone to estrogen, thereby increasing endogenous testosterone levels	While aromatase inhibitors as a nutrition supplement are relatively new, there is research suggesting that AIs can increase endogenous levels of testosterone. However, there is no evidence that these increases in testosterone lead to performance benefits
Zinc magnesium aspartate	Zinc and magnesium are two minerals that are used in a number of metabolic processes and hormonal regulation. Zinc is an essential trace element involved in a range of vital biochemical processes and is required for the activity of more than 300 enzymes. Magnesium is an essential element in human nutrition; it is the cofactor in enzymes of carbohydrate metabolism and is also involved in several hundred enzymatic reactions in which food is metabolized and new products are formed	Preliminary research findings have indicated that training decreases zinc and magnesium availability leading to reductions in testosterone and strength. Zinc and magnesium supplementation have been suggested as a means to maintain zinc and magnesium status and thereby improve training adaptations. However, there is still some discrepancy in the literature

(continued)

Table 10.1 (continued)

Nutrient	Theoretical ergogenic value	Summary of research findings/ recommendations
Glutamine	Glutamine is the most abundant amino acid in the body, representing about 60 % of the amino acid pool in muscles. Glutamine serves a variety of functions in the body including cell growth, immune function, and recovery from stress	Research has shown glutamine to contribute to the prevention of muscle breakdown, increase in growth hormone, protein synthesis, improved intestinal health, decrease in the risk of overtraining, and improved immune system function
β-Hydroxy-β-methylbutyric acid	β-Hydroxy-β-methylbutyric acid, or HMB, is a metabolite of the essential amino acid leucine. HMB is thought to play a role in the regulation of protein breakdown in the body. It appears that HMB supplementation has a protective effect on muscle and may help the body get a head start on the recovery process by minimizing the amount of protein degradation after exercise	There appear to be sound scientific findings that suggest HMB supplementation may affect catabolism and protein synthesis. However, there is not conclusive evidence to suggest that HMB supplementation can increase strength or muscle mass
Antioxidants	Oxidative stress is the steady-state level of oxidative damage in a cell, tissue, or organ, caused by free radicals or the reactive oxygen species (ROS). Reactive oxygen species, such as free radicals and peroxides, represent a class of molecules that are derived from the metabolism of oxygen that is increased during exercise. Antioxidants block the process of oxidation by neutralizing free radicals	Research has determined that antioxidants are effective at reducing free radicals. However, their direct effect on the strength and power athlete has yet to be determined
Vitamins and minerals	Heavy prolonged exercise is associated with numerous hormonal and biochemical changes, many of which potentially have detrimental effects on immune function. Vitamins are organic compounds that have many important roles for normal functioning, growth, and maintenance of the body. They also help extract energy from the macronutrients. Each mineral has a specific role, from components of hormones and enzymes to structural function	It is clear that strength-trained athletes have been shown to exhibit deficiencies in one or more vitamins and minerals. Thus, the need to raise levels to within normal range is supported in the literature. However, it is not clear if supplementation in excess of RDI is advantageous to the strength athlete
CLA	Conjugated linoleic acids are essential fatty acids that have been reported to possess significant health benefits in animals. CLA is a naturally occurring fatty acid primarily found in beef and dairy fats. Research has indicated that CLA may possess a number of health- and performance-enhancing benefits	CLA appears to have many benefits for the strength athlete. While there are conflicting results, it appears that there is plenty of supporting evidence as to the efficacy of CLA supplementation on enhancing immune performance
Carbohydrate	Carbohydrate serves as the primary fuel for moderate- to high-intensity exercise. The amount of carbohydrate that can be stored in the liver and muscle, however, is limited, and it takes time to replenish carbohydrate stores. Therefore, it is imperative that active individuals and athletes consume enough carbohydrate in their diet in order to maintain carbohydrate availability	Based on the current scientific literature, it may be advisable for athletes who are performing high-volume resistance training to ingest carbohydrate supplements before, during, and immediately after resistance training
Caffeine	Caffeine is one of the most widely used stimulants in the world. It occurs naturally in the foods and beverages such as coffee, tea, soft drinks, chocolate, and cocoa. Caffeine acts as a stimulant on the central nervous system, which causes the heart rate and blood pressure to increase. Caffeine and exercise is believed to cause an improvement in time to exhaustion and improved work output during aerobic exercise	Caffeine has been shown in the literature to have both a positive effect on duration of exercise and energy expenditure. Research has also shown an increase in power output. However, further research is needed for conclusive recommendations

no other supplement that has the substantial positive research that creatine has. Creatine has been proven to increase strength, muscle mass, and sprint performance. Protein supplementation is also a necessary component to all strength programs. Protein and amino acids are required for protein synthesis to remain in a positive nitrogen balance. This will ensure the strength athletes that they are getting the most out of their workouts. More recent research suggests that post-workout protein supplementation is a powerful booster to the anabolic process. In conjunction with protein, post-workout carbohydrate supplementation is needed to replace precious glycogen stores that were depleted during the workout. Carbohydrates have received a bad rap in recent years; however, the informed athlete understands the vital importance of carbohydrates in optimizing performance. These three supplements are paramount in the resistance-trained athlete.

The next tier of supplements might take the strength athlete to the next level. β-Alanine is the next great supplement. β-Alanine might be capable of increased time to exhaustion and enhancing the workouts that are necessary to impose substantial overload on the strength athlete. HMB has also been shown to be a powerful anti-catabolic supplement. Sparing precious muscle during rigorous training could prove to be the impetus for growth. Coupled with amino acid supplementation, HMB could enhance the hypertrophic effect. Another supplement that might take the strength athlete to the next level is the aromatase inhibitors. Aromatase inhibitors have been shown in limited studies to increase endogenous testosterone. The strength athlete understands the importance of testosterone in boosting training adaptations. Caffeine is a commonplace additive to the diets of millions of athletes and nonathletes alike. However, the stimulatory effects and the boost in metabolism that caffeine induces mike enhance workouts and assist in the creation of lean powerful muscle.

Finally, the supplements that enhance recovery or support immunity could prove to be the difference in peak performance. Due to the rigorous nature of the training regimens of strength athletes, endogenous levels of vitamins, minerals, and immune markers have been shown to be low. This can be combated by supplementation with multivitamins, antioxidants, glutamine, and CLA. Bring all of these supplements together, couple them with a balanced diet, and a rigorous training program and strength and power athletes are sure to maximize their genetic potential.

Each day new supplements hit the market with the promise of enhancing performance, increasing muscle mass and optimizing strength. However, until valid scientific reports support these claims, there is some risk involved.

References

1. Balsom PD, Soderlund K, Ekblom B. Creatine in humans with special reference to creatine supplementation. Sports Med. 1994;18:268–80.
2. Heymsfield SB, Arteaga C, McManus C, Smith J, Moffitt S. Measurement of muscle mass in humans: validity of the 24-hour urinary creatinine method. Am J Clin Nutr. 1983;37:478–94.
3. Hirvonen J, Rehunen S, Rusko H, Harkonen M. Breakdown of high-energy phosphate compounds and lactate accumulation during short supramaximal exercise. Eur J Appl Physiol Occup Physiol. 1987; 56:253–9.
4. Kreider RB. Species-specific responses to creatine supplementation. Am J Physiol Regul Integr Comp Physiol. 2003;285:R725–6.
5. Norman K, Stubler D, Baier P, et al. Effects of creatine supplementation on nutritional status, muscle function and quality of life in patients with colorectal cancer–a double blind randomised controlled trial. Clin Nutr. 2006;25:596–605.
6. Greenwood M, Kreider RB, Greenwood L, Byars A. Cramping and injury incidence in collegiate football players are reduced by creatine supplementation. J Athl Train. 2003;38:216–9.
7. Kreider RB. Effects of creatine supplementation on performance and training adaptations. Mol Cell Biochem. 2003;244:89–94.
8. Kreider RB, Melton C, Rasmussen CJ, et al. Long-term creatine supplementation does not significantly affect clinical markers of health in athletes. Mol Cell Biochem. 2003;244:95–104.
9. Stout J, Eckerson J, Ebersole K, et al. Effect of creatine loading on neuromuscular fatigue threshold. J Appl Physiol. 2000;88:109–12.
10. Volek JS, Kraemer WJ, Bush JA, et al. Creatine supplementation enhances muscular performance during high-intensity resistance exercise. J Am Diet Assoc. 1997;97:765–70.
11. Peeters B, Lantz C, Mayhew J. Effects of oral creatine monohydrate and creatine phosphate supple-

mentation on maximal strength indices, body composition, and blood pressure. J Strength Cond Res. 1999;13:3–9.
12. Eckerson JM, Stout JR, Moore GA, Stone NJ, Nishimura K, Tamura K. Effect of two and five days of creatine loading on anaerobic working capacity in women. J Strength Cond Res. 2004;18:168–73.
13. Kreider RB, Ferreira M, Wilson M, et al. Effects of creatine supplementation on body composition, strength, and sprint performance. Med Sci Sports Exerc. 1998;30:73–82.
14. Claudino J, Mezenico B, Amaral S, Zanetti V, Benatti F, Roschel H, Gualano B, Amadio A, Serrao J. Creatine monohydrate supplementation on lower-limb muscle power in Brazilian elite soccer players. J Int Soc Sports Nutr. 2014;11:32.
15. De Salles Painelli V, Alves V, Ugrinowitsch C, Benatti F, Artioli G, Lancha A, Gualano B, Roschel H. Creatine supplementation prevents acute strength loss induced by concurrent exercise. The. J Appl Physiol. 2014;114(8):1749–55.
16. Antonio J, Ciccone V. The effects of pre- versus post-workout supplementation of creatine on body composition and strength. J Int Soc Sports Nutr. 2013;10:36.
17. Barber J, McDermott A, McGaughey K, Olmstead J, Hagobian T. Effects of combined creatine and sodium bicarbonate supplementation on repeated sprint performance in trained men. J Strength Cond Res. 2013;27(1):252–8.
18. Phillips SM, Parise G, Roy BD, Tipton KD, Wolfe RR, Tamopolsky MA. Resistance-training-induced adaptations in skeletal muscle protein turnover in the fed state. Can J Physiol Pharmacol. 2002;80: 1045–53.
19. Phillips SM, Tipton KD, Ferrando AA, Wolfe RR. Resistance training reduces the acute exercise-induced increase in muscle protein turnover. Am J Physiol. 1999;276:E118–24.
20. Biolo G, Maggi SP, Williams BD, Tipton KD, Wolfe RR. Increased rates of muscle protein turnover and amino acid transport after resistance exercise in humans. Am J Physiol. 1995;268:E514–20.
21. Biolo G, Tipton KD, Klein S, Wolfe RR. An abundant supply of amino acids enhances the metabolic effect of exercise on muscle protein. Am J Physiol. 1997;273:E122–9.
22. Tipton KD, Ferrando AA, Phillips SM, Doyle Jr D, Wolfe RR. Postexercise net protein synthesis in human muscle from orally administered amino acids. Am J Physiol. 1999;276:E628–34.
23. Esmarck B, Andersen JL, Olsen S, Richter EA, Mizuno M, Kjaer M. Timing of postexercise protein intake is important for muscle hypertrophy with resistance training in elderly humans. J Physiol. 2001;535:301–11.
24. Tipton KD, Elliott TA, Cree MG, Wolf SE, Sanford AP, Wolfe RR. Ingestion of casein and whey proteins results in muscle anabolism after resistance exercise. Med Sci Sports Exerc. 2004;36:2073–81.
25. Rennie MJ, Wackerhage H, Spangenburg EE, Booth FW. Control of the size of the human muscle mass. Annu Rev Physiol. 2004;66:799–828.
26. Kerksick C, Leutholtz B. Nutrient administration and resistance training. J Int Soc Sports Nutr. 2006; 2:57–60.
27. Cooke M, Rybalka E, Stathis C, Cribb P, Hayes A. Whey protein isolate attenuates strength decline after eccentrically-induced muscle damage in healthy individuals. J Int Soc Sports Nutr. 2010;7:30.
28. Wilborn C, Taylor L, Outlaw J, Williams L, Campbell B, Foster C, Smith-Ryan A, Urbina S, Hayward S. The effects of pre- and post- exercise whey vs. casein protein consumption on body composition and performance measures in collegiate female athletes. J Sports Sci Med. 2013;12(1):74–9.
29. Antonio J, Peacock C, Ellerbroek A, Fromhoff B, Silver T. The effects of consuming a high protein diet (4.4 g/kg/d) on body composition in resistance-trained individuals. J Int Soc Sports Nutr. 2014;11:19.
30. Harris R, Dunnett M, Greenhaf P. Carnosine and Taurine contents in individual fibres of human vastus lateralis muscle. J Sports Sci. 1998;16:639–43.
31. Hill CA, Harris RC, Kim HJ, et al. Influence of beta-alanine supplementation on skeletal muscle carnosine concentrations and high intensity cycling capacity. Amino Acids. 2007;32:225–33.
32. Stout JR, Cramer JT, Mielke M, O'Kroy J, Torok DJ, Zoeller RF. Effects of twenty-eight days of beta-alanine and creatine monohydrate supplementation on the physical working capacity at neuromuscular fatigue threshold. J Strength Cond Res. 2006;20: 928–31.
33. Stout JR, Cramer JT, Zoeller RF, et al. Effects of beta-alanine supplementation on the onset of neuromuscular fatigue and ventilatory threshold in women. Amino Acids. 2007;32:381–6.
34. Hoffman J, Ratamess N, Kang J, Mangine G, Faigenbaum A, Stout J. Effect of creatine and beta-alanine supplementation on performance and endocrine responses in strength/power athletes. Int J Sports Nutr Exerc Metab. 2006;16:430–46.
35. Smith-Ryan A, Fukuda D, Stout J, Kendall K. High-velocity intermittent running: effects of beta-alanine supplementation. J Strength Cond Res. 2012;26(10): 2798–805.
36. Walter A, Smith-Ryan A, Kendall K, Stout J, Cramer J. Six weeks of high-intensity interval training with and without B-alanine supplementation for improving cardiovascular fitness in women. J Strength Cond Res. 2010;24(5):1199–207.
37. Mero A, Hirvonen P, Saarela J, Hulmi J, Hoffman J, Stout J. Effects of sodium bicarbonate and beta-alanine supplementation on maximal spring swimming. J Int Soc Sports Nutr. 2013;10:52.
38. Ducker K, Dawson B, Willman K. Effects of beta-alanine and sodium bicarbonate supplementation on repeated spring performance. J Strength Cond Res. 2013;27(12):3450–60.

39. de Salles Painelli V, Saunders B, Sale C, Harris R, Solis M, Roschel H, Gualano B, Artioli G, Lancha A. Influence of training status on high-intensity intermittent performance in response to beta-alanine supplementation. Amino Acids. 2014;46(5):1207–15.
40. Campbell B, Roberts M, Kerksick C, et al. Pharmacokinetics, safety, and effects on exercise performance of l-arginine alpha-ketoglutarate in trained adult men. Nutrition. 2006;22:872–81.
41. Elam RP, Hardin DH, Sutton RA, Hagen L. Effects of arginine and ornithine on strength, lean body mass and urinary hydroxyproline in adult males. J Sports Med Phys Fitness. 1989;29:52–6.
42. Hembree WC, Ross GT. Arginine infusion and growth-hormone secretion. Lancet. 1969;1:52.
43. Merimee TJ, Rabinowitz D, Fineberg S. Arginine-initiated release of human growth hormone. Factors modifying the response in normal man. N Engl J Med. 1969;280:1434–8.
44. Merimee TJ, Rabinowitz D, Riggs L, Burgess JA, Rimoin DL, McKusick VA. Plasma growth hormone after arginine infusion. Clinical experiences. N Engl J Med. 1967;276:434–9.
45. Walberg-Rankin J, Hawkins C. The effect of oral arginine during energy restriction in male weight trainers. J Strength Cond Res. 1994;8:170–7.
46. Besset A, Bonardet A, Rondouin G, Descomps B, Passouant P. Increase in sleep related GH and Prl secretion after chronic arginine aspartate administration in man. Acta Endocrinol (Copenh). 1982; 99:18–23.
47. Marcell T, Taaffe D, Hawkins S. Oral arginine does not stimulate basal or augment exercise-induced GH secretion in either young or old adults. J Gerontol A Biol Sci Med Sci. 1999;54:395–9.
48. Gater DR, Gater DA, Uribe JM, Bunt JC. Effects of arginine/lysine supplementation and resistance training on glucose tolerance. J Appl Physiol. 1992; 72:1279–84.
49. Bhasin S, Bremner WJ. Clinical review 85: emerging issues in androgen replacement therapy. J Clin Endocrinol Metab. 1997;82:3–8.
50. Bhasin S, Buckwalter JG. Testosterone supplementation in older men: a rational idea whose time has not yet come. J Androl. 2001;22:718–31.
51. Bhasin S, Storer TW, Berman N, et al. Testosterone replacement increases fat-free mass and muscle size in hypogonadal men. J Clin Endocrinol Metab. 1997;82:407–13.
52. Bhasin S, Woodhouse L, Casaburi R, et al. Testosterone dose–response relationships in healthy young men. Am J Physiol Endocrinol Metab. 2001; 281:E1172–81.
53. Sinha-Hikim I, Artaza J, Woodhouse L, et al. Testosterone-induced increase in muscle size in healthy young men is associated with muscle fiber hypertrophy. Am J Physiol Endocrinol Metab. 2002;283:E154–64.
54. Sinha-Hikim I, Roth SM, Lee MI, Bhasin S. Testosterone-induced muscle hypertrophy is associated with an increase in satellite cell number in healthy, young men. Am J Physiol Endocrinol Metab. 2003;285:E197–205.
55. Brodie A, Inkster S, Yue W. Aromatase expression in the human male. Mol Cell Endocrinol. 2001; 178:23–8.
56. Zmuda J, Bausserman L, Maceroni D, Thompson P. The effect of supraphysiologic doses of testosterone on fasting total homocysteine levels in normal men. Atherosclerosis. 1997;130.
57. Leder BZ, Rohrer JL, Rubin SD, Gallo J, Longcope C. Effects of aromatase inhibition in elderly men with low or borderline-low serum testosterone levels. J Clin Endocrinol Metab. 2004;89: 1174–80.
58. Mauras N, Lima J, Patel D, et al. Pharmacokinetics and dose finding of a potent aromatase inhibitor, aromasin (exemestane), in young males. J Clin Endocrinol Metab. 2003;88:5951–6.
59. Mauras N, O'Brien KO, Klein KO, Hayes V. Estrogen suppression in males: metabolic effects. J Clin Endocrinol Metab. 2000;85:2370–7.
60. Inclendon T. The chronic effects of androst-4-ene-3,6,17-trione on endocrine responses in resistance-trained men. Unpublished Observation; 2003.
61. Numazawa M, Tsuji M, Mutsumi A. Studies on aromatase inhibition with 4-androstene-3,6,17-trione: its 3 beta-reduction and time-dependent irreversible binding to aromatase with human placental microsomes. J Steroid Biochem. 1987;28.
62. Numazawa M, Mutsumi A, Tachibana M. Mechanism for aromatase inactivation by a suicide substrate, androst-4-ene-3,6,17-trione. The 4 beta, 5 beta-epoxy-19-oxo derivative as a reactive electrophile irreversibly binding to the active site. Biochem Pharmacol. 1996;52.
63. Willoughby DS, Wilborn C, Taylor L, Campbell W. Eight weeks of aromatase inhibition using the nutritional supplement Novedex XT: effects in young, eugonadal men. Int J Sports Nutr Exerc Metab. 2007;17:92–108.
64. Lukasi H. Micronutrients (magnesium, zinc, and copper): are mineral supplements needed for athletes? Int J Sport Nutr. 1995;5.
65. Singh A, Failla ML, Deuster PA. Exercise-induced changes in immune function: effects of zinc supplementation. J Appl Physiol. 1994;76:2298–303.
66. Singh A, Smoak BL, Patterson KY, LeMay LG, Veillon C, Deuster PA. Biochemical indices of selected trace minerals in men: effect of stress. Am J Clin Nutr. 1991;53:126–31.
67. Gleeson M, Lancaster GI, Bishop NC. Nutritional strategies to minimise exercise-induced immunosuppression in athletes. Can J Appl Physiol. 2001; 26(Suppl):S23–35.
68. Nieman DC. Nutrition, exercise, and immune system function. Clin Sports Med. 1999;18:537–48.
69. Nieman DC, Pedersen BK. Exercise and immune function. Recent developments. Sports Med. 1999; 27:73–80.

70. Gleeson M, Nieman DC, Pedersen BK. Exercise, nutrition and immune function. J Sports Sci. 2004; 22:115–25.
71. Shephard RJ, Shek PN. Immunological hazards from nutritional imbalance in athletes. Exerc Immunol Rev. 1998;4:22–48.
72. Golf SW, Happel O, Graef V, Seim KE. Plasma aldosterone, cortisol and electrolyte concentrations in physical exercise after magnesium supplementation. J Clin Chem Clin Biochem. 1984;22:717–21.
73. Golf SW, Bender S, Gruttner J. On the significance of magnesium in extreme physical stress. Cardiovasc Drugs Ther. 1998;12 Suppl 2:197–202.
74. Brilla L, Haley T. Effect of magnesium supplementation on strength training in humans. J Am Coll Nutr. 1992;11:326–9.
75. Newhouse IJ, Finstad EW. The effects of magnesium supplementation on exercise performance. Clin J Sport Med. 2000;10:195–200.
76. Brilla L, Conte V. Effects of a novel zinc-magnesium formulation on hormones and strength. J Exerc Physiol Online. 2000;3:26–36.
77. Prasad AS, Mantzoros CS, Beck FW, Hess JW, Brewer GJ. Zinc status and serum testosterone levels of healthy adults. Nutrition. 1996;12:344–8.
78. Cordova A, Navas FJ. Effect of training on zinc metabolism: changes in serum and sweat zinc concentrations in sportsmen. Ann Nutr Metab. 1998; 42:274–82.
79. Khaled S, Brun JF, Micallel JP, et al. Serum zinc and blood rheology in sportsmen (football players). Clin Hemorheol Microcirc. 1997;17:47–58.
80. Konig D, Weinstock C, Keul J, Northoff H, Berg A. Zinc, iron, and magnesium status in athletes—influence on the regulation of exercise-induced stress and immune function. Exerc Immunol Rev. 1998;4: 2–21.
81. Wilborn C, Kerksick C, Campbell B, et al. Effects of zinc magnesium aspartate (ZMA) supplementation on training adaptations and markers of anabolism and catabolism. J Int Soc Sports Nutr. 2004;1:12–20.
82. Newsholme P, Procopio J, Lima MM, Pithon-Curi TC, Curi R. Glutamine and glutamate–their central role in cell metabolism and function. Cell Biochem Funct. 2003;21:1–9.
83. Candow DG, Chilibeck PD, Burke DG, Davison KS, Smith-Palmer T. Effect of glutamine supplementation combined with resistance training in young adults. Eur J Appl Physiol. 2001;86:142–9.
84. Furst P. Intracellular muscle free amino acids - their measurement and function. Nutr Soc. 1983;45:451–62.
85. Parry-Billings M, Budgett R, Koutedakis Y, et al. Plasma amino acid concentrations in the overtraining syndrome: possible effects on the immune system. Med Sci Sports Exerc. 1992;24:1353–8.
86. Keast D, Arstein D, Harper W, Fry RW, Morton AR. Depression of plasma glutamine concentration after exercise stress and its possible influence on the immune system. Med J Aust. 1995;162:15–8.
87. Newsholme EA. Biochemical mechanisms to explain immunosuppression in well-trained and overtrained athletes. Int J Sports Med. 1994;15 Suppl 3:S142–7.
88. Rohde T, MacLean DA, Pedersen BK. Effect of glutamine supplementation on changes in the immune system induced by repeated exercise. Med Sci Sports Exerc. 1998;30:856–62.
89. Nissen S, Faidley TD, Zimmerman DR, Izard R, Fisher CT. Colostral milk fat percentage and pig performance are enhanced by feeding the leucine metabolite beta-hydroxy-beta-methyl butyrate to sows. J Anim Sci. 1994;72:2331–7.
90. Van Koevering MT, Dolezal HG, Gill DR, et al. Effects of beta-hydroxy-beta-methyl butyrate on performance and carcass quality of feedlot steers. J Anim Sci. 1994;72:1927–35.
91. Peterson AL, Qureshi MA, Ferket PR, Fuller Jr JC. Enhancement of cellular and humoral immunity in young broilers by the dietary supplementation of beta-hydroxy-beta-methylbutyrate. Immunopharmacol Immunotoxicol. 1999;21:307–30.
92. Peterson AL, Qureshi MA, Ferket PR, Fuller Jr JC. In vitro exposure with beta-hydroxy-beta-methylbutyrate enhances chicken macrophage growth and function. Vet Immunol Immunopathol. 1999;67:67–78.
93. Miller P, Sandberg L, Fuller JC. The effect of intensive training and B-hydroxy-B-methylbutyrate (HMB) on the physiological response to exercise in horses. FASEB J. 1997;11:A1683.
94. Nissen S, Sharp R, Ray M. Effect of leucine metabolite beta-hydroxy-beta-methylbutyrate on muscle metabolism during resistance exercise testing. J Am Physiol. 1996;81:2095–104.
95. Knitter AE, Panton L, Rathmacher JA, Petersen A, Sharp R. Effects of beta-hydroxy-beta-methylbutyrate on muscle damage after a prolonged run. J Appl Physiol. 2000;89:1340–4.
96. Vukovich M, et al. The effect of dietary B-hydroxy-B-methylbutyrate (HMB) on strength gains and body composition. FASEB J. 1997;11.
97. Panton L, et al. Effect of B-hydroxy-B-methylbutyrate and resistance training on strength and functional ability in the elderly. Med Sci Sports Exerc. 1998;30.
98. Gallagher P, et al. B-hydroxy-B-methylbutyrate: supplementation during resistance-training. Med Sci Sports Exerc. 1999;31.
99. Kreider RB, Ferreira M, Wilson M, Almada AL. Effects of calcium beta-hydroxy-beta-methylbutyrate (HMB) supplementation during resistance-training on markers of catabolism, body composition and strength. Int J Sports Med. 1999;20:503–9.
100. Fuller J, Sharp R, Angus H, Baier S, Rathmarcher J. Free acid gel form of beta-hydroxy-beta-methylbutyrate (HMB) improves HMB clearance from plasma in human subjects compared with the calcium HMB salt. Br J Nutr. 2011;105:367–72.

101. Wilson J, Lowery R, Joy J, Anderson J, Wilson S, Stout J, Duncan N, Fuller J, Baier S, Naimo M, Rathmacher J. The effects of 12 weeks of beta-hydroxy-beta-methylbutyrate free acid on muscle mass, strength, and power in resistance trained individuals: a randomized, double blind, placebo-controlled study. Eur J Appl Physiol. 2014; 114(6):1217–27.
102. Lowery R, Joy J, Ratchmacher J, Baier S, Fuller J, Jager R, Wilson S, Wilson J. Effects of 12 weeks of beta-hydroxy-beta-methylbutyrate free acid, adenosine triphosphate, or a combination on mass, strength, and power in resistance trained individuals. J Int Soc Sports Nutr. 2013;10 Suppl 1:17.
103. Robinson E, Stout J, Miramonit A, Fukuda D, Wang R, Townsend J, Megnine G, Fragala M, Hoffman J. High-intensity interval training and B-hydroxy-B-methylbutyric free acid improves aerobic power and metabolic thresholds. J Int Soc Sports Nutr. 2014; 11:16.
104. Meydani M, Evans WJ, Handelman G, et al. Protective effect of vitamin E on exercise-induced oxidative damage in young and older adults. Am J Physiol. 1993;264:R992–8.
105. Cannon JG, Meydani SN, Fielding RA, et al. Acute phase response in exercise. II. Associations between vitamin E, cytokines, and muscle proteolysis. Am J Physiol. 1991;260:R1235–40.
106. Rokitzki L, Logemann E, Sagredos AN, Murphy M, Wetzel-Roth W, Keul J. Lipid peroxidation and antioxidative vitamins under extreme endurance stress. Acta Physiol Scand. 1994;151:149–58.
107. Hartmann A, Niess AM, Grunert-Fuchs M, Poch B, Speit G. Vitamin E prevents exercise-induced DNA damage. Mutat Res. 1995;346:195–202.
108. Gerster H. The role of vitamin C in athletic performance. J Am Coll Nutr. 1989;8:636–43.
109. Kaminski M, Boal R. An effect of ascorbic acid on delayed-onset muscle soreness. Pain. 1992;50:317–21.
110. Ackerman J, Clifford T, McNaughton L, Bentley D. The effect of an acute antioxidant supplementation compared with placebo on performance and hormonal response during a high volume resistance training session. J Int Soc Sports Nutr. 2014;11:10.
111. Alf D, Schmidt M, Siebrecht S. Ubiquinol supplementation enhances peak power production in trained athletes: a double-blind, placebo controlled study. J Int Soc Sports Nutr. 2013;10:24.
112. Bloomer R, Farney T, Trepanowski J, McCarthy C, Canale R, Schilling B. Comparison of pre-workout nitric oxide stimulating dietary supplements on skeletal muscle oxygen saturation, blood nitrate/nitrite, lipid perioxidation, and upper body exercise performance in resistance trained men. J Int Soc Sports Nutr. 2010;7:16.
113. Mackinnon LT. Chronic exercise training effects on immune function. Med Sci Sports Exerc. 2000;32: S369–76.
114. Insel PM, Turner RE, Ross D. Discovery Nutrition. MA: Jones & Bartlett Publishers Learning; 2006.
115. Pariza MW, Park Y, Cook ME. Conjugated linoleic acid and the control of cancer and obesity. Toxicol Sci. 1999;52:107–10.
116. MacDonald HB. Conjugated linoleic acid and disease prevention: a review of current knowledge. J Am Coll Nutr. 2000;19:111S–8.
117. Thom E. A pilot study with the aim of studying the efficacy and tolerability of Tonalin CLA on the body composition in humans. Technical Report. Medstat Research Limited, Lillestram, Norway. July, 1997.
118. Lowery LM, Appicelli PA PWRL. Conjugated linoleic acid enhances muscle size and strength gains in novice bodybuilders. Med Sci Sports Exerc. 1998;30:S182.
119. Riserus U, Berglund L, Vessby B. Conjugated linoleic acid (CLA) reduced abdominal adipose tissue in obese middle-aged men with signs of the metabolic syndrome: a randomised controlled trial. Int J Obes Relat Metab Disord. 2001;25:1129–35.
120. Blankson H, Stakkestad JA, Fagertun H, Thom E, Wadstein J, Gudmundsen O. Conjugated linoleic acid reduces body fat mass in overweight and obese humans. J Nutr. 2000;130:2943–8.
121. Miller CC, Park Y, Pariza MW, Cook ME. Feeding conjugated linoleic acid to animals partially overcomes catabolic responses due to endotoxin injection. Biochem Biophys Res Commun. 1994;198:1107–12.
122. Chew BP, et al. Effects of conjugated dienoic derivatives of linoleic acid and beta-carotene in modulating lymphocyte and macrophage function. Anticancer Res. 1999;17:1099–106.
123. Wong MW, Chew BP, Wong TS, Hosick HL, Boylston TD, Shultz TD. Effects of dietary conjugated linoleic acid on lymphocyte function and growth of mammary tumors in mice. Anticancer Res. 1997;17:987–93.
124. Li Y, Watkins BA. Conjugated linoleic acids alter bone fatty acid composition and reduce ex vivo prostaglandin E2 biosynthesis in rats fed n-6 or n-3 fatty acids. Lipids. 1998;33:417–25.
125. Watkins BA, Shen CL, McMurtry JP, et al. Dietary lipids modulate bone prostaglandin E2 production, insulin-like growth factor-I concentration and formation rate in chicks. J Nutr. 1997;127:1084–91.
126. Song HJ, Grant I, Rotondo D, et al. Effect of CLA supplementation on immune function in young healthy volunteers. Eur J Clin Nutr. 2005;59: 508–17.
127. Zhang H, Guo Y, Yuan J. Conjugated linoleic acid enhanced the immune function in broiler chicks. Br J Nutr. 2005;94:746–52.
128. Kreider RB, Ferreira MP, Greenwood M, Wilson M, Almada AL. Effects of conjugated linoleic acid supplementation during resistance training on body composition, bone density, strength, and selected hematological markers. J Strength Cond Res. 2002;16:325–34.
129. Ferreira IM, et al. Effects of conjugated linoleic acid supplementation during resistance training on body

composition and strength. J Strength Cond Res. 1997;11.
130. Kreider R, et al. Effects of conjugated linoleic acid (CLA) supplementation during resistance-training on bone mineral content, bone mineral density, and markers of immune stress. FASEB J. 1998;12.
131. Beuker F, Haak H, Schwietz H. CLA and body styling. Symposium: Vitamine und Zusatzstoffe: Jena (Thhr). 1999;1999:229–37.
132. Berning JR. Energy intake, diet, and muscle wasting. In: Kreider RB, Fry AC, O'Toole ML, editors. Overtraining in sport. Champaign: Human Kinetics; 1998. p. 275–88.
133. Sherman WM, Jacobs KA, Leenders N. Carbohydrate metabolism during endurance exercise. In: Kreider RB, Fry AC, O'Toole ML, editors. Overtraining in sport. Champaign: Human Kinetics; 1998. p. 289–308.
134. Robergs RA, Pearson DR, Costill DL, et al. Muscle glycogenolysis during differing intensities of weight-resistance exercise. J Appl Physiol. 1991;70: 1700–6.
135. Tesch PA, Colliander EB, Kaiser P. Muscle metabolism during intense, heavy-resistance exercise. Eur J Appl Physiol Occup Physiol. 1986;55:362–6.
136. Essen-Gustavsson B, Tesch PA. Glycogen and triglyceride utilization in relation to muscle metabolic characteristics in men performing heavy-resistance exercise. Eur J Appl Physiol Occup Physiol. 1990;61:5–10.
137. Kreider RB. Dietary supplements and the promotion of muscle growth with resistance exercise. Sports Med. 1999;27:97–110.
138. Haff GG, Lehmkuhl MJ, McCoy LB, Stone MH. Carbohydrate supplementation and resistance training. J Strength Cond Res. 2003;17:187–96.
139. Bird SP, Tarpenning KM, Marino FE. Independent and combined effects of liquid carbohydrate/essential amino acid ingestion on hormonal and muscular adaptations following resistance training in untrained men. Eur J Appl Physiol. 2006;97:225–38.
140. Clarkson PM. Nutritional ergogenic aids: caffeine. Int J Sport Nutr. 1993;3:103–11.
141. Armstrong LE. Caffeine, body fluid-electrolyte balance, and exercise performance. Int J Sports Nutr Exerc Metab. 2002;12:189–206.
142. Costill DL, Dalsky GP, Fink WJ. Effects of caffeine ingestion on metabolism and exercise performance. Med Sci Sports. 1978;10:155–8.
143. Graham TE, Spriet LL. Performance and metabolic responses to a high caffeine dose during prolonged exercise. J Appl Physiol. 1991;71:2292–8.
144. Ivy JL, Costill DL, Fink WJ, Lower RW. Influence of caffeine and carbohydrate feedings on endurance performance. Med Sci Sports. 1979;11:6–11.
145. Powers SK, Dodd S. Caffeine and endurance performance. Sports Med. 1985;2:165–74.
146. Falk B, Burstein R, Rosenblum J, Shapiro Y, Zylber-Katz E, Bashan N. Effects of caffeine ingestion on body fluid balance and thermoregulation during exercise. Can J Physiol Pharmacol. 1990;68:889–92.
147. Dodd SL, Herb RA, Powers SK. Caffeine and exercise performance. An update. Sports Med. 1993; 15:14–23.
148. Doherty M, Smith PM. Effects of caffeine ingestion on rating of perceived exertion during and after exercise: a meta-analysis. Scand J Med Sci Sports. 2005;15:69–78.
149. Doherty M, Smith P, Hughes M, Davison R. Caffeine lowers perceptual response and increases power output during high-intensity cycling. J Sports Sci. 2004;22:637–43.
150. Collomp K, Ahmaidi S, Audran M, Chanal JL, Prefaut C. Effects of caffeine ingestion on performance and anaerobic metabolism during the Wingate Test. Int J Sports Med. 1991;12:439–43.
151. Trice I, Haymes EM. Effects of caffeine ingestion on exercise-induced changes during high-intensity, intermittent exercise. Int J Sport Nutr. 1995;5:37–44.
152. Acheson KJ, Gremaud G, Meirim I, et al. Metabolic effects of caffeine in humans: lipid oxidation or futile cycling? Am J Clin Nutr. 2004;79:40–6.
153. Koot P, Deurenberg P. Comparison of changes in energy expenditure and body temperatures after caffeine consumption. Ann Nutr Metab. 1995;39: 135–42.

Nutritional Supplements for Endurance Athletes

11

Conrad P. Earnest and Christopher Rasmussen

Abstract

Endurance athletes often seek nutritional strategies inclusive of dietary supplements to maximize their performance. Effective supplement routines, however, are only beneficial when built on a sound training diet, training regimen, and an appreciation of dietary needs relative to their training schema. While traditional dietary interventions are based on the glycemic index of carbohydrate, coupled with the addition of protein quality and quantity, recent innovations have introduced the potential utility of long chain glucose polymers and dietary nitrates, such as beetroot juice. Consideration is also given to the utility of supplement strategies aimed at attenuating immune responses accompanying training and competition. A key to implementing successful supplementation routines is the appreciation that athletes should be considered on an individual basis and training volume and intensity must be taken into account.

Keywords

Exercise • Nutrition • Endurance • Supplements • Ergogenic

11.1 Introduction

The endurance athlete has special nutritional needs beyond those of sedentary individuals. It is important to note, however, that optimizing performance via supplementation is predicated on the athlete having a solid dietary and training foundation. Proper training should focus on the goals of the individual and the point in time within the training cycle (preseason, in-season, postseason) supplementation is considered. Proper nutrition

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should focus on a variety of macro- and micronutrient-dense foods that adequately meet the energy demands of the athlete. However, supplementing the athletes' diet with additional nutrients is becoming increasingly important for those engaged in heavy endurance training as it is often difficult to obtain an adequate amount of macronutrients through whole foods alone. Several studies have documented that endurance athletes can improve training sessions and performance with a combination of proper everyday nutrition and effective supplementation [1–4].

To better understand how supplementation can improve performance for the endurance athlete, it is important to appreciate the physiologic factors that affect performance. This chapter begins with a description of factors that optimize and limit performance. The second section focuses on specific supplements for endurance athletes and how they can prepare the athlete for action and enhance the training response. The third section discusses how supplementation might aid the immune system during periods of heavy training.

11.2 Factors Limiting Endurance Athletic Performance

It is important to point out that the term "endurance athlete" typically refers to those participating in running, cycling, swimming, and/or combinations of these activities. Much like resistance training, endurance athletes often practice a form of periodization in an effort to improve anaerobic capacity, maximal aerobic power, exercise efficiency/economy, and endurance capacity. While beyond the scope of this chapter, periodization is generally accomplished by manipulating periods of long slow distance (aka, LSD), tempo, interval, and speed training efforts and manipulating the principles of training depending on the overall goals of the athlete and their event. While numerous factors limit performance, heat tolerance, dehydration, the depletion of muscle glycogen, and limited blood glucose availability all play a major role in fatigue during long-duration aerobic exercise.

To dissipate heat, the body transfers heat to the environment through conduction, convection, radiation, evaporation, or a combination of these methods. Conduction involves the transfer of heat from one material to another through direct molecular contact, and convection is the transfer of heat from one place to another by the motion of a gas or a liquid across the heated surface. Radiation involves the dissipation of heat in the form of infrared rays, and evaporation is best defined as the evaporation of sweat from the skin's surface. Evaporation is the primary avenue for heat dissipation during exercise, accounting for roughly 80 % of the total heat loss during exercise. With prolonged exercise or exercise in a hot and humid environment, blood volume is reduced by a loss of water through sweat.

Continued exercise in a hot, humid environment requires a redistribution of blood from the core to the periphery; thus, cardiac filling decreases as the total blood volume gradually decreases with an increase in the duration of exercise. Subsequently, stroke volume is reduced and heart increases in order to maintain oxygen delivery during low- to moderate-intensity exercise. The drawback is that the body is unable to compensate fully for the decreased stroke volume at high exercise intensities as heart rate eventually reaches a maximal level. Important to this phenomena is that a loss in body fluid equal to 1 % of body weight significantly reduces blood volume and limits physical performance [5]. When dehydration reaches 4 %, endurance athletes can experience heat cramps and heat exhaustion [6]; and when it reaches upwards of 6 %, there may be cessation of sweating, a rise in body temperature, and eventually heat stroke [7].

A depletion of muscle glycogen and reduction in blood glucose is also critical to endurance performance. During low-intensity activity (~25 % VO_{2max}), plasma fatty acids and muscle triglycerides are able to supply energy needs, as carbohydrate use is relatively low [8]. As the intensity of exercise increases, the amount of carbohydrate necessary to keep pace with the increased demand also increases and a combination of blood glucose and muscle glycogen contributes a large percentage of the energy requirements at moderate (~65 % VO_{2max}) exercise intensities [8]. At the beginning of exercise, muscle glycogen is the preferred fuel source, but as these levels decline there is increased dependence on blood glucose by the exercising muscles. Higher-intensity exercise (85 % VO_{2max}) is performed at a level that

promotes an even higher rate of muscle glycogen breakdown and carbohydrate oxidation [8].

11.3 Supplements for Endurance Athletes

To aid in the recovery from intense endurance training and help the body respond to training, a well-planned diet and supplement strategy that meets energy intake needs and incorporates proper timing of essential nutrients is vital. A key to understanding supplementation for the endurance athlete is the differentiation between "supplements" and "ergogenic aids." Nutritional supplements are products or ingredients that complete or make an addition to the diet, but are not directly targeted to endurance performance, per se. Ergogenic aids are ingredients that aim to enhance work or improve sport performance. Due to their synonymy, the two terms will be used interchangeably. A well-balanced, micro- and macronutrient-dense diet serves as the foundation for endurance performance. Absence of such a foundation may hinder training adaptations and subsequent performance. The continued practice of dietary inadequacy may also lead to a loss of muscle mass, increased susceptibility to illness, and an increase in the symptoms associated with overtraining.

In general, pre-exercise nutrition should consist largely of moderate- to low-glycemic index foods/supplements (Table 11.1) that provide a slow, sustained release of carbohydrates and

Table 11.1 Partial list of the glycemic index of foods using glucose as the standard

Low GI		Moderate GI		High GI	
Food	GI	Food	GI	Food	GI
Chana dal	8	Apple juice	40	Life Savers™	70
Peanuts	14	Snickers™	41	White bread	70
Plain yogurt	14	Peach	42	Bagel	72
Soy beans	18	Pudding	43	Watermelon	72
Rice bran	19	Pinto beans	45	Graham crackers	74
Peas	22	Orange juice	46	French fries	75
Cherries	22	Baked beans	48	Total™	76
Barley	25	Strawberry jam	51	Vanilla wafers	77
Grapefruit	25	Sweat potato	54	Gatorade™	78
Kidney beans	27	Pound cake	54	Fava beans	79
Link sausages	28	Popcorn	55	Jelly beans	80
Black beans	30	Brown rice	55	Tapioca pudding	81
Lentils	30	Fruit cocktail	55	Rice cakes	82
Butter beans	31	Pita bread	57	Team Flakes™	82
Soy milk	31	PowerBar™	58	Pretzels	83
Lima beans	32	Honey	58	Corn Chex™	83
Skim milk	32	Blueberry muffin	59	Corn flakes™	84
Split peas	32	Shredded wheat	62	Baked white potato	85
Fettucini	32	Black bean soup	64	Mashed potatoes	86
Chickpeas	33	Macaroni and cheese	64	Dark rye	86
Peanut M&M's™	33	Raisins	64	Instant rice	87
Chocolate milk	34	Canteloupe	65	Crispix™	87
Vermicelli	35	Mars Bar™	65	Boiled Sebago	87
Whole wheat spag.	37	Rye bread	65	Rice Chex™	89
Apple	38	Pineapple	66	Gluten-free bread	90
Pear	38	Grapenuts™	67	Baked red potato	93
Tomato soup	38	Angel food cake	67	French baguette	95
Ravioli	39	Stoned wheat thins	67	Peeled Desiree	101
Pinto beans	39	Taco shells	68	Dates	103
Plums	39	Whole wheat bread	69	Tofu frozen dessert	115

GI glycemic index

protein necessary to fuel a workout (see sidebar: What Is the Glycemic Index?). It generally takes about 4 h for dietary carbohydrate to be digested and begins to be stored as muscle and liver glycogen. Thus, pre-exercise meals should be consumed about 4–6 h prior to exercise [9]. Put into practice, this means that for an athlete training in the afternoon, breakfast becomes an important meal to top off muscle and liver glycogen levels. Likewise, for the athlete who trains first thing in the morning, the meal the evening before is vital. Recent research has also indicated that ingesting a light carbohydrate and protein snack 30–60 min prior to exercise (e.g., 50 g carbohydrate and 5–10 g protein) further increases carbohydrate availability toward the end of an intense exercise bout owing to a slight increase in glucose and insulin levels [10, 11]. This may also serve to increase the availability of amino acids and decrease exercise-induced protein catabolism [10–12]. Insulin inhibits protein degradation and apparently offsets the catabolic effects of other hormones (e.g., cortisol) [13]. Anabolic actions of insulin appear to be related to its nitrogen-sparing effects and promotion of nitrogen retention [13]. The choice of foods and supplements selected is largely up to individual athlete and their personal preferences. It is recommended that the endurance athlete consume something familiar on the day of competition rather than experimenting with a new food or supplement.

Sidebar

The glycemic index is a ranking of foods based on their postprandial blood glucose response compared to a reference food, either glucose or white bread. The glycemic index concept was first developed in 1981 to help determine which foods were best for people with diabetes. The glycemic index of a food is based on several factors, including the physical form of the food, the amylose/amylopectin ratio (two types of starch), sugar content, fiber content, fat content, and the acidity of a food. The index consists of a scale from 0 to 100 with 0 (water) representing the lowest ranking and 100 (pure glucose) the highest ranking. The glycemic index is obtained through use of an oral glucose tolerance test utilizing 50 g of carbohydrate from the test food. Blood samples are obtained periodically throughout a 2-h period, glucose levels are measured, and the area under the curve is calculated.

The glycemic index of a carbohydrate has a profound effect on subsequent glucose and insulin responses. High-glycemic index carbohydrates (i.e., dextrose, maltose) produce large increases in glucose and insulin levels. Moderate-glycemic index carbohydrates (i.e., sucrose, lactose) traditionally produce only modest increases in glucose and insulin. Finally, low-glycemic index carbohydrates (i.e., fructose, maltodextrin) have little if any effect on glucose and insulin responses. It has been suggested that manipulating the glycemic index of a sports supplement may optimize carbohydrate availability for exercise, particularly prolonged intense exercise. Caution should be used when applying the glycemic index to whole foods that contain several ingredients.

Nutrition during an intense endurance training session can also aid workout quality as participation time exceeds 60–90 min and usually centers on supplementation more than pre- and post-exercise nutrition if for no other reason than the convenience supplements provide. Convenience supplements include glucose–electrolyte solutions, meal replacement powders, ready-to-drink supplements, energy bars, energy gels, and fitness waters. They are typically fortified with various amounts of vitamins and minerals and differ on the amount of carbohydrate, protein, and fat they contain. The beneficial effects of solid and liquid carbohydrate/protein supplements are similar when thermal stress is not a factor. Liquid supplements also aid rehydration and tend to digest easier for most athletes while exercising.

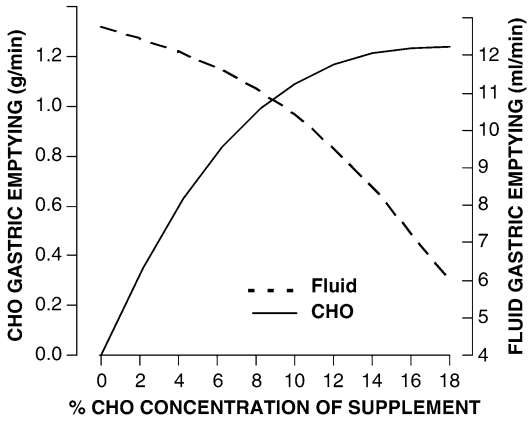

Fig. 11.1 Effect of carbohydrate (CHO) concentration on the rate of gastric emptying of fluids and carbohydrate from the stomach during exercise. Carbohydrate concentrations of 8–10 % maximize carbohydrate gastric emptying without substantially reducing fluid delivery. From Gisolfi and Lamb [16], with permission

Cyclists can generally empty from the stomach up to 1,000 ml of fluid per hour, and therefore 40–60 g of carbohydrate can be easily ingested while consuming a large volume of fluid [14]. On the other hand, runners generally consume less than 500 ml of fluid per hour due to the [15]. Therefore, runners tend to use more concentrated solutions than cyclists in order to consume adequate amounts of carbohydrate. For cyclists, a carbohydrate solution of 4–6 % is generally sufficient when fluid replacement is important. For runners, this concentration may have to be 8–10 % to provide adequate carbohydrate. Glucose concentrations in excess of 10 % seem to delay gastric emptying and compromise fluid replacement (Fig. 11.1).

Adequate sodium intake is also important to combat potential electrolyte imbalances during exercise. Most GES solutions contain sufficient quantities of sodium. If sodium is lacking in the supplement, however, electrolyte tablets are also available. The bottom line is that rapid nutrient availability is especially important during a workout to maintain energy levels and training intensity. Thus, high-glycemic index sources should make up most of the supplements ingested during an endurance-type workout. Once again, athletes should experiment with different formulations to find the one that works best for them prior to competition.

It is now well established that with prolonged continuous exercise the time-to-fatigue at moderate sub-maximum exercise intensities is related to pre-exercise muscle glycogen concentrations—thus the importance of everyday nutrition along with pre-exercise nutrition [17]. In addition, a GES has been the recommended supplement of choice for decades during exercise to preserve muscle glycogen and maintain blood glucose levels. With short-term, high-intensity exercise, the relation between the availability of muscle glycogen and performance is less clear. One study that utilized 15 high-intensity 6-second bouts on a cycle ergometer concluded that a high carbohydrate regimen over 48 h helped subjects maintain a higher power output than did the exercise and dietary regimen that included a low carbohydrate content [18]. This study demonstrated the importance of a high carbohydrate diet in relation to short-term, high-intensity exercise.

Recent research has shown that the addition of protein can have added benefits to a supplement ingested during exercise by reducing muscle protein degradation and speeding post-exercise recovery. Carbohydrate and protein intake significantly alters circulating metabolites and the hormonal milieu (i.e., insulin, testosterone, growth hormone, cortisol) as well as the response of muscle protein and glycogen balance [19]. Furthermore, the addition of protein to a carbohydrate supplement enhances the insulin response of a carbohydrate supplement compared to a placebo [13, 20], which can ultimately lead to performance gains [19].

Saunders et al. examined the effects of a carbohydrate–protein beverage on cycling endurance and muscle damage [21]. They utilized 15 male cyclists who were randomly administered either a carbohydrate or carbohydrate–protein beverage (4:1 ratio) every 15 min during exercise and immediately upon completion of a ride to volitional exhaustion. The carbohydrate–protein beverage produced significant improvement in time-to-fatigue and reduction of muscle damage in the selected endurance athletes. The authors concluded that the benefits observed were the

Table 11.2 Ideal nutrient composition for a sports drink during exercise

Nutrient objectives
Replace fluids and electrolytes
Preserve muscle glycogen
Maintain blood glucose levels
Maintain hydration
Minimize cortisol increases
Set the stage for a faster recovery
Satisfy thirst
Ideal composition (per 12 oz water)
High-glycemic carbohydrates (e.g., glucose, sucrose, maltodextrin): 20–26 g
Whey protein: 5–6 g
Vitamin C: 30–120 g
Vitamin E: 20–60 IU
Sodium: 100–250 mg
Potassium: 60–120 mg
Magnesium: 60–120 mg

Adapted from Ivy and Portman [23], with permission

result of a higher total caloric content of the carbohydrate–protein beverage or were due to specific protein-mediated mechanisms.

Controversy exists among numerous studies examining the addition of protein because such additions increase the total caloric content of the supplement. Anytime a larger amount of calories is consumed, an athlete is likely to perform and recover more rapidly. Therefore, when examining studies that are not based on isocaloric data, one should give them careful consideration.

Whey is the preferred protein to ingest during exercise because of its rapid absorption rates and the fact that is contains all of the essential amino acids as well as a high percentage of leucine and glutamine, which are amino acids the body uses during sustained exercise [22]. High-glycemic index carbohydrates (glucose, sucrose, maltodextrin) should be combined with the protein in a 4:1 ratio to provide optimal benefits. Table 11.2 gives an example of the ideal nutrient composition for a sports drink during exercise [24]. Sports drinks such as that shown in Table 11.2 should be ingested every 20 min during an endurance training session to help improve performance and reduce muscle protein breakdown.

Post-exercise nutrition for the endurance athlete is vital to restore muscle glycogen stores, enhance skeletal muscle fiber repair and growth, and maintain overall health and wellness. After an intense exercise bout, the body is in a catabolic state (thus key muscle nutrients are being broken down). However, the opportunity exists to alter the catabolic state into a more anabolic hormonal profile where the athlete begins to rebuild muscle and thus initiates a much faster recovery. Exercise that results in glycogen depletion activates glycogen synthase, the enzyme responsible for controlling the transfer of glucose from UDP-glucose to an amylase chain [24, 25]. This also happens to be the rate-limiting step of glycogen formation.

The degree of glycogen synthase activation is influenced by the extent of glycogen depletion [24]. Complete resynthesis of muscle glycogen, however, ultimately depends on adequate carbohydrate intake. Carbohydrates composed of glucose or glucose polymers are the most effective for replenishing muscle glycogen, whereas fructose is most beneficial for replenishing liver glycogen [26]. Glucose and fructose are metabolized differently. They have different gastric emptying rates and are absorbed into the blood at different rates [25, 27]. Furthermore, the insulin response to a glucose supplement is generally much greater than that of a fructose supplement [18]. The fact that approximately 79 and 14 % of total carbohydrate is stored in skeletal muscle and the liver, respectively, is further indication of the importance of consuming glucose or glucose polymers after exercise [9].

Blom et al. found that ingestion of glucose and sucrose was twice as effective as fructose for restoring muscle glycogen [28]. The maximum stimulatory effect of oral glucose intake on post-exercise muscle glycogen synthesis was reached at a dose of 0.70 g/kg taken every second hour following exercise in which the muscle glycogen concentration was reduced by an average of 80 %. In addition, the rate of post-exercise muscle glycogen synthesis increases with increasing oral glucose intake, up to a maximum rate of approximately 6 mmol/kg/h. Blom et al. indicated that

the differences between glucose and fructose supplementation were the result of the way the body metabolized these sugars [28]. Fructose metabolism takes place predominantly in the liver, whereas most glucose appears to bypass the liver and is stored or oxidized by muscle [26].

Subsequent research by Burke and associates found that the intake of high-glycemic index carbohydrate foods after prolonged exercise produces significantly more glycogen storage than consumption of low-glycemic index carbohydrate foods 24 h after exercise [29]. Although the meal immediately after exercise elicited exaggerated blood glucose and plasma insulin responses that were similar for the low-glycemic index and high-glycemic index meals, for the remainder of the 24 h the low-glycemic index meals elicited lower glucose and insulin responses than the high-glycemic index meals. As previously mentioned, protein has shown additive effects to that of carbohydrate alone in regard to the rate of muscle glycogen resynthesis and overall post-exercise recovery. The addition of protein to a carbohydrate supplement increases insulin levels more than that produced by carbohydrate or protein alone [30]. Tarnopolsky et al. showed that post-exercise carbohydrate and carbohydrate–protein–fat nutritional supplements can increase glycogen resynthesis during the first 4 h after exercise to a greater extent than placebo for both men and women [31]. The supplements administered were both isoenergetic and isonitrogenous. Insulin has a profound anabolic effect on skeletal muscle. In the resting state, insulin decreases the rate of muscle protein degradation [32].

More recent research suggests that carbohydrate taking the form of a long chain glucose polymer (LCGP) results in faster gastric emptying versus a moderately hypertonic carbohydrate source [33]. Follow-up studies using the same compound also show a faster rate of glycogen synthesis 2 h following ingestion suggesting that LCGP may optimize glycogen replacement following depletion [34]. During exercise, however, two studies by Rowland and colleagues show no improvement in carbohydrate oxidation accompanying LCGP ingestion during exercise [35, 36]. Therefore, the potential ergogenic effects of LGCO during exercise remain questionable without further research. One interesting finding presented by Stephens et al. (2008) does suggest that LCGP may improve exercise responses when training or competition is broken up. In this study, participants consumed a (a) control beverage, (b) a 100 g of a low molecular weight glucose polymer, or (c) 100 g of a LCGP immediately following 90 min of cycling at ~73 % of VO_{2max}. After 2 h of rest, they then performed a 15-min time trial. The results of the time trial showed that participants consuming the LCGP were able to perform more work versus the control or low molecular weight glucose polymer solutions. These latter results suggest that LCGP may be a useful supplement strategy during training or competition requiring heavy exertion during several points within the same day.

To summarize, research has clearly shown that muscle glycogen resynthesis occurs more quickly if carbohydrate is consumed immediately following exercise in contrast to waiting for several hours [37]. Whereas most of the everyday diet for the endurance athlete should be a low- to moderate-glycemic index diet, the post-exercise diet should be centered on moderate- to high-glycemic index sources. This nutritional approach accelerates glycogen resynthesis and promotes a more anabolic hormonal state, which may speed recovery [31].

The increased protein and glycogen synthesis is believed to be due to insulin secretion from the pancreas combined with an increase in muscle insulin sensitivity [38]. This was demonstrated in a study (Fig. 11.2) showing that a carbohydrate–protein combination was 38 % more effective in stimulating protein synthesis than a protein supplement and more than twice as effective as a carbohydrate supplement [39]. Insulin appears to stimulate biosynthetic pathways that lead to increased glucose utilization, increased carbohydrate and fat storage, and increased protein synthesis. This metabolic pattern is characteristic of the absorptive state. The rise in insulin secretion during this state is responsible for shifting metabolic pathways to net anabolism [9]. In contrast,

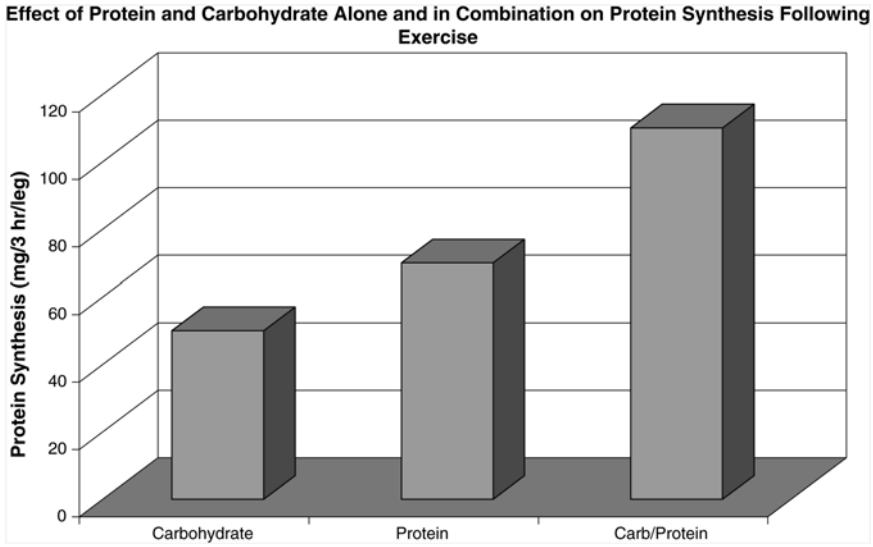

Fig. 11.2 Effect of protein and carbohydrate alone and in combination on protein synthesis, measured after exercise. From Tarnopolsky et al., with permission [30]

when insulin secretion is low, the opposite effect occurs. The rate of glucose entry into the cells is reduced and net catabolism occurs, rather than net synthesis of glycogen, triglycerides, and protein. This pattern is reminiscent of the post-absorptive state.

11.3.1 Branched-Chain Amino Acids

Another popular nutritional ergogenic aid is the branched-chain amino acids (BCAAs): leucine, isoleucine, and valine. They are prevalent in both protein/meal replacement powders and energy drinks. Table 11.3 shows the typical amino acid composition of some common protein preparations. The RDA for BCAAs is less than 3 g per day, although supplementation studies frequently utilize 5–20 g per day in tablet form and 1–7 g per liter in solutions [40]. The theory behind BCAA supplements relates to a phenomenon known as central fatigue, which holds that mental fatigue in the brain can adversely affect physical performance in endurance events. The central fatigue hypothesis suggests that low blood levels of BCAAs may accelerate the production of the brain neurotransmitter serotonin, or 5-hydroxytryptamine (5-HTP), and prematurely lead to fatigue [41]. Tryptophan, an amino acid that circulates in the blood, is a precursor of serotonin and can be more easily transported into the

Table 11.3 Typical amino acid composition of whey, casein, and soy isolates

Amino acid	Whey	Casein	Soy
Alanine	4.6	2.7	3.8
Arginine	2.3	3.7	6.7
Aspartic acid	9.6	6.4	10.2
Cysteine	2.8	0.3	1.1
Glutamic acid	15.0	20.2	16.8
Glycine	1.5	2.4	3.7
Histidine[a]	1.6	2.8	2.3
Isoleucine[a,b]	4.5	5.5	4.3
Leucine[a,b]	11.6	8.3	7.2
Lysine[a]	9.1	7.4	5.5
Methionine[a]	2.2	2.5	1.1
Phenylalanine[a]	3.1	4.5	4.6
Proline	4.4	10.2	4.5
Serine	3.3	5.7	4.6
Threonine[a]	4.3	4.4	3.3
Tryptophan[a]	2.3	1.1	1.1
Tyrosine	3.3	5.7	3.3
Valin [a,b]	4.5	6.5	4.5

Values are expressed per 100 g of product
[a]Essential amino acid
[b]Branched-chain amino acid

brain to increase serotonin levels when BCAA levels in the blood are low because high blood levels of BCAAs can block tryptophan transport into the brain [42]. During endurance exercise, as muscle and liver glycogen are depleted for energy the blood levels of BCAAs also decrease, and fatty acid levels increase to serve as an additional energy source [43]. The issue with extra fatty acids in the blood is that they need to attach to albumin as a carrier protein for proper transport. In doing so, the fatty acids displace tryptophan from its place on albumin and facilitate the transport of tryptophan into the brain for conversion to serotonin [44]. Thus, the combination of reduced BCAAs and elevated fatty acids in the blood causes more tryptophan to enter the brain and more serotonin to be produced, leading to central fatigue [45].

For endurance athletes competing in long races (more than 2 h), BCAA supplements can help delay central fatigue and maintain mental performance [46]. One study looked at BCAA supplementation during a marathon and showed improved performance for slower runners (3+ hours) but no effect on faster runners (less than 3.05 h) [2]. Chronic BCAA supplementation (2 weeks) has also been shown to be effective in improving time-trial performance in trained cyclists [39]. In addition to their effects on prolonging endurance and delaying central fatigue, BCAA supplements have been associated with a reduced rate of protein and glycogen breakdown during exercise and an inhibition of muscle breakdown following exhaustive endurance exercise [41, 47]. A number of studies in trained and untrained subjects, however, have shown no effect of BCAA supplements on exercise performance or mental performance [48]. In some cases, BCAAs have been compared with carbohydrate supplementation during exercise, with results showing they both delay fatigue to similar degrees [43]. The data on BCAA supplements are mixed, but they clearly do not harm endurance performance. Some studies have shown positive adaptations, whereas others have displayed no effect. Biological variations may determine whether BCAAs are effective for the individual athlete and the particular sport or event.

11.3.2 Caffeine

Pharmacological sports ergogenics are drugs designed to function like hormones or neurotransmitter substances that are found naturally in the human body. Like some nutritional sports ergogenics, pharmacological sports ergogenics may enhance physical power by affecting various metabolic processes associated with sport success. The most popular pharmacological sports ergogenics used by endurance athletes today are caffeine and ephedrine. Caffeine is theorized to enhance endurance performance by first stimulating the central nervous system (CNS) and increasing psychological arousal. Caffeine also stimulates the release of epinephrine from the adrenal glad, which may further enhance physiological processes such as cardiovascular function and fuel utilization. The caffeine-mediated increase in free fatty acid mobilization and sparing of muscle glycogen is the primary theory underlying the ergogenic effects of caffeine on prolonged endurance activities. Lastly, caffeine increases myofilament affinity for calcium and/or increases the release of calcium from the sarcoplasmic reticulum in skeletal muscle, resulting in more efficient muscle contractions.

In one of the first studies conducted on caffeine's ergogenic effect, subjects consumed decaffeinated coffee or decaffeinated coffee combined with 330 mg pure caffeine 60 min prior to exercise. Time to exhaustion was more than 19 % longer in the caffeine trial than in the decaffeinated trial [49]. The authors concluded that the performance increase was more likely due to the increase in fat oxidation, as muscle glycogen was not measured. Another study measured muscle glycogen utilization and found that caffeine prior to exercise reduced muscle glycogen utilization by 30 % [50]. A later study supported the muscle glycogen-sparing hypothesis by reporting a 55 % decrease in muscle glycogenolysis during the first 15 min of exercise in the caffeine trial [51]. The decrease in glycogenolysis during the initial stages of exercise allowed more glycogen to be available during the final stages, subsequently leading to an increased time to exhaustion. Further support of caffeine supplementation was

demonstrated in a study examining the effects of acute caffeine ingestion (6 mg/kg) on prolonged, intermittent sprint performance on a cycle ergometer. The total amount of sprint work performed during the caffeine trial was 8.5 % greater than that performed during the placebo trial [52]. The authors concluded that acute caffeine ingestion can significantly enhance performance of prolonged, intermittent sprint ability in competitive male, team-sport athletes.

Despite the overwhelming ergogenic evidence of caffeine supplementation, caution should be exercised when considering its use. A recent study showed that in healthy volunteers a caffeine dose corresponding to two cups of coffee (200 mg) significantly decreased blood flow to the heart during exercise by 22 %. That percentage increased to 39 % for people exercising in a high-altitude chamber, which the researchers used to simulate the way coronary artery disease (CAD) limits the amount of oxygen that gets to the heart [53]. Because an increase in blood to the heart is necessary for aerobic activity, the findings theoretically suggest that caffeine could slow the body down. The study's purpose, however, was not to look at whether caffeine could help athletes go faster or farther. Instead, it set out to investigate the effect caffeine has on blood flow to the heart. It can thus be concluded that people with CAD or those at a high risk for heart disease should avoid loading up on caffeine before a run or at least check with their primary care physician first.

Though a popular concern of caffeine ingestion has been for dehydration, recent research by Killer et al. (2014) appears to dispel this myth [54]. Using a counterbalanced, crossover design, 50 male coffee drinkers consumed either 4 × 200 mL of coffee containing 4 mg/kg caffeine or water. By examining total body water and deuterium oxide techniques, no significant changes in total body water were noted between trials across any hematological markers or in 24 h urine volume following caffeine ingestion; thus coffee provides similar hydrating qualities to water when consumed in moderation [54].

A final note in regard to caffeine supplementation is that the International Olympic Committee lists caffeine as a banned substance. Although some amount of caffeine is allowed because of its occurrence in foods, a urinary level that exceeds 12 μg/ml results in a doping violation and possible disqualification or suspension. Therefore, it is recommended to keep the daily caffeine intake to less than 3 mg/kg body weight (i.e., 50–200 mg of caffeine). Table 11.4 lists typical caffeine content in common beverages, pills, and other products.

Table 11.4 Typical caffeine content in common beverages, pills, and other products

Brewed coffee (cup)[a] = 100 mg
Decaffeinated coffee (cup) = 3 mg
Medium-brewed tea (cup) = 50 mg
Cocoa (cup) = 5 mg
Starbucks' Coffee Grande (cup) = 90
Guarana (100 mg) = 100 mg
Cola-type soda (can) = 40 mg

Adapted from M.H. Williams [40], with permission
[a]Cup = 5–6 oz

Physiological sports ergogenics are substances or techniques designed specifically to augment natural physiological processes that generate physical power. Two popular examples are glycerol and creatine. Physiological sports ergogenics are not drugs per se. In a strict sense, however, some may be regarded as drugs because they are prescribed substances.

11.3.3 Glycerol

Glycerol is also known as glycerin and an alcohol compound that is more commonly found in the diet as a component of fat or triglycerides. It serves as a backbone onto which fatty acid molecules are attached and is marketed as an aid for "hyperhydrating" the body by increasing blood volume and helping to delay dehydration. Thus, glycerol may aid endurance athletes training or competing in hot, humid environments by hydrating tissues, increasing blood volume, and ultimately delaying fatigue and exhaustion associated with dehydration. Glycerin dosages used in research are based on body weight or total body water and have approximated 1 g/kg body weight, with each gram diluted in about 20–25 mL of water or similar fluid [40].

Numerous studies support the theory that glycerol added to fluids increases tissue hydration

compared with drinking fluid without glycerol added. Following glycerol consumption, the heart rate and body core temperature are lower during exercise in the heat, suggesting an ergogenic effect. In endurance type of activities a larger supply of stored water may lead to a delay in dehydration and exhaustion [55, 56]. More specifically, one study examined the effect of glycerol (1 g/kg) supplementation on body temperature while exercising on a treadmill (60 % VO_2max) at 42 °C at 25 % relative humidity for 90 min 2.5 h after ingestion of the glycerol. Results showed that the urine volume decreased before exercise, the sweat rate increased, and the rectal temperature was lower during exercise [57]. These findings imply that glycerol ingestion was helpful in maintaining normal body temperature during exercise in the heat.

Another study reporting positive results gave 11 fit adults glycerol (1.2 g/kg in a 26 ml/kg body weight solution) or a placebo (26 mg/kg body weight aspartame-flavored solution) 1 h prior to cycle exercise to exhaustion at 60 % of maximum workload (temperature 23.5–24.5 °C, humidity 25–27 %). The heart rate for those taking glycerol was 2.8 bpm lower, and endurance time was 21 % longer [58]. In a follow-up study, these same researchers wanted to determine whether the same pre-exercise routine followed by a carbohydrate oral replacement solution during exercise had any further effect. Once again, they found that when glycerol had been taken the endurance time was 25 % longer [58].

It is important to note that not all studies show an ergogenic effect and that the benefits—although noted for trained endurance athletes exercising in hot, humid environments—are not necessarily observed in athletes who are less well trained or are exercising in more temperate climates [56, 59]. These factors should be taken into account when considering glycerol supplements.

11.3.4 Creatine

Although creatine supplements are typically marketed as bodybuilding and "strength-boosting" supplements, some evidence suggests that they may prove beneficial for endurance athletes as well. Though creatine supplementation will not improve longer exercise efforts from equivalent running distances exceeding 5 km, some benefits may be derived for shorter, intermittent bouts of work associated with interval or tempo type training for distances under 2,000 m [60, 61].

Table 11.5 Creatine content in select foods

	Creatine content	
Food	g/lb	g/kg
Cod	1.4	3.0
Beef	2.0	4.5
Herring	3.0–4.5	6.5–10.0
Milk	0.05	0.1
Pork	2.3	5.0
Salmon	2.0	4.5
Shrimp	Trace	Trace
Tuna	1.8	4.0
Plaice	0.9	2.0
Fruits/vegetables	Trace	Trace

Adapted from Williams MH, Kreider RB, Branch D. Human Kinetics, Champaign, IL, (1999) [62]

Normally, about 1–2 g of creatine daily is produced in the body from the amino acids arginine, glycine, and methionine. Dietary sources (Table 11.5) , including meat and fish, add another 1–2 g of creatine per day, although overcooking destroys most of the creatine (the 1 g of creatine in an 8-oz steak may fall to zero if that steak is well done). In the body, creatine plays a vital role in cellular energy production as creatine phosphate (phosphocreatine) in regenerating ATP in skeletal muscle [46]. Most studies utilize doses approximating 20–30 g/day, consumed in four or five equal doses throughout the day for 5–7 days followed by a maintenance dose of 5 g/day [40].

One of the earliest creatine studies utilized well-trained distance runners and demonstrated improved cumulative, repeated running times following four 300-m sprints [63]. Another study demonstrated significant increases in time to exhaustion during intense cycle ergometry with creatine supplementation [64]. Yet another study reported that creatine loading in both male and female athletes resulted in a 12 % increase in the anaerobic threshold as well as a decrease in blood

lactate during incremental cycle tests [65]. One other study showed continued support by delaying the onset of neuromuscular fatigue (a parameter similar to anaerobic threshold) by 13 % in highly trained female athletes [66]. Most scientists agree that creatine's effectiveness can be attributed to one of two scenarios: (1) Phosphocreatine may aid ATP resynthesis for up to 3 min, albeit in a decreasing role with time and intensity of work [67], and (2) it may act as an energy shuttle between the mitochondria and muscle fibers, which suggests that creatine may help produce ATP aerobically [68]. Regardless, increasing muscle creatine phosphate levels through creatine supplementation may decrease the reliance on anaerobic glycolysis and reduce intramuscular lactate accumulation, thereby delaying the onset of fatigue.

11.3.5 Phosphates

In addition to the major macronutrients, phosphorus, an essential mineral distributed widely in foods, may also be classified as a nutritional sports ergogenic. Phosphorus is distributed widely in foods, particularly meat, seafood, eggs, milk, cheese, whole-grain products, nuts, and legumes. The Recommended Dietary Allowance (RDA) is 800 mg for adults and 1,200 mg for those 11–25 years of age [40]. Phosphate salts in both inorganic and organic forms play important roles in human metabolism, particularly as related to sports performance. They may influence all three human energy systems by acting as intracellular buffers. Another theory suggests that phosphate salts increase the formation of 2,3-diphosphoglycerate (2,3-DPG), a compound in the red blood cells (RBCs) that facilitates the release of oxygen to tissues.

An early study on phosphate loading examined highly trained runners who took 1 g sodium phosphate four times daily for 6 days. The phosphate salts increased the concentration of 2,3-DPG in RBCs by 6.6 %, which subsequently resulted in an increase in VO_{2max} [69]. This study also reported decreased production of lactate and reduced sensation of physiological stress. A later study utilizing highly trained cross-country runners found that 1 g sodium phosphate four times daily for 6 days resulted in a 10 % increase in VO_{2max} and an 11.8 % increase in the anaerobic threshold [4]. The authors attributed the improvements in exercise performance to increased metabolic efficiency. Well-controlled studies support the theory that phosphate salt supplementation may enhance function of the oxygen energy system. Furthermore, studies show that phosphate salt supplementation increases VO_2max and improves performance in endurance exercise tasks, including a greater number of stages completed in a progressive treadmill running test, increased time-to-exhaustion on a bicycle ergometer, and a decreased time to complete a 40-km cycling test [40]. However, if phosphate salts are in fact ergogenic, the underlying mechanism has yet to be determined [40]. The scientific literature suggests that phosphates may have an ergogenic effect on endurance athletes, but there is little support for its effectiveness during anaerobic exercise [4, 69]. More research with tight methodological control is still needed to support claims made in regard to phosphorus supplementation in both aerobic and anaerobic events.

11.3.6 Nitrates/Nitrites

A new area of research interest involves the use of dietary nitrates which can be found in green leafy vegetables, such as lettuce, celery, and beetroot [70]. Following ingestion, nitrate levels peak after 1–2 h, where nitrite levels peak between 2 and 3 h [71]. The significance of dietary nitrates is the observation that plasma nitrate and nitrate can be reduced to nitric oxide (aka, NO), which has numerous physiologic effects ranging from vasodilation, mitochondrial respiration, and biogenesis to glucose uptake [72, 73]. With respect to endurance exercise, these effects have the potential to reduce fatigue, improve exercise efficiency, and increase performance. Table 11.6 lists the nitrate content of select foods.

One of the first studies to show an improvement in exercise performance using nitrate supplementation was performed by Larsen et al.

Table 11.6 Nitrate content of select foods

Nitrate content (mg/100 g fresh weight)	Vegetable
Very high, >250	Beetroot, spinach, lettuce, arugula, celery, cress
High, 100–250	Fennel, leek, endive, parsley, carrot, Chinese cabbage, fennel
Moderate, 50–100	Cabbage, turnip, dill, mustard leaf
Low, 20–50	Broccoli, carrot, cauliflower, pumpkin, cucumber, chicory
Very Low, <20	Asparagus, mushrooms, onion, pea, pepper, potato, sweet potato, tomato, Artichoke, asparagus, broad bean, eggplant, garlic, green bean, summer squash, watermelon

Adapted and modified from Hord et al. (2009) [70]

(2007) who supplemented well-trained participants with sodium nitrate at 0.1 mmol/kg for 3 days. Results from this study showed a significant improvement in the oxygen cost, gross efficiency, and delta efficiency of exercise over the first four stages of an incremental exercise test to exhaustion; however, no improvements were noted for VO_{2max}. In a study using dietary nitrates derived from beetroot juice, Bailey and colleagues demonstrated a 5 % decrease in the O_2 cost of moderate-intensity, steady-state exercise, accompanied by a 23 % reduction in the VO_2 slow component. The VO_2 slow component often accompanies prolonged exercise and a reduction is synonymous improved exercise efficiency [74]. An interesting finding from this study is the observation that despite no statistical difference in VO_{2max} between the control and treatment groups, time-to-exhaustion was significantly increased during beetroot supplementation. Time-to-exhaustion, though associated with VO_{2max}, also represents an improvement in exercise efficiency. For example, Earnest et al. (2014) have recently shown that a greater percent increase in time-to-exhaustion (25–30 %) is manifest in light of more minimal changes to VO_{2max} (5–6 %) following exercise training [75]. While these early findings are interesting physiologically, the fundamental issue of "exercise performance" is more a salient point of discussion to this chapter.

Larsen and colleagues (2007) were one of the first to examine exercise performance in club level cyclists who were supplemented acutely with the equivalent of 6.2 mmol of nitrate 2.5 h prior to a 4 and 16 km cycling time trial [76]. While no between-group differences in average VO_2 were observed, beetroot juice improved time trial performance by ~2.8 % for both conditions. While the effects may seem trivial an improvement of this magnitude is sufficient to displace professional cyclists from a podium position in the Tour de France [77]. Using a longer supplement period, Cermak et al. (2012) administered 8 mmol nitrate per day for 6 days subsequently demonstrating a 5 % reduction in the VO_2 cost of 60 min of steady cycling and a 2 % increase in 10 km time-trial performance expressed as time to complete the simulated race, as well as associated time-trial power output [78]. Similar effects have been observed for running and rowing [79, 80]. Though these early studies are promising, recent studies in highly trained endurance athletes (VO_{2max} 60–70 ml/kg/min) do not appear to be efficacious [78, 81–83]. While the reasons for the response differences are not fully clear, candidate mechanisms include the observations that elite athletes have higher NOS activity, increased nitrite concentrations, and greater muscle capillarity and, hence, a potential lower O_2 cost due to greater circulation [84–86].

11.4 Immune System and Endurance Performance

The discussion surrounding endurance training and dietary interventions to improve immune function is a two-edged sword. On the one hand, exercise challenges the immune system, yet, given adequate recovery, strengthens and improves. Thus, it can be argued that dietary interventions aimed at suppressing the natural immune response to exercise may actually hamper exercise-training response. On the other hand, endurance athletes engaged in periods of very intense training run the risk of overtraining. During such a training period, transient signs and symptoms may occur including changes in the profile of

mood state (POMS) where tension, depression, anger, fatigue, and confusion may be present. Other signs include depleted muscle glycogen stores, increased resting heart rate, increased cortisol secretion, decreased appetite, sleep disturbances, head colds, and immunosuppression.

Most of the symptoms that result from overtraining, collectively referred to as overtraining syndrome, are subjective and identifiable only after the individual's performance has suffered. Unfortunately, these symptoms can be highly individualized, which can make it difficult for athletes, trainers, and coaches to recognize that overtraining brings on performance decrements. The first indication of overtraining syndrome is a decline in physical performance. The athlete can sense a loss in muscle strength, coordination, and maximal working capacity.

Unfortunately, one of the most serious consequences of overtraining is the negative effect it has on the body's immune system. Recent studies show that excessive training suppresses normal immune function, increasing the overtrained athlete's susceptibility to infections [87, 88]. Numerous studies show that short bouts of intense exercise can temporarily impair the immune response, and successive days of heavy training can amplify this suppression [89]. In these cases, supplementation may help attenuate the immunosuppression typically seen with overtraining.

A first line of defense is to insure that the athlete consumes adequate calories. Endurance athletes maintaining heavy volume training often do not consume enough calories to keep up with energy demands because of the suppressive effect exercise can have on the appetite [90]. This point can be especially concerning for endurance athletes engaged in prolonged training or competition sessions on the same or successive days. Multiple training sessions on the same day have now become the norm more than the exception for the elite endurance athlete owing to the ever-increasing level of competition and pressure to perform at optimal levels. Although it is unlikely that muscle glycogen stores can be completely resynthesized within a few hours by nutritional supplementation alone, it would behoove all endurance athletes to maximize the rate of muscle glycogen storage after exercise. This ultimately results in faster recovery from training, possibly allowing a greater training volume [91].

11.4.1 Carbohydrate and Protein

To demonstrate the importance of nutrient timing, Flakoll et al. provided a placebo, carbohydrate, or carbohydrate/protein supplement to U.S. Marine recruits immediately after exercise during 54 days of basic training to test the long-term impact of post-exercise carbohydrate/protein supplementation on variables such as health, muscle soreness, and function [92]. Compared to the placebo and carbohydrate groups, the combined carbohydrate/protein group had 33 % fewer total medical visits, 28 % fewer visits due to bacterial/viral infections, 37 % fewer visits due to muscle and joint problems, and 83 % fewer due to heat exhaustion. Muscle soreness was also reduced immediately after exercise by the carbohydrate/protein supplement. The authors postulated that post-exercise carbohydrate/protein supplementation not only enhances muscle protein deposition but also improves overall health, muscle soreness, and tissue hydration during prolonged intense exercise training.

11.4.2 Colostrum

Several ergogenic aids have been reported to aid the immune system. Colostrum is a form of milk produced by the mammary glands in late pregnancy and the few days after giving birth. Colostrum for dietary supplements is usually derived from bovine sources and contains various immunoglobulins (also called antibodies) and antimicrobial factors (i.e., lactoferrin, lactoperoxidase, lysozyme) as well as insulin-like growth factors (e.g., IGF-I, IGF-II). Bovine colostrum is among the highest quality sources of protein; however, it can be expensive.

The most prevalent claims for dietary supplements containing colostrum are in the area of generalized immune function and improved

recovery from intense exercise. One study examined the effects of consuming colostrum (60 g/day) or placebo (whey protein) during an 8-week running program, running three times a week for 45 min per session [93]. Participants conducted two treadmill runs to exhaustion, with 20 min of rest between runs, at baseline and 4 and 8 weeks into the study. No differences existed in treadmill running performance at baseline, and at week four, both groups had similar improvements in running performance. At week 8, however, the colostrum group ran significantly farther and did more work than the placebo group during the treadmill test. In addition, the colostrum supplemented group exhibited lower serum creatine kinase (CK) levels. CK is a muscle cell enzyme that some scientists believe can be used as a marker of muscle cell damage. High CK levels often indicate that significant muscle damage has occurred. However, some scientists believe that if CK levels remain normal, the athlete has experienced little muscle trauma [93, 94].

Another study examined rowing performance in a group of elite female rowers. Eight rowers completed a 9-week training program while consuming either colostrum (60 g/day) or whey protein. By week 9, rowers consuming colostrum had greater increases in the distance covered and work done than the whey protein group [95]. Additional studies on bovine colostrum consumption suggest that it can deliver some generalized anti-inflammatory benefits and help prevent and treat the gastric injury associated with nonsteroidal anti-inflammatory drugs [96–98].

11.4.3 Glutamine

Glutamine is another supplement popular in athletic populations today. It is the most abundant amino acid in the body, comprising approximately half of the free amino acids in the blood and muscle. Glutamine is a nonessential glucogenic amino acid and an anaplerotic precursor that has been shown to be a vital fuel for a variety of cells of the immune system [99]. In skeletal muscle, glutamine has an inhibitory role on proteolysis and branched-chain amino acid catabolism. Recent evidence has placed emphasis on glutamine as a positive component of immune function [99, 100].

Glutamine has two main functions in the body: It is a precursor in the synthesis of other amino acids, and it converts to glucose for energy. Cells of the immune system, small intestine, and kidney are the major consumers of glutamine, making "immune boosting" and "immune maintenance" claims for glutamine supplements quite common. In addition, there are claims for glutamine supplements in maintaining muscle mass, reducing post-exercise catabolism (muscle tissue breakdown), and accelerating recovery from intense exercise. Intense exercise training often exhibited by the endurance athlete results in a drop in plasma glutamine levels. Chronically low glutamine levels have been implicated as a possible contributing factor for athletic overtraining syndrome as well as the transient immunosuppression and increased risk of infections that typically affect competitive athletes during intense training and competition. Under conditions of metabolic stress, the body's need for glutamine may become conditionally essential, meaning that the body cannot produce adequate levels and a dietary source is required to prevent catabolism of skeletal muscle, the primary source of stored glutamine in the body.

A significant body of scientific literature supports the beneficial effects of glutamine supplementation in maintaining muscle mass and immune system function in critically ill patients and in those recovering from extensive burns and major surgery [101]. When plasma glutamine levels fall, skeletal muscles may enter a state of catabolism in which muscle protein is degraded to provide free glutamine for the rest of the body. Because skeletal muscle is the major source of glutamine (other than the diet), prolonged deficits in plasma glutamine can lead to a significant loss of skeletal muscle protein and muscle mass. Postsurgical deposition of collagen (a marker for wound healing) can be enhanced by amino acid supplementation containing 14 g of glutamine, whereas a lower dose of mixed amino acids containing glutamine (2.9 g) provides no change in athletic performance or on adaptations to cycling training [102, 103].

Studies have also been conducted on glutamine supplementation in athletes, and a strong rationale exists for the efficacy of glutamine supplements in athletic populations. One study found that athletes who consumed glutamine immediately and 2 h after running a marathon or ultramarathon reported fewer infections than a placebo group [104]. The levels of infection were lowest in the middle-distance runners and highest in the runners after a marathon or ultramarathon. Glutamine supplements have also been shown to play a role in counteracting the catabolic effects of stress hormones, such as cortisol, which are typically elevated by strenuous exercise. Under conditions of stress-induced protein wasting in adults and children, including burns, surgery, and some forms of cancer, glutamine supplementation has been associated with reduced protein breakdown, enhanced lymphocyte function, reduced gut permeability, and reduced infections [16, 105–107].

11.5 Conclusion

Proper training, maintaining a positive energy balance, and utilizing effective nutritional supplements form the foundation for optimal performance. Training for the endurance athlete should be based on proper utilization of the principles of training, depending on individual goals and the training season (preseason, in-season, postseason). The nutritional base should focus on an everyday diet that emphasizes a combination of all the nutritional ergogenic aids. The types of macronutrients and micronutrients selected and the timing of their use are of utmost importance for developing a well-refined everyday diet. The use of nutritional supplements that research has shown can help improve energy availability (e.g., sports drinks, carbohydrate) and/or promote recovery (e.g., carbohydrate, protein) can provide additional benefits in certain situations. In addition, a combination of effective pharmacological and physiological ergogenic supplements can further propel performance and support the immune system. Following these training and nutritional recommendations can serve as the foundation for a successful endurance athlete.

11.6 Practical Applications

- In preparation for training or competition, endurance athletes should strive for adequate hydration. While hydration is relatively straight forward, consideration may be given to fluids containing moderate concentrations of carbohydrate and sodium be ingested regularly starting several days before prolonged competition, such as marathon running.
- Endurance athletes should try to maximize their muscle glycogen stores prior to competition. This can be accomplished during the training taper by consuming 5–12 g carbohydrates/kg body weight daily depending on the athlete and length of the activity.
- Prior to competition, it is recommended that 500–1,000 ml of fluid be ingested. It may also be beneficial to consume 200–300 g of carbohydrate if supplementation during exercise is limited or not possible.
- During exercise, endurance athletes should try to fully replace fluid losses that occur, although during hot and humid conditions this may be next to impossible.
- It is best to consume small volumes of fluid frequently (150–250 ml every 15 min) rather than consume high volumes of fluid occasionally (e.g., 400 ml every 30 min).
- The endurance athlete should consider electrolyte replacement, especially during periods of un-acclimatized activity involving high heat and humidity. Most sports drinks are formulated to adequately to replace electrolyte losses due to sweating so preference should be given to taste rather than brand.
- To maximize endurance performance, 45–60 g of high-glycemic index carbohydrates should be ingested per hour during exercise. Carbohydrate solutions should not exceed 10 % if maintaining hydration is of importance.
- Carbohydrate ingestion during exercise should begin early to account for transit time from the gut. If fluid replacement is of concern, it is recommended that supplementation with a dilute carbohydrate solution start as soon as possible and continued periodically throughout exercise.

- The addition of small amounts of protein to a carbohydrate supplement (4:1 ratio) may also increase the effectiveness of the supplement.
- For rapid rehydration following exercise, it is important to start fluid consumption early and replace at least 150 % of the fluid lost during exercise with a dilute sodium solution.
- Requirements for the daily recovery of muscle glycogen depend on exercise intensity and duration. If the training duration is moderate and the intensity is low, 5–7 g of carbohydrate (CHO)/kg/day should be consumed. If the training duration is moderate and the intensity is high, 7–12 g CHO/kg/day should be consumed. If the training is extreme (4–6 h per day), 10–12 g CHO/kg/day should be consumed.
- If there is only limited time to replenish the muscle glycogen stores, 1.0–1.2 g CHO/kg/h should be consumed at frequent intervals starting within the first 30 min after exercise.
- The addition of protein to the carbohydrate supplement (4:1 ratio) promotes additional glycogen storage when carbohydrate intake is suboptimal or when frequent supplementation is not possible.
- Post-exercise supplements composed of carbohydrate and protein have the added benefit of limiting muscle tissue damage, stimulating protein accretion, and protecting the immune system from exercise-induced immunosuppression.
- Several pharmacological and physiological ergogenic aids can further propel performance for the endurance athlete and should be considered depending on the individual goal of the athlete.
- There is some evidence that colostrum and glutamine support the immune system. Hence, the athlete should consider these supplements only during periods of very intense training.

References

1. Bell DG, Jacobs I. Combined caffeine and ephedrine ingestion improves run times of Canadian Forces Warrior Test. Aviat Space Environ Med. 1999;70(4):325–9.
2. Blomstrand E, Hassmen P, Ekblom B, Newsholme EA. Administration of branched-chain amino acids during sustained exercise–effects on performance and on plasma concentration of some amino acids. Eur J Appl Physiol Occup Physiol. 1991;63(2):83–8.
3. Bridge CA, Jones MA. The effect of caffeine ingestion on 8 km run performance in a field setting. J Sports Sci. 2006;24(4):433–9.
4. Kreider RB, Miller GW, Williams MH, Somma CT, Nasser TA. Effects of phosphate loading on oxygen uptake, ventilatory anaerobic threshold, and run performance. Med Sci Sports Exerc. 1990;22(2):250–6.
5. Coyle EF, Montain SJ. Benefits of fluid replacement with carbohydrate during exercise. Med Sci Sports Exerc. 1992;24(9 Suppl):S324–30.
6. Armstrong LE, Costill DL, Fink WJ. Influence of diuretic-induced dehydration on competitive running performance. Med Sci Sports Exerc. 1985;17(4):456–61.
7. Sutton JR, Bar-Or O. Thermal illness in fun running. Am Heart J. 1980;100(6 Pt 1):778–81.
8. Coyle EF. Substrate utilization during exercise in active people. Am J Clin Nutr. 1995;61(4 Suppl):968S–79.
9. Krieder RB, Fry AC, O'Toole ML, editors. Overtraining in sport. Champaign, IL: Human Kinetics; 1998.
10. Cade JR, Reese RH, Privette RM, Hommen NM, Rogers JL, Fregly MJ. Dietary intervention and training in swimmers. Eur J Appl Physiol Occup Physiol. 1991;63(3–4):210–5.
11. Carli G, Bonifazi M, Lodi L, Lupo C, Martelli G, Viti A. Changes in the exercise-induced hormone response to branched chain amino acid administration. Eur J Appl Physiol Occup Physiol. 1992;64(3):272–7.
12. Kreider RB. Dietary supplements and the promotion of muscle growth with resistance exercise. Sports Med. 1999;27(2):97–110.
13. Komi PV. Strength and power in sport. Cambridge, MA: Blackwell Scientific; 1992.
14. Coyle EF, Montain SJ. Carbohydrate and fluid ingestion during exercise: are there trade-offs? Med Sci Sports Exerc. 1992;24(6):671–8.
15. Noakes TD, Myburgh KH, du Plessis J, Lang L, Lambert M, van der Riet C, et al. Metabolic rate, not percent dehydration, predicts rectal temperature in marathon runners. Med Sci Sports Exerc. 1991;23(4):443–9.
16. Klimberg VS, Nwokedi E, Hutchins LF, Pappas AA, Lang NP, Broadwater JR, et al. Glutamine facilitates chemotherapy while reducing toxicity. JPEN J Parenter Enteral Nutr. 1992;16(6 Suppl):83S–7.
17. Bergstrom J, Hermansen L, Hultman E, Saltin B. Diet, muscle glycogen and physical performance. Acta Physiol Scand. 1967;71(2):140–50.
18. Gastelu D, Hatfield FC. Nutrition for maximum performance. Garden City Park, NY: Avery; 1997.

19. Andersen LL, Tufekovic G, Zebis MK, Crameri RM, Verlaan G, Kjaer M, et al. The effect of resistance training combined with timed ingestion of protein on muscle fiber size and muscle strength. Metabolism. 2005;54(2):151–6.
20. Ivy JL, Res PT, Sprague RC, Widzer MO. Effect of a carbohydrate-protein supplement on endurance performance during exercise of varying intensity. Int J Sport Nutr Exerc Metab. 2003;13(3):382–95.
21. Saunders MJ, Kane MD, Todd MK. Effects of a carbohydrate-protein beverage on cycling endurance and muscle damage. Med Sci Sports Exerc. 2004; 36(7):1233–8.
22. Dangin M, Boirie Y, Garcia-Rodenas C, Gachon P, Fauquant J, Callier P, et al. The digestion rate of protein is an independent regulating factor of postprandial protein retention. Am J Physiol Endocrinol Metab. 2001;280(2):E340–8.
23. Ivy J, Portman R. The performance zone. North Bergen, NJ: Basic Health; 2004.
24. Costill DL, Hargreaves M. Carbohydrate nutrition and fatigue. Sports Med. 1992;13(2):86–92.
25. Ivy JL. Muscle glycogen synthesis before and after exercise. Sports Med. 1991;11(1):6–19.
26. Ivy JL. Glycogen resynthesis after exercise: effect of carbohydrate intake. Int J Sports Med. 1998;19 Suppl 2:S142–5.
27. Haymond MW. Hypoglycemia in infants and children. Endocrinol Metab Clin North Am. 1989;18(1): 211–52.
28. Blom PC, Hostmark AT, Vaage O, Kardel KR, Maehlum S. Effect of different post-exercise sugar diets on the rate of muscle glycogen synthesis. Med Sci Sports Exerc. 1987;19(5):491–6.
29. Burke LM, Collier GR, Hargreaves M. Muscle glycogen storage after prolonged exercise: effect of the glycemic index of carbohydrate feedings. J Appl Physiol. 1993;75(2):1019–23.
30. Jentjens RL, van Loon LJ, Mann CH, Wagenmakers AJ, Jeukendrup AE. Addition of protein and amino acids to carbohydrates does not enhance postexercise muscle glycogen synthesis. J Appl Physiol. 2001;91(2):839–46.
31. Tarnopolsky MA, Bosman M, Macdonald JR, Vandeputte D, Martin J, Roy BD. Postexercise protein-carbohydrate and carbohydrate supplements increase muscle glycogen in men and women. J Appl Physiol. 1997;83(6):1877–83.
32. Evans WJ. Protein nutrition and resistance exercise. Can J Appl Physiol. 2001;26(Suppl):S141–52.
33. Leiper JB, Aulin KP, Soderlund K. Improved gastric emptying rate in humans of a unique glucose polymer with gel-forming properties. Scand J Gastroenterol. 2000;35(11):1143–9.
34. Piehl Aulin K, Soderlund K, Hultman E. Muscle glycogen resynthesis rate in humans after supplementation of drinks containing carbohydrates with low and high molecular masses. Eur J Appl Physiol. 2000; 81(4):346–51.
35. Rowlands DS, Clarke J. Lower oxidation of a high molecular weight glucose polymer vs. glucose during cycling. Appl Physiol Nutr Metab. 2011;36(2):298–306.
36. Rowlands DS, Wallis GA, Shaw C, Jentjens RL, Jeukendrup AE. Glucose polymer molecular weight does not affect exogenous carbohydrate oxidation. Med Sci Sports Exerc. 2005;37(9):1510–6.
37. Ivy JL, Katz AL, Cutler CL, Sherman WM, Coyle EF. Muscle glycogen synthesis after exercise: effect of time of carbohydrate ingestion. J Appl Physiol. 1988;64(4):1480–5.
38. Garetto LP, Richter EA, Goodman MN, Ruderman NB. Enhanced muscle glucose metabolism after exercise in the rat: the two phases. Am J Physiol. 1984;246(6 Pt 1):E471–5.
39. Miller SL, Tipton KD, Chinkes DL, Wolf SE, Wolfe RR. Independent and combined effects of amino acids and glucose after resistance exercise. Med Sci Sports Exerc. 2003;35(3):449–55.
40. Williams MH. The ergogenic edge. Champaign, IL: Human kinetics; 1998.
41. Blomstrand E, Celsing F, Newsholme EA. Changes in plasma concentrations of aromatic and branched-chain amino acids during sustained exercise in man and their possible role in fatigue. Acta Physiol Scand. 1988;133(1):115–21.
42. Castell LM, Yamamoto T, Phoenix J, Newsholme EA. The role of tryptophan in fatigue in different conditions of stress. Adv Exp Med Biol. 1999;467:697–704.
43. Davis JM, Bailey SP, Woods JA, Galiano FJ, Hamilton MT, Bartoli WP. Effects of carbohydrate feedings on plasma free tryptophan and branched-chain amino acids during prolonged cycling. Eur J Appl Physiol Occup Physiol. 1992; 65(6):513–9.
44. Hassmen P, Blomstrand E, Ekblom B, Newsholme EA. Branched-chain amino acid supplementation during 30-km competitive run: mood and cognitive performance. Nutrition. 1994;10(5):405–10.
45. Tanaka H, West KA, Duncan GE, Bassett Jr DR. Changes in plasma tryptophan/branched chain amino acid ratio in responses to training volume variation. Int J Sports Med. 1997;18(4):270–5.
46. Talbott SM, Hughes K. The health professionals guide to dietary supplements. Philadelphia: Lippincott, William & Wilkens; 2007.
47. Gastmann UA, Lehmann MJ. Overtraining and the BCAA hypothesis. Med Sci Sports Exerc. 1998; 30(7):1173–8.
48. van Hall G, Raaymakers JS, Saris WH, Wagenmakers AJ. Ingestion of branched-chain amino acids and tryptophan during sustained exercise in man: failure to affect performance. J Physiol. 1995;486(Pt 3):789–94.
49. Costill DL, Dalsky GP, Fink WJ. Effects of caffeine ingestion on metabolism and exercise performance. Med Sci Sports. 1978;10(3):155–8.

50. Erickson MA, Schwarzkopf RJ, McKenzie RD. Effects of caffeine, fructose, and glucose ingestion on muscle glycogen utilization during exercise. Med Sci Sports Exerc. 1987;19(6):579–83.
51. Spriet LL, MacLean DA, Dyck DJ, Hultman E, Cederblad G, Graham TE. Caffeine ingestion and muscle metabolism during prolonged exercise in humans. Am J Physiol. 1992;262(6 Pt 1):E891–8.
52. Schneiker KT, Bishop D, Dawson B, Hackett LP. Effects of caffeine on prolonged intermittent-sprint ability in team-sport athletes. Med Sci Sports Exerc. 2006;38(3):578–85.
53. Namdar M, Koepfli P, Grathwohl R, Siegrist PT, Klainguti M, Schepis T, et al. Caffeine decreases exercise-induced myocardial flow reserve. J Am Coll Cardiol. 2006;47(2):405–10.
54. Killer SC, Blannin AK, Jeukendrup AE. No evidence of dehydration with moderate daily coffee intake: a counterbalanced cross-over study in a free-living population. PLoS One. 2014;9(1), e84154.
55. Jimenez C, Melin B, Koulmann N, Allevard AM, Launay JC, Savourey G. Plasma volume changes during and after acute variations of body hydration level in humans. Eur J Appl Physiol Occup Physiol. 1999;80(1):1–8.
56. Wagner DR. Hyperhydrating with glycerol: implications for athletic performance. J Am Diet Assoc. 1999;99(2):207–12.
57. Lyons TP, Riedesel ML, Meuli LE, Chick TW. Effects of glycerol-induced hyperhydration prior to exercise in the heat on sweating and core temperature. Med Sci Sports Exerc. 1990;22(4):477–83.
58. Montner P, Stark DM, Riedesel ML, Murata G, Robergs R, Timms M, et al. Pre-exercise glycerol hydration improves cycling endurance time. Int J Sports Med. 1996;17(1):27–33.
59. Arnall DA, Goforth Jr HW. Failure to reduce body water loss in cold-water immersion by glycerol ingestion. Undersea Hyperb Med. 1993;20(4):309–20.
60. Earnest CP. Effect of acute creatine monohydrate ingestion on anaerobic capacity. Kinesiology. 1997;141.
61. Earnest CP, Almada AL, Mitchell TL. Effect of creatine monohydrate ingestion on intermediate length anaerobic treadmill running to exhaustion. J Strength Cond Res. 1997;4:234–8.
62. Williams MH, Kreider R, Branch JD. Creatine: the power supplement (p 15). Champaign, IL: Human Kinetics; 1999.
63. Harris RC, Soderlund K, Hultman E. Elevation of creatine in resting and exercised muscle of normal subjects by creatine supplementation. Clin Sci. 1992;83(3):367–74.
64. Smith JC, Stephens DP, Hall EL, Jackson AW, Earnest CP. Effect of oral creatine ingestion on parameters of the work rate-time relationship and time to exhaustion in high-intensity cycling. Eur J Appl Physiol Occup Physiol. 1998;77(4):360–5.
65. Blumenthal M, Busse WR, Goldberg A, Gruenwald J, Hall T, Riggins CW, Rister RS, editors. The complete commission E monographs: therapeutic guide to herbal medicines. Boston, MA: Integrative Medicine Communications; 1998.
66. Stout J, Eckerson J, Ebersole K, Moore G, Perry S, Housh T, et al. Effect of creatine loading on neuromuscular fatigue threshold. J Appl Physiol. 2000;88(1):109–12.
67. Bangsbo J, Gollnick PD, Graham TE, Juel C, Kiens B, Mizuno M, et al. Anaerobic energy production and O2 deficit-debt relationship during exhaustive exercise in humans. J Physiol. 1990;422:539–59.
68. Wallimann T, Wyss M, Brdiczka D, Nicolay K, Eppenberger HM. Intracellular compartmentation, structure and function of creatine kinase isoenzymes in tissues with high and fluctuating energy demands: the 'phosphocreatine circuit' for cellular energy homeostasis. Biochem J. 1992;281(Pt 1):21–40.
69. Cade R, Conte M, Zauner C, Mars D, Peterson J, Lunne D, et al. Effects of phosphate loading on 2,3-diphosphoglycerate and maximal oxygen uptake. Med Sci Sports Exerc. 1984;16(3):263–8.
70. Hord NG, Tang Y, Bryan NS. Food sources of nitrates and nitrites: the physiologic context for potential health benefits. Am J Clin Nutr. 2009;90(1):1–10.
71. Webb AJ, Patel N, Loukogeorgakis S, Okorie M, Aboud Z, Misra S, et al. Acute blood pressure lowering, vasoprotective, and antiplatelet properties of dietary nitrate via bioconversion to nitrite. Hypertension. 2008;51(3):784–90.
72. Shiva S, Huang Z, Grubina R, Sun J, Ringwood LA, MacArthur PH, et al. Deoxymyoglobin is a nitrite reductase that generates nitric oxide and regulates mitochondrial respiration. Circ Res. 2007;100(5):654–61.
73. Stamler JS, Meissner G. Physiology of nitric oxide in skeletal muscle. Physiol Rev. 2001;81(1):209–37.
74. Bailey SJ, Winyard P, Vanhatalo A, Blackwell JR, Dimenna FJ, Wilkerson DP, et al. Dietary nitrate supplementation reduces the O2 cost of low-intensity exercise and enhances tolerance to high-intensity exercise in humans. J Appl Physiol. 2009;107(4):1144–55.
75. Earnest CP, Johannsen NM, Swift DL, Gillison FB, Mikus CR, Lucia A, et al. Aerobic and strength training in concomitant metabolic syndrome and type 2 diabetes. Med Sci Sports Exerc. 2014;46(7):1293–301.
76. Larsen FJ, Weitzberg E, Lundberg JO, Ekblom B. Effects of dietary nitrate on oxygen cost during exercise. Acta Physiol. 2007;191(1):59–66.
77. Santalla A, Earnest CP, Marroyo JA, Lucia A. The Tour de France: an updated physiological review. Int J Sports Physiol Perform. 2012;7(3):200–9.
78. Cermak NM, Gibala MJ, van Loon LJ. Nitrate supplementation's improvement of 10-km time-trial performance in trained cyclists. Int J Sport Nutr Exerc Metab. 2012;22(1):64–71.

79. Bond H, Morton L, Braakhuis AJ. Dietary nitrate supplementation improves rowing performance in well-trained rowers. Int J Sport Nutr Exerc Metab. 2012;22(4):251–6.
80. Murphy M, Eliot K, Heuertz RM, Weiss E. Whole beetroot consumption acutely improves running performance. J Acad Nutr Diet. 2012;112(4):548–52.
81. Bescos R, Ferrer-Roca V, Galilea PA, Roig A, Drobnic F, Sureda A, et al. Sodium nitrate supplementation does not enhance performance of endurance athletes. Med Sci Sports Exerc. 2012; 44(12):2400–9.
82. Peacock O, Tjonna AE, James P, Wisloff U, Welde B, Bohlke N, et al. Dietary nitrate does not enhance running performance in elite cross-country skiers. Med Sci Sports Exerc. 2012;44(11):2213–9.
83. Wilkerson DP, Hayward GM, Bailey SJ, Vanhatalo A, Blackwell JR, Jones AM. Influence of acute dietary nitrate supplementation on 50 mile time trial performance in well-trained cyclists. Eur J Appl Physiol. 2012;112(12):4127–34.
84. Jensen L, Bangsbo J, Hellsten Y. Effect of high intensity training on capillarization and presence of angiogenic factors in human skeletal muscle. J Physiol. 2004;557(Pt 2):571–82.
85. McConell GK, Bradley SJ, Stephens TJ, Canny BJ, Kingwell BA, Lee-Young RS. Skeletal muscle nNOS mu protein content is increased by exercise training in humans. Am J Physiol Regul Integr Comp Physiol. 2007;293(2):R821–8.
86. Poveda JJ, Riestra A, Salas E, Cagigas ML, Lopez-Somoza C, Amado JA, et al. Contribution of nitric oxide to exercise-induced changes in healthy volunteers: effects of acute exercise and long-term physical training. Eur J Clin Invest. 1997;27(11): 967–71.
87. Mackinnon LT. Exercise and natural killer cells. What is the relationship? Sports Med. 1989;7(3):141–9.
88. McCarthy DA, Dale MM. The leucocytosis of exercise. A review and model. Sports Med. 1988;6(6): 333–63.
89. Brahmi Z, Bray RA, Abrams SI. Evidence for an early calcium-independent event in the activation of the human natural killer cell cytolytic mechanism. J Immunol. 1985;135(6):4108–13.
90. Berning JR. Energy intake, diet and muscle wasting. In: Kreider RB, Fry AC, O'Toole ML, editors. Overtraining in sport. Champaign, IL: Human Kinetics; 1998.
91. Haff GG, Lehmkuhl MJ, McCoy LB, Stone MH. Carbohydrate supplementation and resistance training. J Strength Cond Res. 2003;17(1):187–96.
92. Flakoll PJ, Judy T, Flinn K, Carr C, Flinn S. Postexercise protein supplementation improves health and muscle soreness during basic military training in Marine recruits. J Appl Physiol. 2004;96(3):951–6.
93. Buckley JD, Abbott MJ, Brinkworth GD, Whyte PB. Bovine colostrum supplementation during endurance running training improves recovery, but not performance. J Sci Med Sport. 2002;5(2):65–79.
94. Buckley JD. Bovine colostrum: Does it improve athletic performance? Nutrition. 2002;18(9):776–7.
95. Brinkworth GD, Buckley JD, Bourdon PC, Gulbin JP, David A. Oral bovine colostrum supplementation enhances buffer capacity but not rowing performance in elite female rowers. Int J Sport Nutr Exerc Metab. 2002;12(3):349–65.
96. Bolke E, Jehle PM, Hausmann F, Daubler A, Wiedeck H, Steinbach G, et al. Preoperative oral application of immunoglobulin-enriched colostrum milk and mediator response during abdominal surgery. Shock. 2002;17(1):9–12.
97. Khan Z, Macdonald C, Wicks AC, Holt MP, Floyd D, Ghosh S, et al. Use of the 'nutriceutical', bovine colostrum, for the treatment of distal colitis: results from an initial study. Aliment Pharmacol Ther. 2002;16(11):1917–22.
98. Playford RJ, MacDonald CE, Calnan DP, Floyd DN, Podas T, Johnson W, et al. Co-administration of the health food supplement, bovine colostrum, reduces the acute non-steroidal anti-inflammatory drug-induced increase in intestinal permeability. Clin Sci. 2001;100(6):627–33.
99. Ardawi MS, Newsholme EA. Metabolism in lymphocytes and its importance in the immune response. Essays Biochem. 1985;21:1–44.
100. Ardawi MS, Newsholme EA. Glutamine metabolism in lymphocytes of the rat. Biochem J. 1983; 212(3):835–42.
101. Carli F, Webster J, Ramachandra V, Pearson M, Read M, Ford GC, et al. Aspects of protein metabolism after elective surgery in patients receiving constant nutritional support. Clin Sci. 1990;78(6):621–8.
102. Vukovich MD, Sharp RL, Kesl LD, Schaulis DL, King DS. Effects of a low-dose amino acid supplement on adaptations to cycling training in untrained individuals. Int J Sport Nutr. 1997;7(4):298–309.
103. Williams JZ, Abumrad N, Barbul A. Effect of a specialized amino acid mixture on human collagen deposition. Ann Surg. 2002;236(3):369–74. discussion 74–5.
104. Castell LM, Poortmans JR, Newsholme EA. Does glutamine have a role in reducing infections in athletes? Eur J Appl Physiol Occup Physiol. 1996; 73(5):488–90.
105. Barbosa E, Moreira EA, Goes JE, Faintuch J. Pilot study with a glutamine-supplemented enteral formula in critically ill infants. Revista do Hospital das Clinicas. 1999;54(1):21–4.
106. des Robert C, Le Bacquer O, Piloquet H, Roze JC, Darmaun D. Acute effects of intravenous glutamine supplementation on protein metabolism in very low birth weight infants: a stable isotope study. Pediatr Res. 2002;51(1):87–93.
107. Yoshida S, Kaibara A, Ishibashi N, Shirouzu K. Glutamine supplementation in cancer patients. Nutrition. 2001;17(9):766–8.

Nutritional Supplements to Enhance Recovery

12

Tim N. Ziegenfuss, Jamie Landis, Darryn Willoughby, and Mike Greenwood

Abstract

The ability to recover from intense exercise often separates good athletes from great ones. In the past, "recovery" often simply included rest, therapeutic modalities (e.g., cryotherapy, thermotherapy, massage, hydration therapy, stretching protocols, myofascial release), and meeting basic nutritional needs for fluid and energy replenishment. Today, athletes have a number of additional options to help them recover from high-intensity training, one of which includes the judicious use of dietary supplements. This chapter briefly reviews nutritional strategies that have a strong theoretical background for enhancing rehydration/electrolyte balance, replenishing energy reserves, minimizing oxidative damage, and stimulating muscle repair after training regiments are complete.

Keywords

Rehydration • Electrolyte • Antioxidant • Essential amino acids • L-Carnitine • Creatine

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12.1 Exercise Recovery

Recovery from exercise is a dynamic process that includes the restoration of body fluids and electrolyte balance, replenishment of energy stores, and repair of damaged tissues. Some aspects of these processes take a few minutes, and others may take days. The ability to continue exercising or competing day after day may be limited by how quickly one's muscles recover after an initial exertion. In general, the more severe the previous exercise stress, the longer and more involved are the body's recovery efforts.

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By eating a nutrient-dense, well-balanced diet that includes adequate fluid intake, the body can generally fully recover from any single bout of exercise if given enough time while also considering the key aspect of individual genetic predisposition. However, by taking proactive steps during the pre- and/or postexercise periods, it is possible to speed the body's recovery from individual bouts while sustaining maximal training and improving exercise performance.

The physical cost of exercise is intimately tied to the intrinsic variables of intensity, duration, and mode. They effectively form the basis of categorizing the stresses on the body that occur during exercise. Consideration of each of the variables requires knowledge of anatomy (extent of muscle mass involved), the kinesiology involved (type of muscle actions), and physiology (e.g., metabolic demands of exercise, hormonal responses to exercise). Other considerations include the ages of the individuals, their current diet, the timing of the exercise bout, their competitive status, training volume, environmental factors, and overall health status. The obvious consequence of the interplay between these factors is clear: distinct strategies for nutritionally enhancing recovery are necessary.

When carefully planned based on both the demands of the exercise and the needs of the athlete, we believe that certain dietary supplements can help improve an athlete's recovery from exercise. This chapter provides some basic guidelines for an evidence-based approach to rational, safe, effective nutritional intervention as a means of enhancing exercise recovery.

12.2 Phases of Recovery

To address and maximize the benefits of nutritional support properly, two distinct phases of exercise recovery should be recognized: fast (partial) and slow (complete). Fast recovery occurs during the period of approximately 30–45 min following an exercise bout in a context where the body's metabolic, cardiovascular, respiratory, and hormonal variables rapidly return to within pre-exercise values. In contrast, the slow phase of recovery can take several days and is only complete when the body maintains a heightened capacity to undertake an additional exercise stimulus.

From a nutritional perspective, the most important characteristics of the rapid phase of recovery involve the cellular transitions from a catabolic (breakdown and mobilization) state to one of anabolism (buildup and storage). In muscle tissue especially, cellular processes shift toward the building of new proteins, the replenishment of energy substrates, reestablishment of optimal fluid and electrolyte levels, and tissue repair. By taking the initiative and maximizing nutritional support during the fast phase of recovery, the complete recovery process is enhanced. Indeed, consider that although a number of recovery processes continue for a day (or even several days) following an intense bout of exercise, the rate of recovery slows appreciably after the first few hours. For example, with no immediate (postexercise) nutritional support, muscle carbohydrate stores may require 24 h or more for complete restoration, and repair of eccentric contraction-induced muscle damage may require several days. As a general rule, the more severe the exercise duration, intensity, and mode, the longer and more involved are the body's recovery processes. Undertaking a second bout of exercise prior to full recovery complicates the recovery processes. As such, individuals undertaking regular intense training benefit from careful dietary planning for optimal recovery and performance. In short, a well-designed nutritional support program can ensure athletes of an advantage for both the rapid and slow phases of recovery.

12.3 Classification of Recovery Supplements

Table 12.1 lists five classes of recovery supplements: oral rehydration and electrolyte balance, replenishment of energy reserves, minimizing oxidative damage, muscle repair, and immune system support. The remaining sections provide an overview of supplements that may lend support

Table 12.1 Classification of recovery supplements

Oral rehydration and electrolyte balance • Traditional oral rehydration solutions are made according to World Health Organization guidelines for the prevention and treatment of dehydration during diarrhea or gastroenteritis. For these medical conditions, effective delivery of oral fluid replacement is best achieved by a solution that is low in carbohydrate (2 %, or 2 g/100 ml) and provides electrolytes in concentrations of sodium 50–80 mmol/l and potassium 10–30 mmol/l (e.g., Pedialyte®) • Newer sports drinks have become available with a higher sodium content (~30 mmol/l) to help replace sodium lost in sweat
Replenishment of energy reserves Sports drinks • Usually a carbohydrate-rich solution (6–8 % carbohydrate), containing mainly sodium (10–25 mmol/l) and potassium (3–5 mmol/l). Drinks with additional electrolytes (calcium, chloride, magnesium, potassium) and micronutrients (chromium) are also available Sports gels • A highly concentrated carbohydrate source (65–70 %) in an easily consumed and quickly digested gel form • Usually has substantially higher carbohydrate concentration than sports drinks. Use with caution as idiosyncratic gastrointestinal distress may occur • Some gels also contain other compounds, such as medium-chain triglycerides (MCTs) and small amounts of caffeine (~20–40 mg) Sports bars • Compact source of carbohydrate and protein in a bar form. Generally low in both fat and fiber, although there are exceptions. Some are fortified with micronutrients (typically containing about 25–50 % RDA per bar of various vitamins and minerals) Liquid meal supplements • Carbohydrate-rich, moderate protein, low-fat powder (or liquid) for mixing with water or milk • Generally intended to supply a balance of macronutrients and micronutrients
Minimizing oxidative damage: antioxidants • Classically, vitamins C and E as well as other micronutrients such as zinc and selenium. Newer additions include L-carnitine, extracts of certain fruits/vegetables, coQ10, and teas
Muscle repair Whole protein and protein hydrolysates • Whey (isolate and concentrate) • Casein • Egg • Soy Amino acids • Essential amino acids • Branched-chain amino acids (leucine, isoleucine, valine) • Glutamine • Creatine • Hydroxy beta-methylbutyrate (HMB) Carbohydrates • See above
Immune system support • Amino acids (glutamine) • Vitamins (ascorbic acid, vitamin D) • Plant extracts (Andrographis paniculata, ginseng, ashwagandha) • Omega-3 fats (from fish oil, krill oil)

RDA recommended daily allowance

in each of these strata. It should be recognized that full recovery from intense exercise is an integrative process, and all of these strata overlap in many ways.

12.4 Rehydration

Fluid loss is inherent in exercise. Indeed, with prolonged activities such as running or cycling, athletes may lose 1–3 l of body water per hour. These losses may in turn produce a dehydration-associated loss of body weight and impairment of cardiovascular and thermoregulatory homeostasis [1]. The loss of vascular fluid volume may then result in intracellular water being drawn out of muscle cells [2], an obvious detriment to performance. Clearly, although it is often overlooked as a postexercise dietary supplement or ergogenic, it is of the utmost importance that the appropriate fluid replacement volume be considered along with the attendant need of proper electrolyte balance.

12.4.1 Water and Sodium

The health benefits of plain water have often been touted and are not disputed here. However, the use of plain water as a sport rehydration beverage may not be ideal under certain circumstances. For example, copious water ingestion may cause relative dilution of the serum sodium level [3], which in turn may cause a decrease in thirst sensation and an increase in urine output, stalling the rehydration process. A better option for ensuring a proper plasma volume is to use a sodium/water solution [4]. In fact, it has been previously demonstrated that when adequate fluid is available, rehydration is achieved more rapidly when the solution sodium content (0.3–0.7 g NaCl per liter of water) is greater than sodium lost via sweat [5, 6]. This level of rehydration sodium is recommended by both the American College of Sports Medicine [7] and the National Athletic Trainers' Association [8]. Potassium may also be added to the rehydration solution after exercising, although experimental evidence has not confirmed substantial improvement in intracellular rehydration [9, 10].

Because of the combination of exercise-associated water losses and the expected increase in urine production during the postexercise consumption period, it is generally recommended that consumption of 150 % or more of the weight lost may be required to achieve euhydration within the short-term postexercise period (i.e., 6 h) [5, 11, 12]. With such impressive fluid losses and the need for considerable fluid consumption, the palatability of a fluid replacement drink is of no small concern. In fact, research suggests that drinks with a slight citrus taste are especially effective at preventing the quenched sensation following ingestion of water alone [13]. It is no coincidence, then, that the popular sports drinks in the American marketplace (e.g., Gatorade, Powerade, Accelerade) all offer a citrus flavor. However, those popular beverages contain sodium concentrations (0.4–0.5 g NaCl per liter of water) at the low end of that recommended for rapid and complete restoration: 0.3–0.7 g NaCl per liter of water. When rapid rehydration is the primary goal during the postexercise period, a better choice may be found in a number of specially concentrated solutions (e.g., Endurox R4, Powerbar Recovery, HEED, etc.). Perhaps also worthy of consideration are the clinical oral rehydration fluids (used to treat diarrhea and dehydration), although a potential drawback of these more concentrated saline solutions is an unpalatable taste, which could affect the total volume consumed. It is also possible to achieve the recommended sodium intake by consuming water with food. Because food consumption slows gastric emptying, the rehydration process is similarly slowed.

In summary, complete and rapid postexercise rehydration requires a special fluid intake plan. Consumption of 150 % of fluid losses allows complete fluid restoration. To enhance the process, a supply of palatable drinks should be made available after exercise. Flavored and lightly sweetened drinks are generally preferred and can contribute to achieving carbohydrate intake needs as well. The main drawback of commercial (nonclinical) rehydration beverages lies in their relatively low sodium content. As previously noted, replacement of sodium lost in sweat is important for maximizing retention of ingested fluids. A sodium content equivalent to 0.3–0.7 g NaCl per liter water may be necessary for optimal rehydration.

12.4.2 Carbohydrate–Electrolyte Solutions

With the rise in consumption of carbohydrate-containing sports drinks has come increased scrutiny of their value to the exercising athlete. In particular, there were concerns regarding the potential for slowing the gastric emptying time. However, subsequent studies have demonstrated that dilute (6–8 %) solutions of glucose, glucose polymers (maltodextrin), and other simple sugars all have suitable gastric emptying characteristics for the delivery of fluid and moderate amounts of carbohydrate substrate [14]. As previously noted, most widely available sports drinks provide a low level of sodium (0.3–0.7 g NaCl per liter of water) and thus may not be the

ideal rehydration beverage (depending on the athlete's needs) despite their carbohydrate value and palatability.

12.4.3 Glycerol

Glycerol (also called glycerine) is a three-carbon molecule that forms the structural backbone of triglycerides and phospholipids. It is technically a sugar alcohol, but it can be converted to glucose in the liver without a major change in plasma glucose or insulin levels. Because of this conversion, the direct energy yield of glycerol is similar to that of glucose, although it is not a major energy source when carbohydrates are freely available. Glycerol is a common ingredient in many nutritional bar products.

Glycerol has a somewhat unique physiological role in terms of its ability to influence water balance. When glycerol is added to rehydration beverages, it blunts the natural decrease in antidiuretic hormone (ADH) release that occurs with rehydration. Sustained ADH activity results in greater retention of body fluids and, potentially, enhancement of postexercise rehydration and thermoregulation during exercise in hot, humid environments [15]. This property has not gone unnoticed clinically, and glycerol is commonly utilized in patients with glaucoma to reduce intraocular pressure.

The use of glycerol in postexercise rehydration supplements has demonstrated improved short-term hydration but not reliable improvement in athletic performance [15–17]. However, the dosage of glycerol is perhaps important, as some studies that utilized lowered amounts (0.5 g/kg versus ~1.0 g/kg body weight) did not improve rehydration [18].

In summary, the potential for glycerol-enhanced rehydration is best attempted at a dosage of 1 g/kg body weight with adequate water ingestion as described in the previous section. It is considered a safe, effective supplement, and it has not been shown to elicit negative effects with regard to postexercise recovery or subsequent exercise performance [19].

12.4.4 Fluid Balance in American Football Players

12.4.4.1 David Chorba

American football players face some unique challenges regarding thermoregulation during preseason training, particularly linemen with relatively high body mass compared to that of other athletes. A small body surface area/body mass ratio and above-average body fat percentage increase the metabolic load of exercise. These athletes are less able to dissipate heat, which is magnified by wearing up to 15 lb. of protective gear.

Sweating rates are similar for football athletes and cross-country runners exercising in the same environmental conditions when adjusted for body size. However, longer practice durations, two-a-day preseason sessions, and insulating equipment create a higher overall sweat production in football players (>2 l/h and in some athletes >3 l/h) [12]. Daily fluid losses from sweating during two-a-day practices can average more than 9 l/day, with some athletes losing more than 14 l/day [12]. This amount of fluid loss requires 125–150 % replacement (during and after practice) to account for urine losses that occur with fluid ingestion [20]. Such a large fluid intake can cause mild symptoms associated with hyponatremia (although rare in football) if too much plain water is ingested and dietary sodium intake is inadequate during preseason meals.

With such large fluid losses through sweating, the electrolyte balance must be considered in football athletes. Sodium losses from sweating range from 20 to 80 mmol/l [21] and have been documented up to 110 mmol/l in professional football players [22]. Normally, sodium and chloride are reabsorbed by sweat glands after excretion. However, this ability does not increase proportionately with the sweating rate, and the electrolyte concentration in sweat increases [23, 24]. A day's sweat loss of 9.4 l with a sodium concentration of 50 mmol/l equates to >10 g of sodium depletion [12]. Significant sodium depletion can occur with excessive sweating, especially in individuals with poor aerobic conditioning

and/or suboptimal heat acclimatization. Some football athletes are prone to large, acute sodium losses during sweating (5.1 g vs. 2.2 g during a 2.5-h practice) and despite consuming sodium-containing fluids on the field are more likely to experience associated heat cramps [25]. These athletes may benefit from ingesting fluids with sodium in addition to making sure they consume sufficient dietary sodium (1.5 g day) [26] during meals.

Despite a significantly larger body mass and heat-trapping protective gear, collegiate football athletes during summer preseason two-a-day practices do not experience the continuous core temperature increases seen in distance runners training in the same environment [27]. Frequent breaks (averaging 71 s, documented for football athletes) cause core temperature fluctuations that may provide the necessary recovery time to dissipate heat. Despite a more intermittent nature of training, however, football athletes were found to be less well hydrated than their endurance-training counterparts. Distance runners may hydrate more frequently throughout the day in preparation for long runs without access to fluids; however, the intermittent nature of football practice should leave adequate opportunity for players to rehydrate.

It is imperative that football athletes properly acclimate to the environment and physical stresses imposed by intense preseason training in order to decrease the risk of adverse health events such as heat exhaustion and heat stroke. Acclimatization requires progressive adaptations to the environment, the physical training, and the protective equipment worn by the athlete. In an effort to decrease the risk of heat-related injury, the National Collegiate Athletic Association (NCAA) has implemented a heat-acclimatization protocol during preseason training [28]. The protocol requires that protective equipment during practice begins with helmets only and progressively increases to full pads. In this way, exercise intensity is also progressed, as more demanding activities usually require additional protective gear. In addition, exercise duration is progressed to two-a-day practices performed on alternate days, with at least 3 h of recovery time between sessions. The new NCAA model has been shown to improve exercise-heat tolerance and heat acclimatization in Division I football players [29]. An added benefit of proper heat acclimatization is the improved ability to reabsorb sodium and chloride, resulting in a 50 % lower sweat sodium concentration for a given sweating rate [23].

Fluid losses greater than 2 % of body weight have been shown to impair cognitive/mental function and athletic (aerobic) performance in temperate to hot conditions [30–32], and losses greater than 3 % increase the risk of heat-related illness [8, 32]. Most individuals replace only half of the fluids lost during exercise voluntarily [33]. Therefore, it is important that all athletes engaging in prolonged exercise in the heat are assessed for hydration status and follow a water replacement schedule. Individual hydration protocols should be developed that consider the athlete's sweat rate, sport dynamics, environmental factors, acclimatization state, exercise duration and intensity, and individual preferences [8, 32]. The American College of Sports Medicine and the National Athletic Trainers' Association provide guidelines to assist in designing customized fluid replacement programs [8, 32].

A simple, effective method to assess hydration status involves tracking body weight before and after practices. An athlete should be weighed first thing in the morning after voiding for 3 days consecutively (more days for women due to menstrual cycle changes) to establish the baseline, euhydrated (normal) state [32]. General recommendations to ensure appropriate hydration from the National Athletic Trainers' Association [8] include consuming 17–20 oz. of water or a sports drink 2–3 h before exercising and 7–10 oz. 20 min prior to exercise. Fluid replacement during exercise should attempt to match sweat and urine losses, with no more than 2 % total body weight loss. This generally equates to 7–10 oz. every 10–20 min of exercise but is highly dependent on the individual athlete, as described above. After exercise, athletes should be weighed (after urination) and then consume 450 ml (15 oz.) for 125–150 % of body weight loss in pounds, ideally within 2 h after exercise. The addition of 0.3–0.7 g NaCl/l is acceptable to stimulate thirst and increase voluntary fluid intake for shorter sessions; it should also be considered during

initial training days in hot weather, during exercise lasting more than 4 h, and when inadequate access to meals is anticipated. For intense sessions or those lasting more than 45–60 min, consuming a sports drink containing 6–8 % carbohydrate can speed replenishment of glycogen stores and delay fatigue, as well as contribute to the palatability of the beverage.

12.4.5 Exercise-Associated Hyponatremia

12.4.5.1 Rita Chorba

At the South African Ironman Triathlon, an experienced 34-year-old male ultramarathoner completing the race in just under 12.5 h was brought to the medical tent near the finish line with mild confusion, sleepiness, and difficulty concentrating and maintaining conversation [34]. His hands and face were swollen, and he complained of feeling ill. Testing revealed an absolute weight *gain* during the race of 3.8 kg (8.4 lb.), which, after consideration of fuel oxidation and fluid release during the race, approximates at least 5 kg (11 lb.) excess fluid. Blood analysis revealed a serum [Na^+] of 127 mmol/l, which was decreased from a before-race value of 143 mmol/l. The athlete was subsequently diagnosed with exercise-associated hyponatremia (EAH).

Despite medical management including sodium replacement, the athlete had initial difficulty producing enough urine to decrease the fluid overload and required overnight hospitalization until his serum [Na^+] normalized and he had excreted 4.6 l of urine. Only then was the athlete permitted to resume drinking fluids. It was later discovered that the athlete had ingested 750 ml fluid per hour during the cycling component (more than 6 h in duration), 750 ml early in the run, and then "as much as possible" throughout the remainder of the run, as he thought his ill feelings were signaling dehydration. This amount of fluid ingestion was contradictory to the briefing given to all athletes before the race, where it was recommended that no more than 500–800 ml/h be ingested during the race. In fact, these new recommendations resulted in only this one athlete being treated for hyponatremia in the South African Ironman (0.2 % of entrants), compared to previous races exhibiting rates of 18 and 27 % [2, 3] Studies of Ironman athletes have revealed an inverse relation between post-race body mass and [Na^+], as those who lost less weight during competition (or gained weight) had the lower plasma [Na^+] [34–36].

Commonly known as water intoxication, EAH is a dilutional hyponatremia caused by consuming too much plain water during periods of prolonged exercise [4]. Although drinking excessive fluids normally stimulates urine production, this mechanism is impaired during sustained endurance exercise, increasing the potential for hyponatremia [37, 38]. EAH can occur when excessive ADH is released, causing fluid retention and maintaining decreased serum [Na^+] with subsequent cell edema. Although symptomatic EAH was previously described in terms of sodium loss, more recent studies confirm significant fluid overload as the primary independent factor, with sodium loss playing a secondary role in the pathogenesis of the condition [34, 37, 39, 40].

Sodium loss through sweating combined with dilution of extracellular sodium due to excessive ingestion of hypotonic fluids (plain water) causes serum sodium concentrations to fall, as sodium is drawn into the unabsorbed water in the intestines. Whereas moderate loss or dilution (serum sodium < 135 mEq/l) can lead to headaches, confusion, nausea, and muscle cramps, concentrations below 125–130 mEq/l can create more life-threatening situations [41–43].

Severely decreased serum sodium concentration creates a significant osmotic imbalance, causing water to rush into brain and lung cells. The subsequent swelling may cause seizures, coma, pulmonary edema, or death. A number of factors lead to EAH [37].

Athlete related	Event related
Low body mass index	Prolonged exercise (>4 h of activity)
Female gender	Extreme cold conditions
Slow performance pace, poor conditioning	Unusually hot conditions

(continued)

(continued)

Athlete related	Event related
Race inexperience	High availability of drinking fluids (frequent aid stations)
Excessive fluid intake behaviors	
Weight gain during the event	
Altered renal excretory capacity (use of NSAIDs or diuretics, renal disease)	

Although continuous, high-intensity exercise for more than 1 h can deplete fluid and sodium levels, athletes at risk for hyponatremia most commonly include ultramarathoners and triathletes, as well as marathoners who take more than 4 h to complete the race [44].

Previous recommendations for the prevention of EAH included drinking ad libitum (according to thirst) no more than 400–600 ml/h (13–20 oz.), the lower limit for slower, lighter persons in cool weather, and the upper limit for faster, heavier athletes in warm weather [37, 45]. As stated previously, similar guidelines were employed in an Ironman Triathlon of significantly longer duration with a dramatically decreased incidence of hyponatremia [34]. That said, we do not promote strict adherence to the above fluid quantities as it is well known that athletes demonstrate a substantial interindividual variation in sweat rates and renal excretory capacity during exercise. The best approach is for athletes to drink according to their thirst levels before, during, and after exercise. In addition, athletes should closely monitor their body weight during exercise, expect a ~2 % decrease under certain conditions, and never *gain* weight (due to fluid ingestion) during exercise. While not foolproof, having a drinking schedule prepared for various competitive situations (that have been tested in practice conditions) provides an effective strategy for reducing the incidence and severity of EAH.

Although it seems prudent to recommend increased sodium intake during prolonged exercise, it might not be necessary and might not be effective in decreasing the risk of EAH. Recent guidelines by the Institute of Medicine suggest that the daily adequate intake of Na^+ (1.5 g/day) is appropriate for physically active people, considering that the sodium intake in a Western diet averages 2.3–4.7 g/day [26]. In another investigation, during the South African Ironman Triathlon [46], ingestion of an additional 3.6 g of sodium (15 tablets, equal to 9 l of Gatorade) during competition along with usual sports drinks and food was not necessary to preserve serum [Na^+] despite more than 12 h of high-intensity activity, nor did supplementation affect any other performance, physiological, or psychological variables collected. The one exception was the athlete with hyponatremia described previously [34] who was part of the placebo group for the current study [34]. However, he was also the only athlete to demonstrate substantial weight gain during competition from overhydrating. It is postulated that during acute Na^+ loss, contraction of the extracellular volume or Na^+ release from intracellular stores may act to buffer Na^+ loss until it is replenished during a subsequent meal [26]. Consumption of electrolyte-containing sports drinks may be able to decrease the severity of EAH [47], although not all studies have shown that their consumption prevents development of EAH in the presence of overdrinking [48, 49]. This may be due to the fact that most electrolyte-containing sports drinks are hypotonic solutions, containing less than 135 mmol/l sodium, and can therefore contribute to further sodium dilution in the presence of fluid excess (see Fig. 12.1).

In summary, exercise-associated hyponatremia is a condition of decreased serum sodium concentration occurring during or up to 24 h after prolonged endurance exercise and is most often associated with excessive fluid consumption. EAH can lead to serious consequences, including pulmonary and cerebral edema. Persons at greatest risk, including deconditioned or race-inexperienced athletes participating in multi-hour events, are advised to drink according to thirst and to prepare race-day fluid replacement strategies that mirror fluid losses measured under practice conditions.

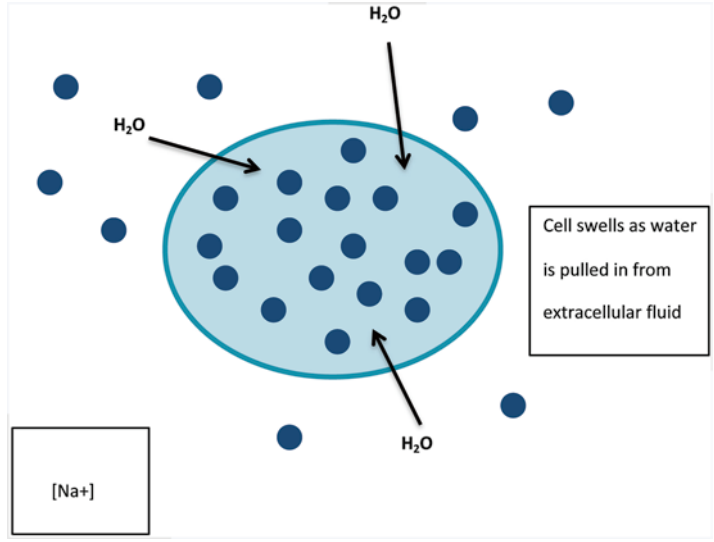

Fig. 12.1 Illustration of sodium dilution due to excess fluid levels

12.4.6 What Are Electrolytes?

Electrolytes are minerals that become ions in solution and acquire the capacity to conduct electricity. Proper electrolyte balance in the body is essential for normal functioning of cells. Loss of body water and subsequent alterations in electrolyte balance can impair cardiovascular and thermoregulatory function. In terms of exercise performance, the most important electrolytes are sodium, chloride, and potassium. Sodium is the primary positive ion (cation) in the extracellular fluid and helps regulate acid–base balance, nerve conduction, blood pressure, and muscle function. Chloride is the primary negative ion (anion) in the extracellular fluid and works in tandem with sodium to regulate nerve impulse conduction and body water balance. During exercise, the body loses fluids and electrolytes (mainly sodium and chloride) via sweat. The resulting decrease in blood volume increases the relative sodium and chloride concentrations in blood and triggers the thirst mechanism. Potassium is the primary cation in intracellular fluid and helps maintain electrical activity in nerves, skeletal muscles, and the heart. Potassium also aids carbohydrate metabolism by enhancing glucose transport and glycogen storage. Finally, calcium and magnesium are cationic electrolytes that play important roles in the regulation of muscle contraction and enzymatic reactions. Because their losses in sweat are minimal, they are usually not included in hydration solutions.

Generally, electrolyte replacement is not needed during short bouts of exercise, as sweat is approximately 99 % water and less than 1 % electrolytes. Adequate water, in combination with a nutrient-dense, well-balanced postexercise diet, can restore normal fluid and electrolyte levels in the body. However, replacing electrolytes may be beneficial during continuous activity of longer than 90 min, particularly in a hot, humid environment. Most research shows there is little evidence of physiological or physical performance differences between consuming a carbohydrate–electrolyte drink versus plain water during exercise lasting less than 1 h [32].

12.5 Muscle Fuel Energy

An important goal of the athlete's everyday diet is to provide the muscle with substrates to fuel the training program and achieve optimal performance, recovery, and long-term adaptation. Carbohydrate and fat constitute most of the exercising muscle's energy fuel, with protein typically playing a minor role. For example, even the leanest

of athletes store enough fat (>100,000 kcal) to fuel exercise, but by comparison the same athlete's carbohydrate stores are limited (~2,500 kcal). It is important to recognize that the initial concentration of stored muscle carbohydrate can dictate performance in a variety of exercises. Therefore, the restoration of muscle energy fuels, particularly carbohydrate, is a principal concern for optimal recovery and subsequent exercise performance.

12.5.1 Carbohydrate

Skeletal muscle stores the simple carbohydrate glucose in highly branched glycogen granules. Stored glucose is then released during muscle contraction for both anaerobic and aerobic energy productions. Approximately 500 g of carbohydrate is stored in the muscle of an average-sized male with an additional 100 g stored in the liver and available for release into the blood. Muscle glycogen is an essential fuel source for sustained moderate- to high-intensity aerobic and anaerobic exercise metabolism [50, 51]. Therefore, replenishment of depleted muscle glycogen levels after strenuous exercise is paramount to complete recovery. Glycogen restoration is of utmost importance for preparation for a subsequent training or competition bout of exercise. Furthermore, failure to restore muscle glycogen between exercise sessions results in compromised training and competition capacity and contributes to symptoms of overtraining [52].

Classic work by Costill et al. found that individuals consuming a high-carbohydrate diet could replenish their postexercise muscle glycogen to normal pre-exercise concentrations within 24 h [53]. These investigators reported that the consumption of 600 g of carbohydrate per day resulted in proportionately greater muscle glycogen restoration during the 24-h period after exercise. However, consumption of more than 600 g provided no additional benefit. When dietary carbohydrate was inadequate (i.e., <150 g in 24 h) during successive days of intense exercise, there was a gradual reduction in muscle glycogen stores and deterioration in performance [52]. Thus, when insufficient carbohydrates are consumed during the 24-h postexercise period, suboptimal glycogen levels result particularly over the course of several successive days of intense training. By applying the appropriate postexercise carbohydrate restoration practices described below, athletes can avoid such a decrement in muscle carbohydrate stores.

12.5.1.1 Glycogen Storage Immediately After Exercise

Recent research has focused on the most effective means of promoting glycogen replenishment during the early hours of exercise recovery. Postexercise synthesis of glycogen occurs in a biphasic fashion, with the initial, rapid phase occurring in the first 30 min and the subsequent, slower phase of resynthesis occurring until muscle glycogen levels are fully restored [54]. Fatigued muscles are highly sensitive to nutrient activation following exercise, with the sensitivity declining over time. Therefore, to maximize the rate of muscle glycogen repletion, an athlete must initiate carbohydrate restoration supplementation immediately after the completion of exercise.

Resynthesis of muscle glycogen is twice as rapid if carbohydrate is consumed immediately after exercise in contrast to waiting several hours [55]. This rapid rate of synthesis can be maintained if carbohydrate is consumed throughout the hours following exercise. For example, supplementing carbohydrate at 2-h intervals at a rate of 1.5 g/kg body weight appears to maximize resynthesis for a period of 4 h after exercise [55]. Carbohydrate provided immediately after exercise can be in the form of solid or liquid provided the glycemic index (GI) is high and the presence of other macronutrients minimized so as not to affect the rate of gastric emptying, intestinal absorption, or glycogen storage [56–58]. Practical considerations, such as the availability and appetite appeal of foods or drinks and gastrointestinal comfort, may determine individual carbohydrate choices and intake patterns. Review of appropriate carbohydrate types is provided later in the chapter. Intriguingly, postexercise muscle glycogen synthesis may be enhanced with the addition

of protein and certain amino acids. Furthermore, the combination of carbohydrate and protein has the added benefit of stimulating amino acid transport, protein synthesis, and muscle tissue repair. Both of these topics are discussed later.

12.5.2 Sustained Postexercise Glycogen Storage

Maehlum et al. [55] and Ivy et al. [55] have demonstrated that the postexercise rate of glycogen storage plateaus at carbohydrate ingestion rates of 1–2 g/kg. Consumption of more than 2 g/kg provides no additional benefit and may result in gastrointestinal distress. Investigators have determined that providing carbohydrate at 1.5 g/kg every 2 h (in either liquid or solid form) after exercise resulted in a near-maximal rate of glycogen resynthesis over the first 4 h of recovery [55, 57]. Other scientists have also reported sustained, rapid resynthesis of muscle glycogen stores from similar rates of carbohydrate intake (i.e., 1.5 g/kg every 2 h), particularly when high-GI carbohydrate foods are consumed [59]. Over a 24-h period, this equates to ingesting carbohydrate at approximately 7–10 g/kg relative to body weight per day. Again, practical considerations, such as the availability and appetite appeal of foods or drinks and gastrointestinal comfort, may determine ideal carbohydrate choices and intake patterns.

12.5.3 Glycogen Supercompensation

Because of the paramount importance of muscle glycogen during intense, prolonged exercise as well as exercise of an anaerobic nature, methods for maximizing initial, pre-exercise levels and replenishing the glycogen stores on a day-to-day basis have been studied extensively [50, 60]. The provision of adequate carbohydrate during the recovery process can result in "supercompensation" of muscle glycogen storage. In other words, more glycogen can be stored than prior to the previous exercise bout. Postexercise carbohydrate feeding promotes glycogen supercompensation by increasing blood concentrations of glucose and insulin. Insulin promotes muscle carbohydrate storage by increasing blood flow through the muscle and by regulating the synthesis of glycogen in the muscle. Specifically, insulin regulates the synthesis of glycogen in two steps: first, by increasing the transport and uptake of glucose into muscle cells and, second, by increasing the intramuscular enzymes involved in glycogen synthesis and decreasing the enzymes involved in degradation [61]. Exercise is important in this process as muscle contraction results in an increase in insulin stimulation of glucose transport into the muscle cell [62, 63] and indirectly enhances insulin-mediated activation of key enzymes of the glycogen synthesis pathway [64].

Bergstrom and Hultman [65] first observed that glycogen synthesis occurred most rapidly in muscle depleted of its related glycogen stores. They also found that consumption of a high-carbohydrate diet for 3 days would elevate the glycogen concentration of the muscle above normal and that this phenomenon was observed only in the muscle that was previously glycogen depleted by exercise. Later, Sherman and colleagues provided findings for a modified glycogen supercompensation regimen in which a 5-day workout taper was accompanied by a moderate (50 % of caloric intake) dietary carbohydrate intake for the first three taper days followed by 3 days of higher carbohydrate intake (i.e., 70 % caloric intake) [66]. In a follow-up study, these investigators determined that pre-exercise muscle glycogen levels could be maintained at high levels despite daily training if carbohydrate was consumed at a rate of 10 g/kg/day. More recently, Bussau and associates described a 1-day glycogen supercompensation regimen [67].

12.5.3.1 Differences Between Simple Carbohydrates

Fructose, sucrose, and glucose are common dietary carbohydrates. However, the physiological responses to the consumption of these "simple" sugars differ considerably. For example, the rise in blood glucose and insulin following ingestion of fructose is significantly lower than that following ingestion of glucose [59]. This is due to the

necessary conversion of fructose to the more readily utilized glucose by the liver. Researchers have demonstrated that ingestion of glucose and high-GI carbohydrate are twice as effective for restoring muscle glycogen [59, 68]. Blom and colleagues suggested that the differences between the glucose and fructose supplements were due to the ways the body handles these sugars [59]. Fructose metabolism takes place predominantly in the liver, whereas most glucose appears to bypass the liver to be stored or oxidized by the muscle [51]. Thus, carbohydrate supplement products containing glucose (dextrose) or glucose polymers are more effective for restoring muscle glycogen after exercise than supplements composed predominantly of fructose. Many postexercise supplement drinks contain glucose or glucose polymers, and, despite its name, the common food sweetener high-fructose corn syrup (HFCS) contains a significant percentage of glucose (~50 %).

12.5.4 Protein

Recent research demonstrates that ideal postexercise meals/beverages should contain both carbohydrate and protein. This combination promotes an accelerated rate of muscle glycogen storage possibly by activating the glycogen synthesis pathway by two mechanisms [69, 70]. First, it raises the plasma insulin level beyond that typical of a carbohydrate supplement, which may augment muscle glucose uptake and activate glycogen synthase, the rate-limiting enzyme for glycogen synthesis. Second, the increase in plasma amino acids that occur as a result of protein consumption may activate glycogen synthase through an insulin-independent pathway, thus having an additive effect on the activity of this enzyme. Continued supplementation at 2-h intervals can maintain an active glycogen recovery for up to 8 h after exercise. The combination of carbohydrate and protein provided immediately after exercise is also ideal for stimulating protein synthesis and tissue repair. This is due to the additive effect of insulin and amino acids on the enzymes controlling amino acid transport, protein translation, and protein degradation. Moreover, research has demonstrated that appropriate nutrient supplementation after exercise can have a significant impact on subsequent physical performance [69].

In summary, general guidelines for postexercise carbohydrate and protein intake are the following: (1) During the first 3 h after exercise, ingest two or three mixed meals providing approximately 400–600 kcal (each). (2) For strength/power athletes, a carbohydrate/protein ratio of 2:1 is recommended. (3) For team sport athletes, a 3:1 ratio is recommended. (4) For endurance athletes, a 4:1 ratio is recommended. (5) Make sure the first postexercise meal includes high-GI carbohydrates (dextrose, maltodextrin) and rapidly digesting protein (whey protein concentrates, hydrolysates). (6) Be sure to provide more energy for larger athletes and/or for higher volumes of training. For endurance athletes engaged in repeated high-volume training, the recommended daily target for carbohydrate consumption of 10–13 g/kg relative to body weight per day is sufficient.

When the period between exercise sessions is short (<12 h), the athlete should begin carbohydrate–protein intake as soon as possible after the first exercise bout to maximize the effective recovery time between sessions. There may be some advantages in meeting carbohydrate–protein intake targets with a series of snacks during the early recovery phase, but during longer recovery periods (1–2 days), the athlete should plan their timing of high-GI, carbohydrate-rich feedings according to what is most practical and comfortable for their individual situation.

12.5.5 Lipids

Athletes rarely ingest dietary fat to improve their performance and recovery, but there are several specialized lipids that may have unique effects on human physiology. Medium-chain triglycerides (MCTs) are fatty acid constituents of coconut and palm kernel oils. They have an important action as energy-providing molecules, in particular for individuals with intestinal

malabsorption syndromes [71]. Indeed, from the medial perspective, MCTs have been shown to be helpful for nutritional support in a number of conditions, including the specialized nutritional need of some infants, the chronically ill, and surgical patients [72–74]. For almost a decade, MCTs have been promoted as useful for weight loss and improving athletic performance. However, to date, most studies have shown that MCTs are ineffective in this regard. For example, researchers have investigated the role of MCTs in the enhancement of long-chain fatty acid oxidation, preservation of muscle glycogen, and the ability to improve overall exercise performance [75–77]. In general, results were unimpressive. More importantly, some studies even reported that exercise performance was impaired in subjects taking high doses of MCTs. This reduction in performance was associated with an increase in gastrointestinal problems, such as intestinal cramping. For these reasons, use of MCTs during the postexercise period cannot be justified at this time.

12.5.5.1 Conjugated Linoleic Acid

Conjugated linoleic acid (CLA) is a group of isomers of the essential fat linoleic acid. CLA is naturally found in a number of animal meats, eggs, and dairy products. CLA has drawn interest in the sports nutrition community because of a reported ability to increase lean body mass and reduce body fat [78–80] and more recently improve immune function [81]. Specifically, Song and associates reported that 12 weeks of supplementation (at 3 g/day) with a 50:50 blend of the *cis*-9, *trans*-11 and *trans*-10, *cis*-12 isomers significantly decreased levels of the pro-inflammatory cytokines tumor necrosis factor-α (TNFα) and interleukin-1β (IL-1β) while simultaneously increasing levels of the anti-inflammatory cytokine IL-10 [81]. Although this study needs to be confirmed by other research studies, it indicates that CLA may be useful for enhancing recovery by limiting exercise-induced inflammation and soreness. It should be noted that although the *trans*-10, *cis*-12 isomer appears to be responsible for the fat-lowering effects of CLA [82, 83], some studies have reported that supplementation with this purified isomer in high doses (i.e., 2.6 g/day) may increase insulin resistance, lower high-density lipoprotein (HDL) cholesterol, and elevate biomarkers of oxidative stress in obese men with metabolic syndrome [84]. In contrast, the aforementioned 50:50 blend of CLA does not appear to have these adverse effects, even after prolonged use (i.e., up to 2 years).

12.5.6 Other Muscle Substrates

12.5.6.1 Creatine

Creatine monohydrate, or methyl guanidine-acetic acid, is presently one of the most popular ergogenic sport supplements. Endogenously, creatine is an amino acid-like compound produced in the liver, kidneys, and pancreas from arginine, glycine, and methionine. Creatine is a nonessential dietary compound that is both endogenously synthesized, primarily in the liver from the amino acids arginine, glycine, and methionine, and naturally ingested through an omnivorous diet by consuming meat, fish, and poultry. However, because of typically having lower total muscle creatine contents, vegetarians possess a greater ability to uptake creatine when compared to their omnivorous counterparts [85]. Endogenously synthesized creatine is released from the liver into the bloodstream and then taken up by muscle fibers predominately by way of a sodium-chloride-dependent creatine transporter (CrT). Creatine ingested through supplementation has been observed to be absorbed into the muscle exclusively by means of CrT [86].

The major rationale of creatine supplementation is to increase the intracellular pool of total creatine (creatine + phosphocreatine). Once taken up into the muscle, approximately 65 % of creatine is phosphorylated by the enzyme creatine kinase to form phosphocreatine (PCr). The remaining 35 % exists in the muscle as free (unphosphorylated) creatine. The intracellular level of phosphocreatine (PCr) plays a significant bioenergetics role during the immediate energy system, typically referred to as the ATP–PCr system, which is predominately active during high-intensity, short-duration, and repeated

bouts of exercise. During this type of exercise, depletion of intracellular PCr stores occur, yet intracellular adenosine triphosphate (ATP) concentration is maintained by a freely reversible reaction, catalyzed by creatine kinase, in which PCr phosphorylates adenosine diphosphate (ADP) to replenish ATP stores. This bioenergetic system provides the impetus to increase the duration of high-intensity exercise from only a few seconds to up to 10–15 s. It should be noted, however, that PCr levels within the muscle are almost 3–4 times more abundant than intramuscular ATP stores. Therefore, the PCr supply is sufficient in providing a temporary ATP source until other bioenergetic systems reach maximal rates. Another role that PCr functions is to act as an acid–base buffer to prevent declines in intracellular pH since the creatine kinase reaction utilizes a hydrogen ion. Muscular contraction can be negatively impacted by metabolic acidosis due to marked reductions in intramuscular pH.

Hundreds of clinical trials have been conducted on creatine monohydrate supplementation as a means of enhancing exercise performance. In general, approximately 70 % of the clinical trials have found beneficial effects, particularly during short, repeated bursts of high-intensity activity. The most common creatine supplementation dosing regimen that has indicated an increase in intracellular PCr and performance is 20 g/day (divided into four equal doses each day) for 5–7 days and is usually followed by a maintenance phase of 5 g/day. While this approach seems more appropriate for someone who is using creatine to prepare for a sporting even 1–3 weeks following initiation of supplementation, for those who intend on supplementing on a daily basis for an extended period, a loading phase is not necessary to achieve positive results [87]. Studies examining pre- vs. postexercise consumption of creatine are in their nascent stages. Consequently, until a general consensus is reached regarding timing of creatine consumption relative to exercise, the authors recommend "bracketing" the exercise session with multiple doses (i.e., ingest 2.5 g pre-exercise and another 2.5 g postexercise).

It should be noted that at least one study has reported that longer-term (e.g., 3–6 months) creatine supplementation reduced CrT activity and muscle creatine uptake [88]. These findings imply that it would be undesirable to consume high doses of creatine for an extended amount of time. Thus, a 1 month washout period following 1–3 months of supplementation would be prudent to avoid downregulation of the creatine transporters. Furthermore, it would also be advisable to avoid consuming extremely high doses of creatine, as this would likely downregulate the CrT over time. As a result, some experts suggest creatine cycling (i.e., 4 weeks of use followed by a 4-week break) based on the premise that once muscle creatine stores are elevated they can remain so (with performance enhanced) for an additional 4–5 weeks without creatine supplementation.

Another issue worth considering is since creatine uptake will most likely differ in regard to weight and muscle mass, ingesting creatine at an absolute dose may not be best but rather at a relative amount based upon body weight (approximately 0.7 g/kg of body mass) or fat-free mass (approximately 0.1 g/kg of fat-free mass). In light of these dosing strategies, some researchers have found no improvement via supplementation; thus the term nonresponders has been established. Since intracellular creatine rather than PCr levels determine the regulation of creatine uptake and CrT activity [89], it is likely that this variability is due to the regulatory process of the CrT that controls both the influx and efflux of creatine across the muscle cell membrane. Another possibility is that "nonresponders" already have high levels of intramuscular creatine stores. Although responses are quite variable from person to person, the ingestion of creatine typically produces an average 2–5 lb. greater gain in muscle mass and 5–15 % greater increases in muscle strength and power compared to control (or placebo) subjects [90–92].

Efforts have been made to attempt to determine the most effective means to enhance muscle creatine uptake. Because it is also known that the uptake and storage of creatine can be augmented

by up to 60 % when blood levels of insulin are elevated [93], many individuals co-ingest creatine with high-GI carbohydrates (usually dextrose, maltodextrin, or fruit juice). Adding Cr with a carbohydrate source has been observed to enhance uptake, primarily through the effect of an insulin response. Additionally, research has indicated that combining creatine with sodium and/or chloride may additionally enhance Cr uptake via the manipulation of increasing the gradient in which the CrT functions [94]. Finally, it should be noted that no study has ever been published demonstrating greater benefits to strength, lean mass, or performance with creatine salts (e.g., creatine hydrochloride, creatine citrate, creatine pyruvate) compared to creatine monohydrate.

12.5.6.2 D-Ribose

D-Ribose is an organic pentose monosaccharide (five-carbon sugar) found in all living cells. Ribose (β-D-ribofuranose) forms part of the backbone of RNA. Ribose is sometimes referred to as a "genetic sugar" because of its importance in the nucleosides of RNA as well as ATP. All foods have some D-ribose, but certain substances, such as brewers' yeast, are rich in RNA and thus are thought to be good sources of D-ribose. Ribose is related to deoxyribose, which is found in DNA. Phosphorylated derivatives of ribose such as ATP and NADH play central roles in metabolism. The cyclic monophosphates, cAMP and cGMP, formed from ATP and GTP serve as secondary messengers in some signaling pathways. However, there is a mismatch between ATP hydrolysis and synthesis rates that are associated with high-intensity exercise that lead to an overall reduction of total adenine nucleotides [(AdN) = ATP + ADP + AMP] within the myocyte. Once the ATP-derived purine molecule is lost from the muscle cell, recovery of the AdN pool must depend on the de novo synthesis and/or the purine salvage metabolic pathways, and these pathways proceed at relatively slow rates [95]. Studies have shown that repeated days of short-term, high-intensity exercise in humans led to a significant reduction in resting ATP concentration in the previously exercised muscles [96, 97]. Although the pathways for skeletal muscle AdN synthesis proceed slowly, an impactful increase in their rates occurs with ribose supplementation [98]. It has also been shown that ribose supplementation increased adenine salvage rates in resting skeletal muscle and that high-intensity exercise had no diminishing effect on adenine salvage rates in the postexercise recovery period in ribose-supplemented muscle [99].

Current thinking is that ribose supplementation would be an effective ergogenic aid by virtue of its ability to resynthesize ATP and "boost energy" based on the fact that ribose supplementation has been shown effective at increasing AdN synthesis and adenine salvage. Even though a number of studies have been performed attempting to demonstrate the role of ribose as a performance enhancer, overall the data do not support this presumption. For example, single-bout studies providing 3–32 g of D-ribose before exercise did not report improvements in anaerobic exercise capacity or adenine nucleotide breakdown [100, 101]. Also, a study in which 10 g of D-ribose was ingested for five consecutive days indicated no beneficial effect on anaerobic exercise capacity or metabolic markers [102]. A similar study involving 6 days of oral ribose supplementation (4×4 g doses) was shown to have no effect on maximal intermittent exercise performance or postexercise muscle ATP recovery [103]. Thus, although there may be clinical applications of high-dose (~60 g/day) D-ribose in chronic fatigue syndrome and fibromyalgia, at present the use of D-ribose as an ergogenic nutritional supplement cannot be adequately justified.

12.6 Oxidative Stress

Although some oxidative stress is necessary for optimal adaption to exercise training, excessive oxidative stress results in an imbalance between the systemic manifestation of reactive oxygen species and the body's ability to readily detoxify the reactive intermediates or to repair the resulting damage. Disturbances in the normal redox state of cells can cause toxic effects through the production of peroxides and free radicals that

damage all components of the cell, including proteins, lipids, and DNA. Further, some reactive oxidative species act as cellular messengers in redox signaling. Thus, oxidative stress can cause disruptions in normal mechanisms of cellular signaling. In regard to the redox state of cells, oxidation–reduction or "redox" reactions are usually defined as a transfer of electrons from one chemical compound to another. During an oxidation–reduction reaction, one reactant gains one or more electrons from another reactant, which in turn is losing one or more electrons. The process of gaining electrons is called reduction, and the process of losing electrons is called oxidation. The oxidizing agent, or oxidant, is the substance that causes other chemical species to be oxidized while it is reduced. The reducing agent, or reductant, is the substance that causes other chemical species to be reduced while it is oxidized.

In humans, oxidative stress is thought to be involved in the development of a number of diseases involving skeletal muscle including cancer, Parkinson's disease, infection, and chronic fatigue syndrome [104]. Chemically, oxidative stress is associated with increased production of oxidizing species or a significant decrease in the effectiveness of antioxidant defenses, such as glutathione [105]. The effects of oxidative stress depend upon the magnitude of these changes, with a cell being able to overcome small perturbations and regain its original state. Moderate oxidation can trigger apoptosis-mediated cell damage, whereas more severe oxidative stress typically associated with very high-intensity exercise can cause apoptosis-mediated cell death [106].

Production of reactive oxygen species is a particularly destructive aspect of oxidative stress. Such species include free radicals and peroxides. Some of the less reactive of these species (such as superoxide) can be converted by oxidoreduction reactions with transition metals or other redox cycling compounds (including quinones) into more aggressive radical species that can cause extensive cellular damage [107]. Most long-term effects are caused by damage to DNA, which has been implicated in aging and cancer [108].

Oxidative stress in known to occur in response to exercise and seems to play a role in muscle protein breakdown and impaired cellular function in the muscle. As a result, recent attention has been focused attempting to elucidate the link between free-radical formation and muscle damage. Free radicals are continuously formed as a normal consequence of body processes, including exercise. Therefore, attempting to determine a way in which to attenuate exercise-induced oxidative stress may play a beneficial result in enhancing muscle recovery from exercise and subsequent improvements in muscle performance during exercise. A free radical is an atom with one unpaired electron in its outermost shell, making it unstable and highly reactive. A free-radical sequesters an electron from any cellular component it can but typically from the lipid membrane of a cell, initiating a process called *lipid peroxidation*. The most common radical atom is oxygen, and the process whereby this element gains another electron is termed *oxidation*. The resultant cellular damage caused by these processes is known as *oxidative stress*, and the free radicals formed via oxygen are called reactive oxygen species (ROS). The most common ROS include the superoxide anion (O_2), the hydroxyl radical ($OH^{\bullet}$), singlet oxygen ($^1O_2$), and hydrogen peroxide (H_2O_2).

Free radicals damage cell membranes and increase protein breakdown, and they are partially to blame for the local inflammation and soreness associated with the postexercise period [95]. Aerobic metabolism increases oxidative stress due to the increased amount of oxygen processed throughout the exercising muscle cell [109–111]. The generation of free radicals is related to the rate of oxygen consumption in working muscles and therefore increases as the intensity of exercise increases [112, 113]. The body maintains several natural antioxidants whose levels increase with endurance training as an adaptation to the chronic exposure to aerobic metabolism-derived oxidative stress [114]. In addition to the body's natural antioxidants, several dietary sources of antioxidants consisting of vitamin and vitamin-like substances are available to aid recovery from exercise.

12.6.1 Oxidation and Reduction Reactions

Oxidation–reduction or "redox" reactions are usually defined as a transfer of electrons from one chemical species to another. During an oxidation–reduction reaction, one reactant gains one or more electrons from another reactant, which in turn is losing one or more electrons. The process of gaining electrons is called *reduction*, and the process of losing electrons is called *oxidation*. The oxidizing agent, or oxidant, is the substance that causes other chemical species to be oxidized while it is reduced. The reducing agent, or reductant, is the substance that causes other chemical species to be reduced while it is oxidized. Redox reactions are ubiquitous. We can find them in our cell phone batteries, on our cars as rust, and in our bodies during combustion reactions. A common mnemonic for redox reactions is OIL RIG (*o*xidation *i*s *l*oss, *r*eduction *i*s *g*ain).

In biological systems, it is important to recognize that free radicals are powerful oxidizing agents. They are highly reactive chemical species that have an odd number of electrons. These chemicals oxidize other chemicals in an attempt to pair their odd electrons. In these free-radical reactions, the free radicals must gain electrons and therefore be reduced. In the body, the antioxidant enzymes superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) are thought to be our most important lines of defense for destroying free radicals.

SOD first reduces (adds an electron to) the radical superoxide (O_2^-) to form hydrogen peroxide (H_2O_2) and oxygen (O_2).

$$2O_2^- + 2H \rightarrow SOD \rightarrow H_2O_2 + O_2$$

Catalase and GPx then work simultaneously with the protein glutathione to reduce hydrogen peroxide and ultimately produce water (H_2O).

$$2H_2O_2^- - CAT \rightarrow H_2O + O_2$$

$$H_2O_2 + 2\,\text{glutathione} \rightarrow GPx$$
$$\rightarrow \text{oxidized glutathione} + 2H_2O$$

Oxidized glutathione is then reduced by another antioxidant enzyme called glutathione reductase.

12.6.2 Vitamins C and E

The water-soluble vitamin C (also known as ascorbic acid) and the fat-soluble vitamin E are well-known antioxidants that minimize cellular damage from oxidative stress. These vitamins are consumed during exercise but not synthesized in the body, so repetitive exercise training can reduce tissue levels of these highly important vitamins. Vitamins C and E may work in a synergistic fashion providing a greater protective benefit when combined by inhibiting the release of the inflammation-promoting molecule IL-6 from working muscle [115]. Indeed, postexercise supplements containing both antioxidant vitamins have proven effective [116, 117]. However, vitamin E seems to be the more relevant of the two with respect to postexercise applications. Vitamin E protects the cell membrane phospholipids from becoming oxidized from free-radical molecules [118]. This vitamin is especially beneficial for preventing muscle soreness in individuals who undergo a vigorous exercise bout to which they are unaccustomed. In addition to protecting membrane phospholipids, vitamin E has been shown to increase immune cell migration to damaged muscle cells and decrease the number of free radicals produced during a given bout of exercise [119].

Research involving 4 weeks of daily vitamin C (250 mg/day), vitamin E (400 IU/day), and vitamin C + E supplementation in trained female athletes demonstrated a decrease in serum markers of muscle damage in all three groups when compared to placebo [120]. Another study provided vitamins C and E to professional soccer players during their 3-month preseason training period. Results showed that the vitamin C and E supplement significantly lowered markers of lipid peroxidation and muscle damage compared to placebo [121]. Similarly, a study involving oral vitamin C and E supplementation for 35 days in maximal exercising basketball players found that the combined provision of these two antioxidant vitamins resulted in elevated plasma vitamin E levels and improvements in the glutathione antioxidant defense system in erythrocytes [122].

In contrast to the positive postexercise effects of vitamin E, the findings for its counterpart vitamin C are less compelling. Thompson and colleagues investigated the effects of 200 mg vitamin C supplementation following an intense shuttle-running test [123]. These investigators did not observe improved indices of muscle damage, muscle function, or muscle soreness compared to a placebo group. Similar results were reported in a study by Close and colleagues [124]. In this study, supplementation with ascorbic acid after downhill running exercise decreased indices of oxidative muscle damage compared to placebo but did not attenuate delayed-onset muscle soreness. In fact, at least two studies have reported that postexercise vitamin C supplementation may delay the recovery process, especially following prolonged eccentric exercise [123, 125]. Thus, although pre-exercise vitamin C supplementation has been clearly demonstrated to play a protective role in the muscle [126–128], its application to postexercise recovery is less clear.

In terms of supplementation, there are no known adverse effects of increased consumption of either of these antioxidant vitamins at the dosages mentioned earlier [129]. However, a daily intake of more than 400 IU vitamin E, particularly in the *d*α form, is ill-advised [130]. It is important to note that the term "vitamin E" actually describes a family of eight antioxidants, four tocopherols and four tocotrienols, and the effects of the latter two families of vitamin E are largely unstudied at this time.

Although it could be argued that high dosages of certain antioxidants are necessary to observe benefits on exercise recovery, it is important to recognize that at low concentrations ROS have important functional roles in the body (i.e., defense against infectious agents and various cell signaling pathways). Thus, when it comes to antioxidant supplementation, "more is not necessarily better." There is also the pending argument that routinely ingesting antioxidants is detrimental as this practice may actually weaken the body's own endogenous antioxidant defense mechanisms. There are data to support this presumption. For example, a study was performed attempting to show that exercise-induced oxidative stress ameliorates insulin resistance and causes an adaptive response promoting endogenous antioxidant defense capacity in humans. The study involved the combination of vitamin C (1,000 mg/day) and vitamin E (400 IU/day) supplementation for 4 weeks in conjunction with an exercise protocol, and the results demonstrated that the supplementation of the antioxidants vitamins C and E precluded the potential health-promoting effects of exercise [131]. In light of this information, it is not overly conclusive to the overall beneficial effects of antioxidant supplementation in minimizing exercise-induced oxidative stress and subsequently improving muscle performance. Thus, until more research is available, we feel it is prudent to keep doses of antioxidant vitamins low during the peri-exercise period (i.e., immediately pre- and postexercise).

12.6.3 L-Carnitine

L-Carnitine is a quaternary ammonium compound biosynthesized from the amino acids lysine and methionine [132]. L-Carnitine is an amino acid derivative found abundantly in skeletal muscles. L-Carnitine is a substrate for the mitochondrial enzyme, carnitine palmitoyltransferase I (CPT-I), the rate-limiting enzymatic step in fatty acid transports across the mitochondrial membrane for subsequent fat oxidation in skeletal muscle. L-Carnitine seems to also play a role against muscle wasting. Evidence from clinical studies exists that the L-carnitine supplementation causes an improved nitrogen balance either due to increased protein synthesis or reduced protein degradation, an inhibition of apoptosis, and an abrogation of inflammatory processes under pathologic conditions. Furthermore, L-carnitine supplementation has also been shown to prevent oxidative stress and ameliorates mitochondrial function [133].

Although L-carnitine supplementation does not appear to improve body composition, recent studies demonstrate that doses of 1–2 g/day decrease the production of free radicals, reduce tissue damage, and enhance recovery from intense resistance exercise [134–136]. L-Carnitine may have

additional health benefits and appears to be safe during long-term use [137–139]. Of particular interest is the effect of coadministering L-carnitine with other compounds that can improve its uptake into target tissues (e.g., choline, insulinemic carbohydrates, etc.).

12.7 Immune Function

12.7.1 Glutamine

Glutamine is the most abundant amino acid in plasma and skeletal muscle [140] and accounts for more than 60 % of the total intramuscular free amino acid pool [141]. Although produced in the body from branched-chain amino acids (BCAAs), under certain circumstances (e.g., injury, surgery, overtraining), the body may not be able to synthesize sufficient glutamine to match demand. As such, glutamine is considered as a "conditionally essential" amino acid [142]. Glutamine plays a minor role in most cells' energy metabolism and may be important for muscle hypertrophy, but this carbon source seems to be a vital fuel for some cells of the immune system [143]. Typically, glutamine (9 g/day) is released from muscle and is available for lymphocyte and macrophage fuel use [144]. However, after prolonged (>2 h) exhaustive exercise, there is a significant decrease in the circulating plasma glutamine concentration [145, 146]. Exercise-associated suppression of circulating glutamine may remain for many hours upon cessation of exercise [147].

Reactive oxygen species generated during oxidative stress can induce severe damage to biomolecules. To prevent this damage, cells are endowed with both enzymatic and nonenzymatic defenses. One of the most important antioxidant molecules is glutathione. Since glutamine is a precursor of glutathione, its supplementation in the clinical diet can be used to maintain high levels of glutathione and to avoid oxidative stress damage [148]. Glutamine is a multifaceted amino acid used for hepatic urea synthesis, renal ammonia genesis, gluconeogenesis in both liver and kidney, and as a major respiratory fuel for many cells. Decreased glutamine concentrations are found during catabolic stress and are related to susceptibility to infections. Besides, glutamine is not only an important energy source in mitochondria but is also a precursor of the brain neurotransmitter glutamate, which is likewise used for biosynthesis of the cellular antioxidant glutathione. Reactive oxygen species, such as superoxide anions and hydrogen peroxide, function as intracellular second messengers activating, among others, apoptosis, whereas glutamine is an apoptosis suppressor. In fact, it could contribute to block apoptosis induced by exogenous agents or by intracellular stimuli [149].

A single bout of resistance exercise which created muscle damage was not lessened compared to placebo when 240 mg of glutamine was orally ingested immediately after exercise [150]. Although the significance of postexercise glutamine alterations in the intracellular environment of previously exercised muscle has not been determined, the effects on the cells of the immune system are another matter. Because it is now widely accepted that glutamine is utilized at high rates by isolated cells of the immune system such as lymphocytes, macrophages, and neutrophils [151, 152], and considerable demand can be placed on these cells as a result of the elevated stress of exercise, there is concern regarding the possibility of an exercise-associated immunosuppression. For example, it is known that strenuous exercise can decrease plasma glutamine concentrations, which in turn may result in an increased risk of developing infection [145, 153]. Furthermore, it has previously been documented that the depression of glutamine results in a concomitant drop in lymphocyte-activated killer cell activity (LAK) [154]. Although more data regarding this potential phenomenon are needed, it seems possible that even small changes in immune function following daily exercise may be amplified with chronic high-intensity training. As such, an attempt regarding the dietary remediation of glutamine depletion between exercise sessions seems appropriate.

In recent years several studies have investigated the value and safety of glutamine supplementation. For example, one study indicated that glutamine is well tolerated and not associated

with toxicity in healthy subjects at dosages up to 0.9 g/kg of lean body mass per day during 6 weeks of resistance training [154]. This study also reported no benefits vs. placebo with respect to muscle performance (isotonic and isokinetic strength), body composition, or muscle protein degradation (measured via urinary 3-methylhistidine). That said, other investigators have demonstrated decreased rates of postexercise infection following supplementation of 5–12 g of glutamine within the first 2 h after exercise (in conjunction with adequate rehydration) [145]. Thus, although glutamine supplementation probably does not improve exercise performance or training adaptations (i.e., lean mass or body fat), its inclusion in the postexercise period for immune system surveillance/recovery may be warranted under certain conditions.

12.8 Repair of Muscle Damage

Resistance exercise training, in tandem with appropriate nutrition and recovery, leads to significant increases in skeletal muscle mass (hypertrophy). Depending on the training stimulus, muscle hypertrophy typically occurs via increases in muscle protein content, fluid volume, and mitochondrial mass. From a dietary perspective, the changes in muscle protein metabolism are the aspects of growth most readily influenced. Additionally, the body's overall hormonal milieu can also have an impact on the regulation of muscle growth (Table 12.2). Pre- and postexercise nutrient availability play a critical factor in regulating the degree of hypertrophy by promoting and supporting net protein accumulation in previously exercised muscle as well as driving the anabolic hormonal environment to support muscle recovery and growth [155].

With respect to postexercise supplement considerations, it is important to identify the key ingredients for nurturing muscle hypertrophy. Essentially, blood and muscle tissue amino acids are used by the previously exercised muscle for synthesis of proteins that contribute greatly to the strength and size increases observed in resistance-trained muscle. This elaborate synthetic mechanism is supported by energy from carbohydrates, which have the additional role of glycogen resynthesis following exercise. Increased blood levels of carbohydrate and protein can stimulate insulin release from the pancreas. Insulin is important in the process of muscular growth, as this highly anabolic hormone increases skeletal muscle blood flow, promotes glycogen and protein synthesis in previously exercised muscle, and may influence the effectiveness of other anabolic hormones such as testosterone and growth hormone during the recovery process (Table 12.2).

Table 12.2 Major anabolic hormones and putative and established secretagogues

Insulin/insulin signaling
Carbohydrates[a]
Proteins[a]
4-Hydroxyisoleucine[a]
Chromium
α-Lipoic acid
Growth hormone/IGF-1
α-Glycerylphosphorylcholine[a]
L-DOPA[a]
L-Arginine[a]
L-Glutamine
L-Ornithine
Glycine[a]
Ornithine α-ketoglutarate
Mucuna pruriens
Testosterone
Aromatase inhibitors[a]
Eurycoma longifolia[a]
Boron
Fenugreek[a]
Avena sativa
Tribulus terrestris/alatus
D-*Aspartic acid*

IGF-1 insulin-like growth factor-1
[a]Established secretagogues

12.8.1 Protein and Amino Acid Intake

Dietary protein provides the amino acids necessary to rebuild muscle tissue that is damaged during intense, prolonged exercise. The amino acids in dietary protein are subjected to digestion

(hydrolysis) in the stomach and intestine, are subsequently absorbed into the blood, and finally can circulate to the muscle for synthesis of muscle protein. Purified amino acids and larger molecules of protein hydrolysates (i.e., predigested proteins) are both effective in increasing the circulating levels of amino acids available to the muscle [156]. Extensively hydrolyzed proteins containing mostly dipeptides and tripeptides (chains of two and three amino acids, respectively) are absorbed more rapidly than isolated amino acids and much more rapidly than intact (non-hydrolyzed) proteins [157]. Although protein hydrolysate is preferred by many athletes because it results in a faster increase in blood amino acid concentration [158] and it strongly stimulates insulin secretion [159], there are no studies available that attest to its superiority (when compared to intact protein) in stimulating muscle growth in humans.

Several studies have demonstrated the beneficial effects of postexercise protein supplementation [159]. The timing of protein supplementation may also be important. For example, when compared to protein consumption several hours after exercise, protein consumption (10 g) immediately following exercise has been shown to enhance the accumulation of muscle protein [160, 161]. However, because of the enhanced insulin response to supplements containing protein and carbohydrate (also noted above), supplementing with 6 g of essential amino acids and 35 g of carbohydrate after exercise has demonstrated a markedly higher anabolic response when compared to those supplemented on protein alone [162]. This finding is supported by other studies as well [163]. In addition, it has been recently demonstrated that consuming ~20 g of intact protein (or ~9 g of essential amino acids) maximizes muscle protein synthetic rates during the early stages of the postexercise period. However, it should be noted that the majority of these studies have been conducted in untrained subjects and that total energy (and protein) intake throughout the day is probably more important than any single postexercise meal [164].

12.8.2 Leucine and Muscle Protein Synthesis

The branched-chain amino acid leucine appears to be the most important amino acid signal for the stimulation of muscle protein anabolism. Leucine is a potent activator of muscle protein synthesis, and dietary leucine supplements have been used as putative muscle mass builders [165]. Leucine's role in muscle protein synthesis is thought to be related to its ability to increase circulating levels of insulin and to activate a key molecule involved in the regulation of protein synthesis, mTORC1 (mammalian target of rapamycin complex 1), even in the absence of an increase in circulating insulin concentration [166]. Furthermore, studies have indicated that the effects of leucine occur not only through enhancement of protein synthesis but also through suppression of protein breakdown [167]. However, reports observing a stimulatory effect of leucine on human muscle protein synthesis have been inconsistent [168]. For example, a recent study [169] found no improvement in *resting* muscle protein synthesis in adults who consumed a 10 g essential amino acid (EAA) supplement providing added leucine (3.5 g leucine) when compared to a control 10 g EAA supplement (1.8 g leucine). Such data are important because they suggest that an essential amino acid profile consistent with that found in high-quality dietary proteins may be sufficient for the stimulation of muscle protein synthesis in humans at rest. More research is obviously necessary, but at this point in time, most experts recommend that athletes ingest meals containing at least 3 g of leucine during the peri-workout period. Whether slightly lower doses of leucine are adequate during other times of the day is still being examined.

12.8.3 Carbohydrate and Protein Intake

As mentioned previously, consumption of protein/amino acids and carbohydrate immediately before and after individual training sessions may

augment protein synthesis and muscle glycogen resynthesis and reduce protein degradation. The optimal rate for carbohydrate (choose one with a high GI) ingestion immediately after a training session is ~1.2 g/kg/h at 30-min intervals for at least 4 h. However, the effects of repeated supplementation on long-term adaptations to training are currently unclear.

To shed additional light on this issue, Bird and coworkers examined the effects of postexercise, high-GI carbohydrate, and/or essential amino acid supplementation on hormonal and muscular adaptations in untrained young men [170]. Subjects followed the same supervised, resistance-training protocol twice a week for 12 weeks. Following resistance exercise, the subjects consumed a high-GI carbohydrate (CHO), an essential amino acids (6 g), a combined high-GI CHO + essential amino acid (EAA) supplement, or a placebo containing only aspartame and citrus flavoring. The results revealed that CHO + EAA supplementation enhances muscular and hormonal adaptations to a greater extent than either CHOs or EAAs consumed independently. Specifically, CHO + EAA ingestion demonstrated the greatest relative increase in type I muscle fiber cross-sectional area. Changes in type II muscle fibers exhibited a similar trend. More studies are needed to confirm these results and refine nutritional recommendations that optimize postexercise muscle protein kinetics [171, 172].

12.8.4 Glutamine

As previously noted, glutamine may have some important postexercise immune-supporting effects. However, there has been much speculation as to how glutamine might be of benefit to athletes wanting to gain lean muscle mass. The observation that the cells of the gastrointestinal tract require a large supply of glutamine has led to the supposition that glutamine may offer anticatabolic effects and thereby be useful in sparing muscle protein [173]. This position has been bolstered by evidence suggesting that glutamine is a potent agent for enhancing cellular swelling [174]. Such an association could have implications for muscular growth because recent evidence suggests that the state of cellular hydration (i.e., cellular swelling) is an important factor in the control of many important cell functions, including modulation of hormones, oxidative stress, and gene expression. Cell swelling also inhibits protein breakdown (i.e., anti-catabolism) [174].

The mechanisms proposed for improved protein turnover as mediated via glutamine-induced cell swelling are twofold. First, it may influence the function of cyclic AMP, a chemical messenger associated with many cell functions including inhibition of protein synthesis. Second, it may have a direct effect on cell stability [174].

Not all research regarding the potential glutamine-associated effects on muscle building have been encouraging. For example, a recent study investigated the effect of glutamine on strength and lean tissue mass during a 6-week resistance-training program [154]. The study reported that glutamine did not enhance adaptations to the strength-training program. However, the scientists suggested that the lack of any beneficial effect of glutamine in the study might have been attributed to the fact that the resistance-training program may not have been stressful enough. This conclusion tends to be in line with the prevalent, and previously noted, current scientific opinions that indicate glutamine is most likely of use only under conditions of severe stress.

12.9 Conclusion

Recovery supplements can be classified into four overlapping categories based on their mechanism(s) of action: oral rehydration/electrolyte balance, replenishment of energy reserves, restoring redox balance, and stimulation of muscle repair. Because of ongoing clinical trials and continuous advances in new ingredients, this chapter is in no way intended to be an exhaustive review of supplements that can improve recovery from exercise. In addition, as with any dietary supplement, the decision to use a specific supplement regimen is ideally made

with input from a knowledgeable health-care professional, exercise scientist, and/or dietitian (with expertise in sports nutrition).

Based on the current body of research data, it is our contention that the following supplements have the potential to safely enhance recovery from intense exercise: multivitamin–mineral blends (when dietary intake of micronutrients is suboptimal), antioxidant blends (especially in aging athletes and during multiple training sessions within the same day), sports drinks (especially during prolonged exercise in high heat/humidity and/or altitude), certain amino acids (creatine, EAAs, BCAAs, L-carnitine), and perhaps special lipids (CLA, omega-3 fatty acids). Readers are encouraged to study other chapters in this text that cover the potential applications of HMB and β-alanine for their potential benefits during training as well.

12.10 Practical Applications

- Proper recovery from intense exercise begins during the pre-exercise period. The athlete must pay attention to macronutrient and micronutrient needs and, in most circumstances, should avoid training in a dehydrated or glycogen-depleted state.
- In the postexercise period, athletes need to replenish carbohydrate stores based on their daily energy (caloric) requirements. Obviously, these needs can vary substantially, but a general recommendation is to consume 0.5–1.0 g of carbohydrates per kg body mass. Athletes training/competing in endurance events require more carbohydrates than those engaged in resistance training.
- Depending on age and training experience, athletes should consume 20–40 g of protein in the immediate postexercise period and every 3–5 h thereafter for the next 24 h. Food combinations, chocolate milk, and various dietary supplements can all meet these needs.
- Most athletes can benefit from daily supplementation with 3–5 g with creatine monohydrate. This includes endurance athletes, since co-ingestion of creatine with carbohydrates can enhance glycogen loading.
- Strong preliminary evidence suggests that supplementation with L-carnitine (1–2 g/day) may enhance recovery from acute bouts of intense resistance exercise.
- Although speculative at this time, CLA and omega-3 fatty acids have strong theoretical bases for enhancing recovery during prolonged training.

References

1. Montain SJ, Coyle EF. Influence of graded dehydration on hyperthermia and cardiovascular drift during exercise. J Appl Physiol. 1992;73:1340–50.
2. Nose H, Morimoto T, Ogura K. Distribution of water losses among fluid compartments of tissues under thermal dehydration in the rat. Jpn J Physiol. 1983; 33:1019–29.
3. Costill DL, Sparks KE. Rapid fluid replacement after thermal dehydration. J Appl Physiol. 1973;34: 299–303.
4. Nose H, Mack GW, Shi X, Nader ER. Role of osmolality and plasma volume during rehydration in humans. J Appl Physiol. 1988;65:325–31.
5. Shirreffs SM, Taylor AJ, Leiper JB, Maughan RJ. Post-exercise rehydration in man: effects of volume consumed and sodium content. Med Sci Sports Exerc. 1996;28:1260–71.
6. Meyer F, Bar-Or O. Fluid and electrolyte loss during exercise. Sports Med. 1994;18:4–9.
7. Convertino VA, Armstrong LE, Coyle EF, et al. American College of Sports Medicine position stand: exercise and fluid replacement. Med Sci Sports Exerc. 1996;28:i–vii.
8. Casa DJ, Armstrong LE, Hillman SK, et al. National Athletic Trainers' Association position statement: fluid replacement for athletes. J Athl Train. 2000; 35:212–24.
9. Maughan RJ, Owen JH, Shirrefs SM, Leiper JB. Post-exercise rehydration in man: effects of electrolyte addition to ingested fluids. Eur J Appl Physiol. 1994;69:209–15.
10. Yawata T. Effect of potassium solution on rehydration in rats: comparison with sodium solution and water. Jpn J Physiol. 1990;40:369–81.
11. Maughan RJ. Restoration of water and electrolyte balance after exercise. Int J Sports Med. 1998;(Suppl 2):s136–8.
12. Shirreffs SM, Maughan RJ. Rehydration and recovery of fluid balance after exercise. Exerc Sport Sci Rev. 2000;28:27.

13. Maughan RJ, Leiper JB. Post-exercise rehydration in man: effects of voluntary intake of four different beverages. Med Sci Sports Exerc. 1993;25(Suppl):S2.
14. Vist GE, Maughan RJ. Gastric emptying of ingested solutions in man: effect of beverage glucose concentration. Med Sci Sports Exerc. 1994;26:1269–73.
15. Scheett TP, Webster MJ, Wagoner KD. Effectiveness of glycerol as a rehydrating agent. Int J Sport Nutr Exerc Metab. 2001;11:63–71.
16. Montner P, Stark DM, Riedesel ML, et al. Pre-exercise glycerol hydration improves cycling endurance time. Int J Sports Med. 1996;17:27–33.
17. Magal M, Webster MJ, Sistrunk LE, Whitehead MT, Evans RK, Boyd JC. Comparison of glycerol and water hydration regimens on tennis-related performance. Med Sci Sports Exerc. 2003;35:150–6.
18. Kavouras SA, Armstrong LE, Maresh CM, et al. Rehydration with glycerol: endocrine, cardiovascular, and thermoregulatory responses during exercise in the heat. J Appl Physiol. 2006;100:442–50.
19. Wagner DR. Hyperhydrating with glycerol: implications for athletic performance. J Am Diet Assoc. 1999;99:207–12.
20. Godek SF, Bartolozzi AR, Godek JJ. Sweat rate and fluid turnover in American football players compared with runners in a hot and humid environment. Br J Sports Med. 2005;39:205–11.
21. Shirreffs SM, Maughan RJ. Whole body sweat collection in humans: an improved method with preliminary data on electrolyte content. J Appl Physiol. 1997;82:336–41.
22. Stofan JR, Zachwiega JJ, Horswill CA, et al. Sweat and sodium losses during practice in professional football players: field studies. Med Sci Sports Exerc. 2002;34:S113.
23. Allan JR, Wilson CG. Influence of heat acclimatization on sweat sodium concentration. J Appl Physiol. 1971;30:708–12.
24. Costill DL, Cote R, Miller E, Miller T, Wynder S. Water and electrolyte replacement during repeated days of work in the heat. Aviat Space Environ Med. 1975;46:795–800.
25. Stofan JR, Zachwieja JJ, Horswill CA, Murray R, Anderson SA, Eichner ER. Sweat and sodium losses in NCAA football players: a precursor to heat cramps? Int J Sport Nutr Exerc Metab. 2005;15:641–52.
26. Institute of Medicine of the National Academies. Dietary reference intakes for water, potassium, sodium, chloride, and sulfate. Washington, DC: National Academies Press; 2004.
27. Godek SF, Godek JJ, Bartolozzi A. Thermal responses in football and cross-country athletes during their respective practices in a hot environment. J Athl Train. 2004;39:235–40.
28. NCAA Membership Service Staff. 2005-2006 NCAA division I manual. Indianapolis, IN: The National Collegiate Athletic Association; 2005.
29. Yeargin SW, Casa DJ, Armstrong LE, et al. Heat acclimatization and hydration status of American football players during initial summer workouts. J Strength Cond Res. 2006;20:463–70.
30. Casa DJ, Clarkson PM, Roberts WO. American College of Sports Medicine roundtable on hydration and physical activity: consensus statements. Curr Sports Med Rep. 2005;4:115–27.
31. Cheuvront SN, Carter III R, Montain SJ, Sawka MN. Fluid balance and endurance exercise performance. Curr Sports Med Rep. 2003;2:202–8.
32. Sawka MN, Burke LM, Eichner ER, Maughan RJ, Montain SJ, Stachenfeld NS. American College of Sports Medicine position stand: exercise and fluid replacement. Med Sci Sports Exerc. 2007;39:377–90.
33. Noakes D. Fluid replacement during exercise. Exerc Sport Sci Rev. 1993;21:297.
34. Noakes TD, Sharwood K, Collins M, Perkins DR. The dipsomania of great distance: water intoxication in an Ironman triathlete. Br J Sports Med. 2004;38, E16.
35. Speedy DB, Noakes TD, Rogers IR, et al. Hyponatremia in ultradistance triathletes. Med Sci Sports Exerc. 1999;31:809–15.
36. O'Toole M, Douglas PM, Laird RH, et al. Fluid and electrolyte status in athletes receiving medical care at an ultradistance triathlon. Clin J Sport Med. 1995;5:116–22.
37. Hew-Butler T, Almond C, Ayus JC, et al. Consensus statement of the 1st International Exercise-Associated Hyponatremia Consensus Development Conference, Cape Town, South Africa 2005. Clin J Sport Med. 2005;15:208–13.
38. Zambraski EJ. The renal system. In: Tipton CM, Tate CA, Terjung RL, editors. ACSM's advanced exercise physiology. Philadelphia, PA: Lippincott Williams & Wilkins; 2005. p. 521–32.
39. Garigan TP, Ristedt DE. Death from hyponatremia as a result of acute water intoxication in an Army basic trainee. Mil Med. 1999;164:234–8.
40. Speedy DB, Rogers IR, Noakes TD. Exercise-induced hyponatremia in ultradistance triathletes is caused by inappropriate fluid retention. Clin J Sport Med. 2000;10:272–8.
41. McArdle WD, Katch FI, Katch VL. Exercise physiology: energy, nutrition, and human performance. 6th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2007.
42. Androgue HJ, Madias NE. Hyponatremia. N Engl J Med. 2000;342:1581.
43. Gardner JW. Death by water intoxication. Mil Med. 2002;5:432.
44. Almond CS, Shin AY, Fortescue EB, et al. Hyponatremia among runners in the Boston marathon. N Engl J Med. 2005;352:1550–6.
45. Noakes T. Fluid replacement during marathon running. Clin J Sport Med. 2003;13:309–18.
46. Hew-Butler TD, Sharwood K, Collins M, Speedy D, Noakes T. Sodium supplementation is not required to maintain serum sodium concentrations during an Ironman triathlon. Br J Sports Med. 2006;40:255–9.

47. Twerenbold R, Knechtle B, Kakebeeke TH, et al. Effects of different sodium concentrations in replacement fluids during prolonged exercise in women. Br J Sports Med. 2003;37:300–3.
48. Weschler LB. Exercise-associated hyponatremia: a mathematical review. Sports Med. 2005;35: 899–922.
49. Barr SI, Costill DL, Fink WJ. Fluid replacement during prolonged exercise: effects of water, saline, or no fluid. Med Sci Sports Exerc. 1991;23:811–7.
50. Ahlborg B, Bergstrom J, Ekelund LG, Hultman E. Muscle glycogen and muscle electrolytes during prolonged physical exercise. Acta Physiol Scand. 1967;70:129–42.
51. Bergstrom J, Hultman E. Synthesis of muscle glycogen in man after glucose and fructose infusion. Acta Med Scand. 1967;182:93–107.
52. Costill DL, Bowers R, Branam G, Sparks K. Muscle glycogen utilization during prolonged exercise on successive days. J Appl Physiol. 1971;31:834–8.
53. Costill DL, Sherman WM, Fink WJ, Maresh C, Witten M, Miller JM. The role of dietary carbohydrate in muscle glycogen resynthesis after strenuous running. Am J Clin Nutr. 1981;34:183–6.
54. Maehlum S, Hostmark AT, Hermansen L. Synthesis of muscle glycogen during recovery after prolonged severe exercise in diabetic and non-diabetic subjects. Scand J Clin Lab Invest. 1977;37:309–16.
55. Ivy JL, Katz AL, Cutler CL, Sherman WM, Coyle EF. Muscle glycogen synthesis after exercise: effect of time of carbohydrate ingestion. J Appl Physiol. 1988;64:1480–5.
56. Keizer HA, Kuipers H, van Kranenburg G, Geurten P. Influence of liquid and solid meals on muscle glycogen resynthesis, plasma fuel hormone response, and maximal physical working capacity. Int J Sports Med. 1987;8:99–104.
57. Reed MJ, Brozinick Jr JT, Lee MC, Ivy JL. Muscle glycogen storage postexercise: effect of mode of carbohydrate administration. J Appl Physiol. 1989;66: 720–6.
58. Maehlum S, Hermansen L. Muscle glycogen concentration during recovery after prolonged severe exercise in fasting subjects. Scand J Clin Lab Invest. 1978;38:557–60.
59. Blom PC, Hostmark AT, Vaage O, Kardel KR, Maehlum S. Effect of different post-exercise sugar diets on the rate of muscle glycogen synthesis. Med Sci Sports Exerc. 1987;19:491–6.
60. Bergstrom J, Hermansen L, Hultman E, Saltin B. Diet, muscle glycogen and physical performance. Acta Physiol Scand. 1968;1968:71140–50.
61. Villar-Palasi C, Larner J. Uridinediphosphate glucose pyrophosphorylase from skeletal muscle. Arch Biochem Biophys. 1960;86:61–6.
62. Richter EA, Garetto LP, Goodman MN, Ruderman NB. Enhanced muscle glucose metabolism after exercise: modulation by local factors. Am J Physiol. 1984;246:E476–82.
63. Garetto LP, Richter EA, Goodman MN, Ruderman NB. Enhanced muscle glucose metabolism after exercise: the two phases. Am J Physiol. 1984; 246:E471–5.
64. Nuttal FQ, Mooradian MC, Gannon C, Billington C, Krezowski P. Effect of protein ingestion on the glucose and insulin response to a standardized oral glucose load. Diabetes Care. 1984;7:465–70.
65. Bergstrom J, Hultman E. Muscle glycogen synthesis after exercise: an enhancing factor localized to the muscle cells in man. Nature. 1967;210:309–10.
66. Sherman WM, Doyle JA, Lamb DR, Strauss RH. Dietary carbohydrate, muscle glycogen, and exercise performance during 7 d of training. Am J Clin Nutr. 1993;57:27–31.
67. Bussau VA, Fairchild TJ, Rao A, Steele P, Fournier PA. Carbohydrate loading in human muscle: an improved 1 day protocol. Eur J Appl Physiol. 2002;87:290–5.
68. Burke LM, Collier GR, Hargreaves M. Muscle glycogen storage after prolonged exercise: effect of glycemic index of carbohydrate feedings. J Appl Physiol. 1993;75:1019–23.
69. Williams MB, Raven PB, Fogt DL, Ivy JL. Effects of recovery beverages on glycogen restoration and endurance exercise performance. J Strength Cond Res. 2003;17:12–9.
70. Zawadzki KM, Yaspelkis 3rd BB, Ivy JL. Carbohydrate-protein complex increases the rate of muscle glycogen storage after exercise. J Appl Physiol. 1992;72:1854–9.
71. Wanke CA, Pleskow D, Degirolami PC, et al. A medium chain triglyceride-based diet in patients with HIV and chronic diarrhea reduces diarrhea and malabsorption: a prospective, controlled trial. Nutrition. 1996;12:766–71.
72. Craig GB, Darnell BE, Weinsier RL, et al. Decreased fat and nitrogen losses in patients with AIDS receiving medium-chain-triglyceride-enriched formula vs. those receiving long-chain-triglyceride-containing formula. J Am Diet Assoc. 1997;97:605–11.
73. Fan ST. Review: nutritional support for patients with cirrhosis. Gastroenterol Hepatol. 1997;12:282–6.
74. Jiang ZM, Zhang SY, Wang XR, et al. A comparison of medium-chain and long-chain triglycerides in surgical patients. Ann Surg. 1993;217:175–84.
75. Bach AC, Ingenbleek Y, Frey A. The usefulness of dietary medium-chain triglycerides in body weight control: fact or fancy? J Lipid Res. 1996;37:708–26.
76. Hawley JA, Brouns F, Jeukendrup A. Strategies to enhance fat utilization during exercise. Sports Med. 1998;25:241–57.
77. Jeukendrup AE, Thielen JJ, Wagenmakers AJ, et al. Effect of medium-chain triacylglycerol and carbohydrate ingestion during exercise on substrate utilization and subsequent cycling performance. Am J Clin Nutr. 1998;67:397–404.
78. West DB, Delany JP, Camet PM, et al. Effects of conjugated linoleic acid on body fat and energy

metabolism in the mouse. Am J Physiol. 1998; 275(Pt 2):R667–72.
79. Park Y, Albright KJ, Liu W, et al. Effect of conjugated linoleic acid on body composition in mice. Lipids. 1997;32:853–8.
80. Ostrowski E, Muralitharan M, Cross RF. Dietary conjugated linoleic acids increase lean tissue and decrease fat deposition in growing pigs. J Nutr. 1999;129:2037–42.
81. Song HJ, Grant I, Rotondo D, Mohede I, Sattar N, Heys SD, Wahle KW. Effect of CLA supplementation on immune function in young healthy volunteers. Eur J Clin Nutr. 2005;59:508–17.
82. Gavino VC, Gavino G, Leblanc MJ, Tuchweber B. An isomeric mixture of conjugated linoleic acids but not pure cis-9, trans-11-octadecadienoic acid affects body weight gain and plasma lipids in hamsters. J Nutr. 2000;130:27–9.
83. Pariza MW, Park Y, Cook ME. Mechanisms of action of conjugated linoleic acid: evidence and speculation. Proc Soc Exp Biol Med. 2000;223:8–13.
84. Riserus U, Arner P, Brismar K, Vessby B. Treatment with dietary trans10-cis12 conjugated linoleic acid causes isomer-specific insulin resistance in obese men with the metabolic syndrome. Diabetes Care. 2002;25:1516–21.
85. Watt K, Garnham A, Snow R. Skeletal muscle total creatine content and creatine transporter gene expression in vegetarians prior to and following creatine supplementation. Int J Sport Nutr Exerc Metab. 2004;14:517–31.
86. Persky AM, Brazeau GA, Hochhaus G. Pharmacokinetics of the dietary supplement creatine. Clin Pharmacokinet. 2003;42:557–74.
87. Willoughby D, Rosene J. Effects of oral creatine and resistance training on myosin heavy chain expression. Med Sci Sports Exerc. 2001;33:1674–81.
88. Guerrero-Ontiveros ML, Wallimann T. Creatine supplementation in health and disease. Effects of chronic creatine ingestion in vivo: down-regulation of the expression of creatine transporter isoforms in skeletal muscle. Mol Cell Biochem. 1988;184: 427–37.
89. Murphy R, McConell G, Cameron-Smith D, et al. Creatine transporter protein content, localization, and gene expression in rat skeletal muscle. Am J Physiol Cell Physiol. 2001;280:C415–22.
90. Branch JD. Effect of creatine supplementation on body composition and performance: a meta-analysis. Int J Sport Nutr Exerc Metab. 2003;13:198–226.
91. Kreider RB. Effects of creatine supplementation on performance and training adaptations. Mol Cell Biochem. 2003;244:89–94.
92. Rawson ES, Volek JS. Effects of creatine supplementation and resistance training on muscle strength and weightlifting performance. J Strength Cond Res. 2003;17:822–31.
93. Green A, Hultman E, Macdonald I, Sewell D, Greenhaff P. Carbohydrate ingestion augments skeletal muscle creatine accumulation during creatine supplementation in humans. Am J Physiol. 1996; 271(5 Pt 1):E821–6.
94. Peral MJ, Garcia-Delgado M, Calonge ML, Durán JM, De La Horra MC, Wallimann T, Speer O, Ilundáin A. Human, rat and chicken small intestinal Na+– Cl– -creatine transporter: functional, molecular characterization and localization. J Physiol. 2002; 545(1):133–44.
95. Brault J, Terjung R. Purine salvage to adenine nucleotides in different skeletal muscle fiber types. J Appl Physiol. 2001;91:231–8.
96. Hellsten Y, Sjodin B, Richter E, Bangsbo J. Urate uptake and lowered ATP levels in human skeletal muscle after high-intensity intermittent exercise. Am J Physiol Endocrinol Metab. 1998;274:E600–66.
97. Hellsten-Westing Y, Balsom P, Norman B, Sjodin B. The effect of high-intensity training on purine metabolism in man. Acta Physiol Scand. 1993;149: 405–12.
98. Tullson P, John-Alder H, Hood D, Terjung R. De novo synthesis of adenine nucleotides in different skeletal muscle fiber types. Am J Physiol Cell Physiol. 1988;255:C271–7.
99. Zarzeczny R, Brault J, Abraham K, Hancock C, Terjung R. Influence of ribose on adenine salvage after intense muscle contractions. J Appl Physiol (1985). 2001;91:1775–81.
100. Kerksick C, Rasmussen C, Bowden R, Leutholtz B, Harvey T, Earnest C, Greenwood M, Almada A, Kreider R. Effects of ribose supplementation prior to and during intense exercise on anaerobic capacity and metabolic markers. Int J Sport Nutr Exerc Metab. 2005;15:653–64.
101. Berardi J, Ziegenfuss T. Effects of ribose supplementation of repeated sprint performance in men. J Strength Cond Res. 2003;17:47–52.
102. Kreider R, Melton C, Greenwood M, Rasmussen C, Lundberg J, Earnest C, Almada A. Effects of oral D-ribose supplementation on anaerobic capacity and selected metabolic markers in health males. Int J Sport Nutr Exerc Metab. 2003;13:76–86.
103. Eijnde B, Van Leemputte M, Brouns F, Van Der Vusse G, Labarque V, Ramaekers M, Van Schuylenberg R, Verbessem P, Wijnen H, Hespel P. No effects of oral ribose supplementation on repeated maximal exercise and de novo ATP resynthesis. J Appl Physiol. 2001;91:2275–81.
104. Kennedy G, Spence V, McLaren M, Hill A, Underwood C, Belch J. Oxidative stress levels are raised in chronic fatigue syndrome and are associated with clinical symptoms. Free Radic Biol Med. 2005;9:584–98.
105. Schafer F, Buettner G. Redox environment of the cell as viewed through the redox state of the glutathione disulfide/glutathione couple. Free Radic Biol Med. 2001;30:1191–212.
106. Lennon SV, Martin SJ, Cotter TG. Dose-dependent induction of apoptosis in human tumour cell lines by widely diverging stimuli. Cell Prolif. 1991;24: 203–14.

107. Valko M, Morris H, Cronin M. Metals, toxicity and oxidative stress. Curr Med Chem. 2005;12: 1161–208.
108. Evans M, Cooke M. Factors contributing to the outcome of oxidative damage to nucleic acids. Bioessays. 2004;26:533–42.
109. Alessio HM. Exercise-induced oxidative stress. Med Sci Sports Exerc. 1993;25:218–24.
110. Davies KJ, Quintaniha AT, Brooks GA, Packer L. Free radicals and tissue damage produced by exercise. Biochem Biophys Res Commun. 1982;107:1198–205.
111. Jackson MJ, Edwards RH, Symons MC. Electron spin resonance studies of intact mammalian skeletal muscle. Biochim Biophys Acta. 1985;847:185–90.
112. Novelli GP, Bracciotti G, Falsini S. Spin-trappers and vitamin E prolong endurance to muscle fatigue in mice. Free Radic Biol Med. 1990;8:9–13.
113. Quintanilha AT. Effects of physical exercise and/or vitamin E on tissue oxidative metabolism. Biochem Soc Trans. 1984;12:403–4.
114. Ji LL. Exercise, oxidative stress, and antioxidants. Am J Sports Med. 1996;24(Suppl):S20–4.
115. Fischer CP, Hiscock NJ, Penkowa M, et al. Supplementation with vitamins C and E inhibits the release of interleukin-6 from contracting human skeletal muscle. J Physiol. 2004;558:633–45.
116. Bloomer RJ, Goldfarb AH, McKenzie MJ. Oxidative stress response to aerobic exercise: comparison of antioxidant supplements. Med Sci Sports Exerc. 2006;38:1098–105.
117. Goldfarb AH, Bloomer RJ, McKenzie MJ. Combined antioxidant treatment effects on blood oxidative stress after eccentric exercise. Med Sci Sports Exerc. 2005;37:234–9.
118. Sumida S, Tanaka K, Kitao H, Nakadomo F. Exercise-induced lipid peroxidation and leakage of enzymes before and after vitamin E supplementation. Int J Biochem. 1989;21:835–8.
119. Evans WJ, Cannon JG. The metabolic effects of exercise-induced muscle damage. Exec Sport Sci Rev. 1991;19:99–125.
120. Taghiyar M, Darvishi L, Askari G, Feizi A, Hairi M, Mashhadi N, Ghiasvand R. The effect of vitamin C and E supplementation on muscle damage and oxidative stress in female athletes: a clinical trial. Int J Prev Med. 2013;4:S16–23.
121. Zoppi C, Hohl R, Silva F, Lazarin F, Neto J, Stancanneli M, Macedo D. Vitamin C and E supplementation effects in professional soccer players under regular training. J Int Soc Sports Nutr. 2006;3:37–44.
122. Naziroglu M, Kilinc F, Uguz A, Celik O, Bal R, Butterworth P, Baydar M. Oral vitamin C and E combination modulates blood lipid peroxidation and antioxidant vitamin levels in maximal exercising basketball players. Cell Biochem Funct. 2010;28: 300–5.
123. Thompson D, Williams C, Garcia-Roves P, McGregor SJ, McArdle F, Jackson MJ. Post-exercise vitamin C supplementation and recovery from demanding exercise. Eur J Appl Physiol. 2003;89: 393–400.
124. Close GL, Ashton T, Cable T, et al. Ascorbic acid supplementation does not attenuate post-exercise muscle soreness following muscle-damaging exercise but may delay the recovery process. Br J Nutr. 2006;95:976–81.
125. Childs A, Jacobs C, Kaminski T, Halliwell B, Leeuwenburgh C. Supplementation with vitamin C and N-acetyl-cysteine increases oxidative stress in humans after an acute muscle injury induced by eccentric exercise. Free Radic Biol Med. 2001; 15:745–53.
126. Bryer SC, Goldfarb AH. Effect of high dose vitamin C supplementation on muscle soreness, damage, function, and oxidative stress to eccentric exercise. Int J Sport Nutr Exerc Metab. 2006;16:270–80.
127. Thompson D, Williams C, McGregor SJ, et al. Prolonged vitamin C supplementation and recovery from demanding exercise. Int J Sport Nutr Exerc Metab. 2001;11:466–81.
128. Goldfarb AH, Patrick SW, Bryer S, You T. Vitamin C supplementation affects oxidative-stress blood markers in response to a 30-min run at 75% VO_2max. Int J Sport Nutr Exerc Metab. 2005;15:279–90.
129. Hathcock JN, Azzi A, Blumberg J, et al. Vitamins E and C are safe across a broad range of intakes. Am J Clin Nutr. 2005;81:736–45.
130. Consumers Union. Is E for you? Consum Rep Health. 1996;8:121–4.
131. Ristow M, Zarse K, Oberbach A, Lkoting N, Birringer M, Kiehntopf M, Stumvoll M, Kahn C, Bluher M. Antioxidants prevent health-promoting effects of physical exercise in humans. Proc Natl Acad Sci U S A. 2009;106:8665–70.
132. Steiber A, Kerner J, Hoppel C. Carnitine: a nutritional, biosynthetic, and functional perspective. Mol Aspects Med. 2004;25:455–73.
133. Ringseis R, Keller H, Eder K. Mechanisms underlying the anti-wasting effect of L-carnitine supplementation under pathologic conditions: evidence from experimental and clinical studies. Eur J Nutr. 2013;52:1421–42.
134. Kraemer WJ, Volek JS, French DN, et al. The effects of L-carnitine L-tartrate supplementation on hormonal responses to resistance exercise and recovery. J Strength Cond Res. 2003;7:455–62.
135. Volek JS, Kraemer WJ, Rubin MR, Gomez AL, Ratamess NA, Gaynor P. L-Carnitine L-tartrate supplementation favorably affects markers of recovery from exercise stress. Am J Physiol Endocrinol Metab. 2002;282:E474–82.
136. Spiering BA, Kraemer WJ, Vingren JL, et al. Responses of criterion variables to different supplemental doses of L-carnitine L-tartrate. J Strength Cond Res. 2007;21:259–64.
137. Brass EP, Hiatt WR. The role of carnitine and carnitine supplementation during exercise in man and in individuals with special needs. J Am Coll Nutr. 1998;17:207–15.

138. Kraemer WJ, Volek JS. L-Carnitine supplementation for the athlete: a new perspective. Ann Nutr Metab. 2000;44:88–9.
139. Rubin MR, Volek JS, Gomez AL, et al. Safety measures of L-carnitine L-tartrate supplementation in healthy men. J Strength Cond Res. 2001;15: 486–90.
140. Curi R, Lagranha CJ, Doi SQ, Selliti DF, Procópio J, Pithon-Curi TC, Corless M, Newsholme P. Molecular mechanisms of glutamine action. J Cell Physiol. 2005;204:392–400.
141. Antonio J, Sanders M, Kalman D, Woodgate D, Street C. The effects of high-dose glutamine ingestion on weightlifting performance. J Strength Cond Res. 2002;16:157–60.
142. Newsholme EA, Castell LM. Amino acids, fatigue and immunosuppression in exercise. In: Maughan RJ, editor. Nutrition in sport, IOC encyclopedia of sport. Oxford: Blackwell; 2000. p. 153.
143. Ardawi MSM, Newsholme EA. Metabolism in lymphocytes and its importance in the immune response. Essays Biochem. 1985;21:1–44.
144. Elia M, Wood S, Khan K, Pullicino E. Ketone body metabolism in lean male adults during short-term starvation, with particular reference to forearm muscle metabolism. Clin Sci. 1990;78:579–84.
145. Castell LM, Poortmans JR, Newsholme EA. Does glutamine have a role in reducing infections in athletes? Eur J Appl Physiol Occup Physiol. 1996;73:488–90.
146. Kargotich S, Goodman C, Dawson B, Morton AR, Keast D, Joske DJ. Plasma glutamine responses to high-intensity exercise before and after endurance training. Res Sports Med. 2005;13:287–300.
147. Rennie MJ, Edwards RHT, Krywawych S, et al. Effect of protein turnover in man. Clin Sci (Lond). 1981;61:627–39.
148. Amores-Sanchez M, Medina M. Glutamine, as a precursor of glutathione, and oxidative stress. Mol Genet Metab. 1999;67:100–5.
149. Matés J, Pérez-Gómez C, Núñez de Castro I, Asenjo M, Márquez v. Glutamine and its relationship with intracellular redox status, oxidative stress and cell proliferation/death. Int J Biochem Cell Biol. 2002;34:439–58.
150. Ramallo B, Charro M, Foschini D, Prestes J, Pihon-Curi T, Evangelista A, Lopes C, Galatti L. Acute glutamine supplementation does not affect muscle damage profile after resistance training. Int J Sport Sci. 2013;3:4–9.
151. Castell LM. Glutamine supplementation in vitro and in vivo, in exercise and in immunodepression. Sports Med. 2003;16:323–45.
152. Castell LM, Newsholme EA. The relation between glutamine and the immunodepression observed in exercise. Amino Acids. 2001;20:49–61.
153. Juretic A, Spagnoli GC, Horig H, et al. Glutamine requirements in the generation of lymphokine activated killer cells. Clin Nutr. 1994;13:42–9.
154. Candow DG, Chilibeck PD, Burke DG, Davison KS, Smith-Palmer T. Effect of glutamine supplementation combined with resistance training in young adults. Eur J Appl Physiol. 2001;86:142–9.
155. Fujita S, Rasmussen BB, Cadenas JG, Grady JJ, Volpi E. Effect of insulin on human skeletal muscle protein synthesis is modulated by insulin-induced changes in muscle blood flow and amino acid availability. Am J Physiol Endocrinol Metab. 2006;291: E745–54.
156. Biolo G, Fleming RYD, Wolfe RR. Physiologic hyperinsulinemia stimulates protein synthesis and enhances transport of selected amino acids in human skeletal muscle. J Clin Invest. 1995;95:811–9.
157. Claessens M, Calame W, Siemensma AD, Van Baak MA, Saris WH. The effect of different protein hydrolysate/carbohydrate mixtures on postprandial glucagon and insulin responses in healthy subjects. Eur J Clin Nutr. 2009;63(1):48–56 [Epub 2007 Sep 12].
158. Manders RJ, Wagenmakers AJ, Koopman R, et al. Co-ingestion of a protein hydrolysate and amino acid mixture with carbohydrate improves plasma glucose disposal in patients with type 2 diabetes. Am J Clin Nutr. 2005;82:72–83.
159. Kreider RB, Miriel V, Bertun E. Amino acid supplementation and exercise performance: analysis of the proposed ergogenic value. Sports Med. 1993;16: 190–209.
160. Levenhagen DK, Carr C, Carlson MG, Maron DJ, Borel MJ, Flakoll PJ. Postexercise protein intake enhances whole-body and leg protein accretion in humans. Med Sci Sports Exerc. 2002;34:828837.
161. Levenhagen DK, Gresham JD, Carlson MG, Maron DJ, Borel MJ, Flakoll PJ. Postexercise nutrient intake timing in humans is critical to recovery of leg glucose and protein homeostasis. Am J Physiol Endocrinol Metab. 2001;280:E982–93.
162. Rasmussen BB, Tipton KD, Miller SL, Wolf SE, Wolfe RR. An oral essential acid-carbohydrate supplement enhances muscle protein anabolism after resistance exercise. J Appl Physiol. 2000;88: 386–92.
163. Koopman R, Wagenmakers AJ, Manders RJ, et al. Combined ingestion of protein and free leucine with carbohydrate increases postexercise muscle protein synthesis in vivo in male subjects. Am J Physiol Endocrinol Metab. 2005;288:E645–53.
164. Stephens B, Braun B. Impact of nutrient intake timing on the metabolic response to exercise. Nutr Rev. 2008;66(8):473–6.
165. Dodd KM, Tee AR. Leucine and mTORC1: a complex relationship. Am J Physiol Endocrinol Metab. 2012;302(11):E1329–42.
166. Norton LE, Layman DK. Leucine regulates translation of protein synthesis in skeletal muscle after exercise. J Nutr. 2006;136:533S–7.
167. Dardevet D, Remond D, Peyron MA, Papet I, Savary-Auzeloux I, Mosoni L. Muscle wasting and resistance of muscle anabolism: the "anabolic

threshold concept" for adapted nutritional strategies during sarcopenia. Sci World J. 2012;2012:269531.
168. Pasiakos SM, McClung JP. Supplemental dietary leucine and the skeletal muscle anabolic response to essential amino acids. Nutr Rev. 2011;69(9):550–7.
169. Glynn EL, Fry CS, Drummond MJ, et al. Excess leucine intake enhances muscle anabolic signaling but not net protein anabolism in young men and women. J Nutr. 2010;140:1970–6.
170. Bird SP, Tarpenning KM, Marino FE. Independent and combined effects of liquid carbohydrate/essential amino acid ingestion on hormonal and muscular adaptations following resistance training in untrained men. Eur J Appl Physiol. 2006;97:225–38.
171. Koopman R, Saris WH, Wagenmakers AJ, van Loon LJ. Nutritional interventions to promote post-exercise muscle protein synthesis. Sports Med. 2007;37(10):895–906.
172. Koopman R, Pannemans DL, Jeukendrup AE, et al. Combined ingestion of protein and carbohydrate improves protein balance during ultra-endurance exercise. Am J Physiol Endocrinol Metab. 2004;287:E712–20.
173. Watford M, Wu G. Glutamine metabolism in uricotelic species: variations in skeletal muscle glutamine synthesis, glutaminase, glutamine levels and rates of protein synthesis. Comp Biochem Physiol B Biochem Mol Biol. 2005;140:607–14.
174. Jayakumar AR, Rao KV, Murthy CR, Norenberg MD. Glutamine in the mechanisms of ammonia-induced astrocyte swelling. Neurochem Int. 2006;48:623–8.

Nutrient Timing

13

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Abstract

Nutrient timing is a popular strategy used by athletes, coaches, and researchers to maximize performance and the adaptations resulting from exercise training. Ingestion of key nutrients before, during, and after various forms of exercise has been shown to favorably impact a number of factors that go on to effect health, performance, and recovery. Research in this area is rapidly expanding, and findings are changing on an annual basis. This chapter is broken into sections discussing current recommendations and scientific findings concerning the administration of macronutrients, micronutrients, and other non-nutrients before, during, and after both endurance and resistance exercise. Finally, recommendations are put forth regarding when to employ various strategies, as well as whether certain strategies are worthy of consideration. Key points related to protein timing, caffeine timing, meal patterns, and caloric distribution are all covered in this chapter.

Keywords

Exercise • Nutrition • Timing • Macronutrients • Performance • Micronutrients • Nutrients

13.1 Introduction

The concept of nutrient timing continues to be a popular area of interest for coaches and athletes, as well as a popular area of investigation for researchers. As a strategy to enhance performance and maximize training outcomes, it has evolved into a full-fledged sector of the sports nutrition market with numerous products being released touting various timing advantages. In a unique sense, nutrient timing is entirely based

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upon the application of information. In simplest terms, nutrient timing involves the purposeful ingestion of all types of nutrients at various times throughout the day to favorably impact physiological and metabolic adaptations such as improvements in strength, power, body composition, substrate utilization, or performance. Most notably, these changes are discussed in the context of various forms of athletic performance and exercise training, but it is possible that applications into unique, nonathletic populations and even clinical populations are possible.

Nutrient timing was conceptualized in the 1970s and 1980s with the very first studies examining the impact of increased carbohydrate feedings on glycogen status and exercise performance [1, 2]. Subsequent work explored the impact of carbohydrate timing on glycogen resynthesis [3], and while research involving proteins and amino acids initially lagged behind, the past 20 years have seen scores of publications that begin to explore the potential impact of amino acids and proteins, as well as their timing on adaptations to various types of exercise training [4, 5]. The majority of work completed to date has focused primarily on the macronutrients; however, the nutrient timing category also involves the use of micronutrients as well as "non-nutrients" (e.g., caffeine). Thus, it is imperative for the reader and other investigators to keep in context the inherent differences that exist between timing conversations related to macronutrient, micronutrients, and non-nutrients, particularly until more work is available clearly detailing the potential efficacy of all different types of nutrients. Finally, several papers have been published in obese as well as healthy, active populations examining various manipulations in meal patterns and/or timing for their impact on muscle protein synthesis, weight loss, metabolic alterations, and body composition changes.

13.2 Macronutrient Timing

13.2.1 Carbohydrates

An argument could be made that the entire basis of nutrient timing started with carbohydrates and carbohydrate "loading." Moderate-to-high-intensity activities rely extensively upon carbohydrate metabolism to provide necessary fuel, and as a result, glycogen stores found in the liver and muscle are of high importance. Because typical endogenous stores can readily supply the fuel for activities lasting 60–90 min [6], maintaining adequate carbohydrate intake is an extremely important consideration for a number of athletes. Current dietary recommendations for carbohydrate loading include consuming a diet that provides 8–10 g per kilogram of body mass daily for a period of 3–4 days, assuming no appreciable amounts of muscle damage have occurred [4, 7]. Other common recommendations call for an athlete to consume 55–65 % of their daily caloric intake as carbohydrates, but this strategy comes with a caveat, namely, that the athlete is consuming enough total kilocalories (kcals). It should be noted that much of the recommendations for carbohydrate intake are based on the needs of endurance athletes. Perhaps those involved in strength-power sports need a lower intake of carbohydrate, but more research is required. Nonetheless, a number of reports indicate that athletes are often challenged to consume enough kcals and carbohydrates [7, 8], and as a result, strategies to quickly replenish lost carbohydrate may be warranted, particularly for athletes who need rapid replenishment to maximize their performance.

The practice of carbohydrate "loading" dates to the 1970s with Karlsson and Saltin first reporting that a period of high volume exercise training for 3–4 days followed by a diet providing >70 % carbohydrate, or 8–10 g per kilogram of body weight per day, while sharply reducing training volume facilitated supersaturation of muscle glycogen and an improved pace of training for more prolonged periods of time [2]. A number of more practical modifications to this approach have since been proposed, first by Sherman in a pair of studies [1, 9] and later by Bussau in 2002 [10]. These authors reported that no "glycogen depletion" phase was necessary, and simply reducing training volume for 3–4 days while consuming a very high-carbohydrate diet (8–10 g per kilogram of body mass per day) for 1–3 days was sufficient to maximize muscle glycogen stores. Overall, the ability of carbohydrate loading strategies to rapidly increase

and maximize muscle glycogen levels is currently unquestioned, and a number of athletes and coaches are encouraged to consider making use of such a dietary regimen in the days leading up to a competitive event.

The preexercise phase leading up to a competitive event is an important period for feeding considerations. Overall, carbohydrate feedings undisputedly facilitate increased muscle glycogen levels and help to maintain blood glucose levels, though definitive and consistent reports indicating an improvement in performance are still somewhat lacking. Typically, it is recommended for athletes to consume high-carbohydrate meals, foods, or liquids during this period of time, and this is of increased importance when other recovery efforts (e.g., low-carbohydrate intake, failure to rest or reduce training volume, lack of adequate sleep, etc.) have been neglected. In 1985, Coyle reported that consumption of a high-carbohydrate meal 4 h prior to exercise after an overnight fast significantly increased both muscle and liver glycogen [11]. In addition to increasing stored glycogen, other studies have reported significant improvements in aerobic exercise performance [12–14]. For these reasons, it is commonly recommended to consume snacks or meals high in carbohydrate at dosages ranging from 1 to 4 g of carbohydrate per kilogram of body mass for several hours before exercise [7, 15].

As the preexercise time period shrinks to within 4 h prior to the start of activity, other considerations are needed. In particular, the athlete must be cautious of overwhelming the digestive system with too much food or fluid immediately prior to exercise. Many prolonged endurance races begin early in the morning, and finding the right balance between optimal sleep and food intake is something each athlete should experiment with prior to the day of competition. A certain level of dogma still pervades some recommendations regarding the intake of the correct form of carbohydrate prior to an event. At its source, Foster and colleagues in 1979 first reported a negative, hypoglycemic response to carbohydrate ingestion directly preceding (<60 min) exercise [16]. Since that report, it is commonly indicated that too much carbohydrate consumption in the initial hours before exercise may negatively impact exercise performance. A subsequent review by Hawley and Burke in 1997 examined a number of studies providing some form of carbohydrate at least 60 min prior to beginning a bout of exercise and concluded no negative impact on performance had been established. In fact, many studies reported that performance may actually increase anywhere from 7 to 20 % [17]. A 2013 double-blind, placebo-controlled study by Galloway compared the effects of a placebo to a 6.4 % carbohydrate beverage ingested 30 or 120 min prior to a standardized bout of cycling exercise at 90 % peak power output. The authors reported that when the carbohydrate beverage was consumed 30 min before the exercise bout, exercise capacity was significantly greater than all other times [18].

Once the exercise bout or competition period begins, a number of factors will dictate the extent to which timing should be considered. The majority of research has explored such manipulations in the context of continuous aerobic exercise, and while it is evident that optimal carbohydrate availability can drive performance in nearly all sporting activities, the physiological requirements of the sport or activity will dictate the overall impact of nutrient timing. This is an important point to highlight, as nutrient timing research may have different implications for any number of individual or team sports that regularly have breaks between quarters, halves, or throughout the course of play that can allow for short, discrete periods of feeding. In regard to continuous exercise, a number of studies have provided information indicating that the pattern or timing of carbohydrate feedings may be important. For example, Fielding and investigators in 1985 required cyclists to ingest the same dose of carbohydrate every 30 min or every hour over the course of a 4-h exercise bout. When carbohydrate was ingested more frequently, performance was improved [19].

Two additional studies nicely highlight a number of practical considerations relative to carbohydrate feeding and exercise performance. Febbraio et al. in 2000 required study participants to complete four carbohydrate feedings and exercise conditions in conjunction with a 2-h bout of cycling exercise at 63 % of their peak power [20].

The authors concluded that preexercise carbohydrate ingestion only increased exercise performance when carbohydrate ingestion continued throughout the 2-h exercise bout. Therefore, the findings of this study somewhat prioritized carbohydrate feeding during the exercise bout, as performance was improved in both situations when carbohydrate was delivered during activity. Thus, to some extent, one might argue that if an individual fails to adequately consume carbohydrates prior to the exercise bout, then employing an aggressive feeding strategy throughout exercise may help to offset the potential for performance detriment. Too much consumption of fluid, however, may challenge the storage ability of the stomach resulting in gastrointestinal cramping and discomfort; thus athletes and coaches must experiment with the optimal pattern of consumption. Another study by Widrick and colleagues combined the impact of preexercise muscle glycogen with carbohydrate feeding throughout a prolonged bout of exercise [21]. In this study, participants began a 70-km self-paced time trial with either high or low levels of muscle glycogen. Then, in each respective condition, a carbohydrate or placebo beverage was provided. As one might expect, the greatest power outputs were recorded when exercise was started with high levels of muscle glycogen, and even greater power outputs were reported when carbohydrate was provided regularly throughout the exercise protocol. Similarly, times to exhaustion were greatest when muscle glycogen levels were high and next when carbohydrate was provided throughout the exercise bout. Key take-away messages from these two studies tell us first that preexercise levels of muscle glycogen are very important. Additionally, a preexercise meal doesn't hurt performance, but may only help performance if carbohydrate is provided throughout the exercise bout. Both studies also tell us that if insufficient recovery or poor dietary efforts occur prior to activity, that consuming carbohydrate throughout a bout of exercise will effectively work to maintain and potentially enhance exercise performance, but this is dependent upon the overall state of recovery.

Postexercise ingestion of carbohydrate is a popular nutrient timing strategy intended to facilitate maximal recovery of lost muscle glycogen. In 1998, Ivy published a seminal paper that showed faster and more complete restoration of muscle glycogen over a 4-h postexercise period when the carbohydrate dose was delivered within 30 min of completing the exercise bout versus waiting until 2 h after the activity before consuming an identical amount of carbohydrate [22]. Since that time, other published studies have shown that postexercise timing remains important, primarily when fast glycogen restoration is required, or only an inadequate amount of carbohydrate is available. In this respect, a carbohydrate intake of 0.6–1.0 g of carbohydrate per kilogram of body mass within the first 30 min of completing a glycogen depleting exercise bout and again every 2 h for the next 4–6 h has been shown to adequately replace muscle glycogen stores [23, 24]. Other studies have recommended a similar but more aggressive strategy in which 1.2 g of carbohydrate per kilogram of body mass was ingested every 30 min over a 3.5-h period to maximally replenish lost muscle glycogen [23, 25]. A key pragmatic point underlying these strategies, however, is the need for a rapid restoration of glycogen. From a substrate availability and restoration perspective, studies show that maximal glycogen levels are restored within 24 h if a diet containing 8 g of carbohydrate per kilogram of body weight is provided, and only moderate levels of muscle damage are present [26]. Similarly, Nicholas and investigators reported that a daily carbohydrate intake of 9–10 g of carbohydrate per kilogram of body mass was adequate to replace lost muscle glycogen in athletes completing consecutive days of intense exercise [27]. Certainly, the impact of timing to blunt cortisol production, inflammation, and proteolytic cascades is an attractive supposition, but more research is needed to fully discuss these possibilities.

13.2.2 Carbohydrate and Protein

Consuming a combination of protein and carbohydrate continues to be a popular strategy for both endurance and strength and power athletes. Regarding endurance exercise, there is currently limited research available exploring the provision

of protein or amino acids prior to endurance-style exercise, but research is available examining the impact of carbohydrate and protein combinations throughout such exercise. One study required participants to cycle at 45–75 % VO_{2Max} for 3 h before completing a time-to-exhaustion trial at 85 % VO_{2Max}. A 7.75 % carbohydrate solution or a 7.75 % carbohydrate + 1.94 % protein solution was consumed at regular intervals throughout the exercise bout, and while carbohydrate ingestion improved time to exhaustion, the addition of protein led to significantly improved endurance [28]. Using similar nutritional combinations, Saunders and colleagues had participants complete two separate exhaustive bouts of cycling exercise within a 24-h time period and concluded that when a combination of carbohydrate and protein was consumed, performance was significantly improved and muscle damage was significantly reduced [29]. Additionally, Koopman et al. in 2004 also found that adding protein to carbohydrate resulted in significantly improved protein balance in a 6-h ultra-endurance event [30].

From a postexercise perspective, Ivy and coworkers in 2002 completed a study that required cyclists to complete a 2.5-h bout of cycling before consuming varying combinations of carbohydrate, protein, and fat. The groups were developed to match total energy intake, as well as carbohydrate and fat intake, to effectively determine the impact of providing protein at an approximate 3.5:1 ratio (carbohydrates to protein). From this work, Ivy's research group concluded that the addition of protein facilitated greater restoration of lost muscle glycogen [31, 32]. These findings were later supported by two similar studies published by Berardi [33, 34], who concluded that providing a combination of carbohydrate and protein facilitated greater recovery of muscle glycogen when ingested soon after completion of a workout and prior to a subsequent exercise bout. These results were somewhat refuted by Jentjens and colleagues, who failed to show an improvement in muscle glycogen restoration with a combination of carbohydrate (1.2 g of carbohydrate per kilogram of body mass per hour) and protein (0.4 g of protein per kilogram of body mass per hour) in comparison to providing carbohydrate alone over a 3-h recovery period [24]. These findings involving a combination of carbohydrate and protein at the exact same dosage were later supported by Howarth et al. and extended to illustrate that a greater rate of carbohydrate ingestion (1.6 g of carbohydrate per kilogram of body mass per hour) did not further augment muscle glycogen changes [35]. An important difference between the studies conducted by Jentjens and Howarth and the studies conducted by Ivy and Berardi was that the Jentjens and Howarth studies provided a higher dose of carbohydrates, which was likely the key factor resulting in optimal recovery of muscle glycogen. As it stands, adding protein to carbohydrate has been shown to favorably impact muscle glycogen recovery and maximize the rate of muscle glycogen resynthesis, but this effect may be eliminated when adequate amounts of carbohydrate are provided. If fast recovery of muscle glycogen is truly needed, then the work of Jentjens in 2001 [24] supported some of the fastest rates of glycogen recovery, which involved high amounts of carbohydrates being delivered every 30 min for a 3.5-h time period. In addition, the work of Saunders seems to indicate that the addition of protein to carbohydrate may favorably impact muscle damage [29], but more work is needed to fully explore the impact of carbohydrate and protein combinations on this endpoint, as the 2001 work of Jentjens did not incorporate an assessment of muscle damage. Toward this point, greater rates of postexercise muscle protein synthesis were reported when protein (0.4 g of protein per kilogram of body mass per hour) was added to carbohydrate (1.2 g of carbohydrate per kilogram of body mass per hour), as compared to an identical dose of carbohydrate alone or a larger, isoenergetic dose of carbohydrate (1.6 g of carbohydrate per kilogram of body mass per hour). While not a true question of timing, the coingestion of carbohydrates and protein during the postexercise window remains a popular strategy for athletes, and subsequent review articles have highlighted the fact that ingestion of protein may help to potentiate intramuscular adaptations that can go on to impact changes in performance, such as mitochondrial biogenesis [36, 37]. Whether or not the postexercise strategy of protein ingestion is a determinative factor remains up for

debate, while subsequent sections of this chapter will further discuss considerations related to protein timing.

13.2.3 Protein

When Kevin Tipton and researchers at the University of Texas Medical Branch in Galveston, TX, published a paper suggesting that higher rates of muscle protein synthesis were achieved when a combination of 35 g of carbohydrate and 6 g of essential amino acids was ingested immediately before a single bout of lower body resistance exercise, as compared to ingesting them immediately after the same exercise bout, they blew the proverbial top off the popularity of nutrient timing [38]. Up until that time, the majority of the focus was placed upon the postexercise time period as the most important window for nutrient consumption. Since that time, an entire category of sports nutrition products has evolved, and the formulations have grown to include various combinations of protein, carbohydrates, caffeine, creatine, beta-alanine, and other nutrients. A few years later, a very similar paper was published by Fujita and colleagues, which refuted the initial report by Tipton, and concluded that ingestion of carbohydrates and essential amino acids immediately before or immediately after a single bout of resistance exercise both significantly increased rates of muscle protein synthesis, with no difference between the two time periods [39].

Nonetheless, several examples of well-controlled studies have been published in peer-reviewed journals highlighting changes in resistance training performance after pre-workout ingestion of nutrients. For example, Gonzalez and investigators had eight resistance-trained college-aged men complete a single workout consisting of four sets of no more than ten repetitions using the squat and bench press and concluded that a mixture of caffeine, creatine, beta-alanine, and the branched-chain amino acids (BCAAs) resulted in a significantly greater number of repetitions being completed in addition to increasing average and peak power outputs [40]. Ormbsee and colleagues have recently published two papers from the same study showing that ingesting a pre-workout formulation versus a placebo over a 6-week period of heavy resistance training resulted in significantly greater increases in lean mass, fat-free mass, and peak anaerobic power [41, 42]. Similarly, University of Tampa scientists reported that 8 weeks of supplementing with a combination of BCAAs, creatine, beta-alanine, quercetin, nitrate sources, alanyl-L-glutamine, and B vitamins while completing a whole-body heavy resistance training program significantly improved strength while generating greater improvements in lean mass and muscle thickness [43]. Lastly, a team of investigators supplemented study participants in a pre-workout fashion with a combination of beta-alanine, BCAAs, nitrates, caffeine, choline, and cinnamon extract and concluded that pre-workout supplementation increased reaction time, muscular endurance, and feelings of energy while reducing feelings of fatigue [44]. Exploring another angle, an interesting study by Hackney and colleagues compared the impact of carbohydrate or protein consumption prior to a single bout of resistance exercise in a group of eight healthy, college-aged men and women and reported that preexercise protein ingestion significantly increased resting energy expenditure rates when compared to carbohydrate ingestion [45]. At present, several papers are available that have purposefully delivered single or combined nutrients prior to bouts of resistance training, but limited research is available to allow for a better determination of the comparative impact of disparate nutrients ingested preexercise. Until that research becomes available, and spans several weeks to months of resistance training while providing differential supplementation, the overall impact of this nutrient timing strategy will be poorly understood.

When it comes to ingesting nutrients during resistance exercise, only a limited number of studies are available. Initial research by Greg Haff and a team of colleagues in 2000 had resistance-trained males consume a noncaloric placebo or a carbohydrate solution at a dose of 1 g of carbohydrate per kilogram of body mass before, and every 10 min during, a single bout of resistance exercise. When compared to the placebo group,

muscle glycogen levels were 49 % higher, and an overall higher volume of training was completed when carbohydrate was consumed throughout the exercise bout [46]. A few years later, a research group led by Stephen Bird had 32 untrained, young participants consume a combination of carbohydrate and protein, carbohydrate alone, or a noncaloric placebo during a 6-min bout of resistance training and then compared changes in blood and urine samples. Carbohydrate was provided at a standard dose of 6 % carbohydrate, while added protein consisted of 6 g of the essential amino acids. Cortisol levels increased by 105 % in the placebo group, while increases in the carbohydrate (11 %) and the carbohydrate + protein group (7 %) were significantly reduced. Urinary levels of muscle protein breakdown were decreased by 27 % in the carbohydrate + protein group, with a corresponding 56 % increase in the placebo group [47, 48]. Similarly, significant reductions in whole-body protein breakdown were found when a combination of carbohydrate and protein hydrolysate was ingested during a 2-h bout of resistance exercise. These changes, overall, resulted in a more positive net balance of protein and significantly greater rates (49 % higher) of muscle protein fractional synthetic rates when a combination of carbohydrate + protein was ingested [49]. No studies, to date, have examined the impact of ingesting a combination of carbohydrate + protein during several weeks of resistance training on changes in strength, performance, and body composition, and findings from this type of work will greatly strengthen our understanding of the impact of consuming nutrients throughout resistance training.

Upon fully considering the popularity of nutrient timing, it is surprising to highlight that no published studies are yet available in which researchers have directly examined the impact of ingesting various individual or combined nutrients before, during, or after prolonged resistance training. One exception is a 12-week study published by Esmark and investigators, in which 13 elderly men (average age of 74 years) consumed a small combination of carbohydrates (7 g), proteins (10 g), and fats (3 g) either immediately (within 30 min) or 2 h after bouts of resistance exercise. The authors examined changes in strength, muscle size, etc. and concluded that when nutrients were ingested immediately after the exercise bout, greater changes in strength and muscle cross-sectional area occurred [50]. While interesting and exciting, these overall findings have been questioned due to the lack of typical and expected adaptations that have been shown to occur when a population of elderly individuals resistance train for this period of time.

Without question, a number of studies are available that have examined the impact of providing protein or a combination of protein and carbohydrate after resistance exercise over the course of several weeks of resistance training. Consistently, these studies tell us that providing a 15–40-g dose of a high-quality protein in conjunction with a workout program consisting of heavy resistance training will facilitate improvements in strength, endurance, power, and body composition [51–55]; furthermore, a recent systematic review has been published in support of this thesis [5]. Adding support, a number of studies have published data indicating significant increases in rates of muscle protein synthesis after ingestion of single doses of the essential amino acids alone (typical dosages of 6–12 g) or in combination with carbohydrates. In addition to maximizing muscle protein synthesis, ingestion of essential amino acids at these dosages, whether immediately after or up to 3 h post-workout, has been shown to cause significant improvements in overall muscle protein balance [56–58]. In conclusion, compelling evidence suggests that ingesting essential amino acids with or without carbohydrate immediately 1, 2, or 3 h after exercise all have the potential to maximally stimulate increases in muscle protein synthesis [31, 38, 56, 59, 60].

From a timing perspective, in conjunction with resistance training, no study seemed to better illustrate the potential impact of timing than that published by Cribb [61]. In this investigation, the authors required two groups of males involved in recreational bodybuilding to complete several weeks of resistance training while supplementing with the exact same nutrients. The primary difference between these groups

was that one ingested their nutrients immediately before and immediately after each workout session, while the other study group ingested their nutrients in the morning and evening of each workout day. Independent of how the nutrients were ingested, both groups experienced favorable increases in strength and lean mass. When these groups were compared, however, the group that ingested the provided nutrients at times closely surrounding each training bout experienced significantly greater increases in lean mass, maximal strength, and muscle cross-sectional area [61]. For a few years, these results were strongly considered as evidence that nutrient timing was a favorable strategy to optimize widespread positive adaptations to resistance training. In 2009, Jay Hoffman and his team of investigators published a near-identical study using trained collegiate athletes and reported that no differences in performance or body composition were observed between the group of athletes ingesting protein timed close to each workout and the group of athletes consuming identical nutrients in the morning and evening of training days [62]. A closer analysis of this research highlighted the fact that the study participants in the Hoffman study were already ingesting a level of daily protein that met current protein recommendation for strength and power athletes [63], while the participants in the Cribb study were ingesting less than the recommended amounts. Thus, as it stands and much like with carbohydrate, disparate timing strategies may offer secondary importance to ingesting recommended amounts of protein on a daily basis when considering changes in performance, lean tissue accretion, and body composition.

In summary, a large number of studies have been published documenting positive outcomes associated with the ingestion of single as well as repeated doses of protein surrounding resistance exercise. Recent review articles published by Aragon [64] and Schoenfeld [65] have questioned the popular acceptance of recommendations suggesting that protein timing differentiates positive adaptations to several weeks of resistance training. It should be noted that this is specifically in reference to the "anabolic window" that ostensibly occurs 1 h or less post-workout and doesn't necessarily relate to recommendations made related to protein timing and meal patterns (discussed later in chapter) and other nutrients and non-nutrients. While debate can ensue as to whether or not protein timing is indeed beneficial within this narrow range, the authors make an excellent point in that, similar to what is known about carbohydrate ingestion, when recommended levels of protein are consumed, the impact of timing appears to be at best, minimal, and, at worst, nonexistent. However, when one examines the few studies in which protein intake is matched between the control and treatment groups, the evidence suggests that timing either increases skeletal muscle size or has a neutral effect. Thus, from a purely pragmatic standpoint, it would make sense to utilize a nutrient timing strategy (i.e., the specific post-workout window) rather than dismiss it. In fact, Schoenfeld et al. [65] concluded that "Since causality cannot be directly drawn from our analysis, however, we must acknowledge the possibility that protein timing was in fact responsible for producing a positive effect and that the associated increase in protein intake is merely coincidental." Certainly, the need for more training studies spanning several weeks that utilize sound methodology, matching of protein intake, and double-blind, randomized approaches is present.

13.2.4 Fat

13.2.4.1 Timing of Fat Intake for Health

The prevalence rates of overweight and obese individuals continue to rise, both in the United States and globally. While a multitude of activity, nutrition, genetic, and lifestyle factors contribute to this change, patterns of sleep and eating continue to be explored as contributing factors. In the context of nutrient timing and providing meals with varying fat contents at various points throughout the day, a small handful of studies have examined outcomes in both animals and humans to determine the impact of fat timing on factors related to health, weight loss, body composition, etc. For example, Arble and colleagues

reported that limiting high-fat intake to the period of time when laboratory mice were typically inactive and/or sleeping resulted in significantly greater weight gain than when high-fat meals were given during a time when the mice were typically more active [66]. Bray et al. in 2010 fed laboratory mice either a control diet or a high-fat diet in various patterns intended to simulate scenarios in which high-fat meals were delivered toward the beginning or end of the active period for each animal. These authors concluded that when a high-fat meal was given at the end of the active phase for each animal, versus the beginning, then weight gain, adiposity, and glucose intolerance were all increased in addition to other negative changes in various factors related to cardiometabolic syndrome [67].

From a human perspective, an observational study of 375 male and 492 female study participants had a 7-day food record analyzed for the proportion of energy and macronutrient ingestion over the course of a 24-h period. Specifically related to fat intake, the authors reported that when a higher proportion of fat was ingested in the morning, then less total energy, carbohydrate, and fat were ingested across the day. Conversely, a proportionally high-fat intake in the evening was associated with a high overall rate of caloric intake [68].

13.2.4.2 Timing of Fat Intake for Performance

High-fat diets (typically defined as ≥50 % total energy intake from fat) have been examined a great deal for their potential ability to impact physical performance. The basis of this dietary regimen is grounded on solid rationale, namely, that higher fat intakes will enhance intramuscular triglyceride levels, increase their rate of utilization, and subsequently preserve muscle glycogen [69]. For example, previous studies have reported that eating a high-fat (~65–70 % of energy), low-carbohydrate (<2.5 g/kg/day) diet for 2–4 weeks can markedly increase fat oxidation and reduce utilization of muscle glycogen during the latter stages of a submaximal exercise bout [70, 71]. A number of scientific reviews have reported upon the impact of dietary fat intake and fat loading, leading to a general consensus that short-term and long-term high-fat diets do promote higher fat oxidation, but can, at best, maintain performance and in multiple instances have been shown to actually decrease performance [72]. Other reports have also highlighted that while fat loading may be based on intriguing theory, the lack of performance improvements alongside consistent reports of ergolytic outcomes typically discourages the practice of fat loading [7].

More specifically, several papers have attempted to explore combinations of high-fat diets preceded by short-term periods of carbohydrate loading [73]. Results from these strategies have been mixed, and data from both Burke and Havemann indicate that unfavorable changes in carbohydrate metabolism can result [74]. Additionally, while performance in a 100-km time trial is not impacted, the equally important ability of endurance athletes to complete short periods of high-intensity work can be compromised [75]. An excellent editorial by Burke and Kiens succinctly summarizes this data [73].

Note Table 13.1 for a variety of study design selections regarding viable macronutrient timing options.

13.3 Micronutrient Timing

While much of the academic attention devoted to nutrient timing has centered exclusively on the macronutrients, especially protein and carbohydrates, there is emerging research suggesting that timing may also influence the impact of various micronutrients and non-nutrient dietary compounds. As can be expected, the number of studies available at this point in time is quite low, which only underscores the relative infancy of nutrient timing research, as well as the potential for further investigation in these areas. The next section will discuss the research of micronutrients, followed by a summary of timing considerations involving non-nutrients.

Because certain endurance exercise modalities, particularly cycling, have been associated with a negative effect on bone mineral density, Barry et al. (2011) compared the impact of

Table 13.1 Summary table of selected studies examining timing of macronutrients

Reference	Subjects	Study design	Duration	Nutrient	Outcome/comments
Schoenfeld et al. [65]	• 23 studies ($n=525$) examining strength • 20 studies ($n=478$) examining hypertrophy	Meta-analysis	N/A	Protein	• Strength: no effect • Hypertrophy: total protein intake was strongest predictor • ND between treatment and control for strength or hypertrophy
Weisgarber et al. [114]	• 17 healthy young adults • No RT for 6 weeks prior	Randomized, double-blind, repeated measures, placebo controlled	4 d/wk for 8 w	• Protein (0.3 g/kg WPI w/ 0.15 g/kg essential AAs) • 50 % of total daily dose before and after	• Significant ↑ in muscle mass and some strength measures • ND between groups
Jakubowicz et al. [100]	• 93 obese/overweight women • 45.8 ± 7.1 years • All have metabolic syndrome	Randomized, open-label, parallel-arm design	• 12 weeks • 2 isocaloric diets (~1,400 kcal) • 50 % kcals w/breakfast • 50 % kcals w/dinner	Mixed meals	• Breakfast: ↑ weight loss, ↓ waist circumference, and ↓ blood triglyceride • Daily glucose, insulin, ghrelin, and mean hunger scores were significantly lower in breakfast group • Higher mean satiety scores in the breakfast group
Moore et al. [112]	• 24 male subjects participating in regular high-intensity resistance training • 4–6 x/wk	Randomized grouping	Leg ext (4 × 10 at 80 % 1RM, 3-min rest b/w sets 80-g WPI over 12 h in three patterns: • 8 × 10g/90 min • 4 × 20g/3 h • 2 × 40g/6 h	Whey protein isolate	• ND in net protein balance between groups • Small to moderate effect for 8 × 10g or 4 × 20g
Mamerow et al. [115]	• 8 healthy adult men [5] and women [3] • 36.9 ± 3.1 y • BMI: 25.7 ± 0.8	Randomized 7-d crossover feeding study with a 30-d washout period	• 7-d crossover w/30-d washout • 24-h diet with protein skewed to dinner or evenly distributed	Protein (feeding study)	• 24-h mixed muscle FSR was 25 % ↑ with even distribution of protein • Daily protein intake: ~1.2 g/kg • The animal-to-vegetable protein ratio was ~2:1

Bray et al. [67]	Male wild-type mice	• Randomly assigned to one of four groups • Access to low- or high-fat diets in various diurnal patterns	• 12 weeks • Mice were fed either a high-fat or control diet in a time-of-day-dependent manner	Lipid (dietary)	• Independent of feeding patterns, food intake and energy expenditure were spontaneously adjusted • Altered dietary composition during the active period markedly influences metabolic health
Res et al. 2012 [116]	16 healthy, young, recreationally active men	Randomized, parallel group design	• Single RT bout at 2,000 h • Post-RT recovery meal delivered 30 min before sleep (2,330 h) with 40 g protein or PLA	• Phenylalanine-labeled casein protein	• Protein ingested immediately before sleep is: (1) effectively digested and absorbed, ↑ overnight plasma AA availability, (2) ↑ MPS leading to ↑ net balance
Minor et al. [117]	• Hypocaloric (−15 % kcal): $n=10$ (2 M 8 F; 64 ± 2 y; 23.3 ± 0.8 kg/m^2) • Hypercaloric (+15 % kcal): $n=6$ (2 M 4 F; 65 ± 2 y; 24.6 ± 1.5 kg/m^2)	Each participant completed 2 consecutive, 3-day trials in a randomized crossover design	• 6 days total • Each 3-day trial were reproduced and identical • Immediately after exercise vs. earlier in day	Protein	• Anabolic effect of postexercise feeding was evident during positive energy balance but not negative energy balance
Jordan et al. [118]	• 9 healthy, sedentary adults • 64.5 ± 2.0 y	Each participant completed 2 consecutive, 3-day trials in a randomized crossover design	• 6 days total • Each 3-day trial were reproduced and identical • Immediately after exercise vs. earlier in day	Protein (chocolate milk, 15.3 g protein)	• Older individuals were better able to maintain nitrogen balance by simply changing when a portion of an identical amount of daily protein was consumed
Galloway et al. [18]	• 17 male active team-sports players • 23.6 ± 4.8 years	Randomized, double-blind, crossover design	• 4 trials (cycling at 90 % of PPO) • 7-d crossover ingestion of a 6.4 % GES or PLA 30 or 120 min before exercise	• Glucose-electrolyte solution (6.4 % CHO)	• ↑ in HI ex capacity when 32 g of CHO taken 30 min before exercise (14–17 % increase) vs. 2 h preexercise
Greer et al. [119]	• 9 trained subjects (6 M, 3 W) • 21.4 ± 1.0 year	Randomized, blinded, crossover design	• CHO + PRO vs. PLA before and after downhill run • 7d b/w trials • ~3wks total	72 g carbohydrate +18 g protein (Accelerade®")	• ND in the 1.5-mile time trial or soreness between trials, regardless of timing • No impact of CHO + PRO beverage on next day running performance or soreness vs. placebo

(continued)

Table 13.1 (continued)

Reference	Subjects	Study design	Duration	Nutrient	Outcome/comments
Heesch et al. 120]	• 8 trained male cyclists • 34.5 ± 8.3 years	Randomized, counterbalanced, crossover design	4 separate trials, each with 2-h cycling at 60 % VO_2max then 10-km TT: • No CHO • Early CHO (1st hour) • Late CHO (2nd hour) • CHO throughout ≥3 day washout	• 250 mL of 6 % CHO (early and late conditions) • 3 % CHO every 15 min	• ND in O_2 uptake, HR, RPE, or substrate use between trials ($p > 0.05$) • CHO ingestion throughout or late during a 2-h cycling bout can improve subsequent 10-km time trial performance
Trabelsi et al. [121]	16 male recreational bodybuilders (9 Ramadan fasters and 7 nonfasters)	• Anthropometric measurements • Diet record • Fasting blood and urine • Samples taken before and after Ramadan	• 31days (29-d Ramadan+2d) • 4 d/wk RT; 4–6 exercises, w/ 4 sets at 10RM and 2–3 min b/w sets • Progress to 10RM loads	Mixed ~15 h fasting	• Hypertrophic training through Ramadan had no effect on body mass and body composition of bodybuilders • State of dehydration and reduced renal function were apparent

The interested reader is encouraged to download the Aragon et al. [64] and Schoenfeld et al. [65] articles for additional summary tables that highlight this information

cycling exercise on calcium homeostasis following two different timing strategies for calcium supplementation [76]. Twenty trained male cyclists were asked to perform intense 35-km cycling time trials while consuming a fortified beverage containing one total gram of calcium either 20 min prior to exercise or in equal doses ingested at quarter-hour intervals during the 1-h cycling bout. For each trial, a placebo beverage was provided during the alternate consumption period, and the results were compared against a placebo-only session. These trials were performed in a double-blind, crossover fashion, with at least 48 h between bouts. The authors found that only calcium supplementation prior to exercise was able to significantly diminish ($p = 0.04$) the expected increase in parathyroid hormone provoked by exercise, though a similar trend ($p = 0.07$) was seen for supplementation during exercise. Because parathyroid hormone increases in response to even minor decrements in serum calcium levels, the blunted increases reported by this project indicate an improved maintenance of serum calcium as a result of calcium supplementation, and this effect appears to be at least partially moderated by the timing of supplement consumption [76].

These results were bolstered by another recent project presented at the 2013 Endocrine Society annual meeting in San Francisco, CA, which also looked at the impact of calcium supplement timing on cycling exercise-induced disruptions in calcium homeostasis [77]. This study worked with 52 competitive male cyclists, who were randomly assigned to groups consuming supplements containing 1 g calcium and 1,000 IU vitamin D either 30 min before or 1 h after a strenuous 35-km cycling time trial. These researchers found that the observed decrease in serum ionized calcium postexercise was significantly less for the group receiving supplements prior to exercise, and while parathyroid hormone increased after cycling for both groups, the increase was attenuated by preexercise supplementation [77].

In a similar study performed by Shea et al. (2014), researchers again compared the effects of disparate timing strategies for calcium supplementation on the disruptions to calcium homeostasis caused by endurance exercise [78]. This project carried out two separate double-blinded, crossover experiments using healthy, postmenopausal women aged 50–75 years performing 60 min of treadmill walking at 75–80 % VO_2peak. The first experiment asked ten subjects to consume a calcium-fortified beverage or placebo in equal quantities every 15 min, beginning 1 h prior to exercise and continuing throughout the hour-long bout to deliver a total dose of 1 g of calcium. The second experiment asked a group of 23 subjects to consume an equivalent total measure of calcium or placebo, this time beginning just 15 min prior to exercise and once again continuing throughout the exercise session. This project found that the anticipated increase in parathyroid hormone following exercise was significantly reduced for only those subjects beginning calcium supplementation 60 min before activity. Additionally, all conditions saw a significant decrease in serum ionized calcium except the group receiving supplementation for a full hour prior to exercise [78].

Altogether, these projects provide firm support for a variable influence of calcium supplementation on exercise-induced disruptions to calcium homeostasis, which seems to be largely dependent on the timing of intake relative to exercise. While there is currently a paucity of research examining the influence of micronutrient timing on their subsequent effects, especially in relation to exercise, this is largely because many vitamins and minerals are present in durable stores built up over time throughout the physiological system, so that daily timing of intake seems less pivotal to the overall impact of these nutrients. The results of these projects investigating calcium dynamics help indicate that more research is necessary to provide a solid empirical foundation for that assumption on a nutrient-by-nutrient basis, though not every nutrient is likely to demonstrate a timing-dependent effect.

In a recent animal study conducted by Fujii, Matsuo, and Okamura (2011), the research team used rats with induced iron deficiency to examine the impact of resistance training and postexercise meal timing on iron status and heme synthesis [79]. In light of previous research demonstrating

an increase in heme synthesis following resistance exercise in iron-deficient rats [80], these researchers hypothesized that earlier postexercise feeding may potentiate this effect. Two groups of 4-week-old male rats were then given similar, iron-deficient feed either immediately or 4 h after performing a climbing exercise three times per week over a 3-week period. While plasma iron was significantly elevated after climbing for only the group receiving immediate postexercise feeding, the hematocrit and hemoglobin levels were similar between groups pre- to postexercise [79]. As such, the researchers determined that postexercise meal timing had no effect on the hemoglobin concentration, and this project helps highlight that the complexity of intake timing, nutrient handling, and exercise interactions is such that repeated, comprehensive investigation may be required to tease out the underlying chain of effects.

13.4 Non-nutrient Timing

In addition to micronutrients, the timing component of other dietary constituents or non-nutritive supplements, particularly those intended to provide an ergogenic benefit, is rarely included in nutrient timing considerations. Nonetheless, timing is often a crucial and underexplored component of many supplemental strategies for ergogenic aid. Table 13.2 outlines the study design of the small number of studies examining timing of non-nutrients.

Caffeine is one of the most commonly consumed psychoactive substances in the world and has been widely demonstrated to have ergogenic properties when applied to a variety of exercise modalities [81]. Unlike many other ergogenic supplements, the widespread social consumption of caffeine means that it is often both available

Table 13.2 Summary table of selected studies examining timing of non-nutrients

Reference	Subjects	Study design	Duration	Nutrient	Outcomes/comments
Ryan et al. 2013 [82]	• 8 college-aged (25 ± 5 years) male cyclists • 50 ± 5 ml·kg^{-1}·min^{-1})	A within-subject, repeated measure, placebo-controlled design	• 4 sessions w/in 1 month • 3 sessions with caffeine given a different time point each • 1 PLA trial	Caffeine	• Performance ↑ when gum was given immediately before • ND when offered 1 or 2 h before
Candow et al. [90]	• 22 adults (9 M, 13 F) • 50–64y • No RT for 6 months prior	Randomized, double-blind, repeated measure design	• RT 3 d/wk × 12 wks • CRE (0.1 g/kg) before PLA after • PLA before CRE after	Creatine (0.1 g/kg)	• Both groups ↑ strength and muscle mass • ND between groups
Antonio et al. 2013 [89]	• 19 healthy males • 23.1 ± 2.9 years • 80.2 ± 10.4 kg	• Randomized trial • Ingest 5 g before or after training	~60-min RT 5 d/wk for 4 weeks	5-g/d creatine	• Postexercise group had significantly greater increase in FFM and bench press strength
Siegler et al. [94]	• 8 active and healthy males • 22 ± 2 years • 76.2 ± 9.1 kg	• Randomized (counterbalanced) • Repeated measure design • Subjects ingested 0.3 g·kg^{-1}$NaHCO_3$ at 60, 120, or 180 min before exercise	3 × 10s sprints separated by 50s of active recovery (1:5 work-to-rest) on a nonmotorized treadmill	$NaHCO_3$ (0.3 g·kg^{-1})	• ND b/w groups in blood buffering or ergogenic potential of $NaHCO_3$ • 180-min group reported significantly less GI upset

and acceptable for athletes to use during training and even competition. Despite this pervasive popularity and established ergogenic efficacy, a recent project conducted by Ryan et al. (2013) was one of the first to examine the differential impact on performance ensuing from a range of timing strategies for preexercise caffeine consumption [82]. In a randomized, double-blinded, crossover fashion, these researchers provided eight male cyclists with 300 mg of caffeine in a chewing gum at 2 h, 1 h, or 5 min prior to a standardized warm-up and cycling time trial. This method of administration was chosen largely because it has been demonstrated to provide faster absorption than pill consumption, and a matched placebo was supplied at all other time points. The authors found that a significant improvement in time trial performance was only observed when caffeine was dispensed to athletes immediately prior to exercise [82]. Overall, these results were the first to illustrate the impact of timing of caffeine on cycling performance while also employing an administration method that may offer benefits over capsule or liquid delivery systems.

Outside of the recent work by Ryan, a number of studies using both endurance and resistance exercise have provided varying dosages of caffeine prior to beginning a workout or competition and have reported widespread improvements in performance. In endurance-style exercise, caffeine prior to exercise is known to favorably impact substrate utilization, reduce perceptions of fatigue, increase drive to exercise, and enhance overall performance [81, 83, 84]. Similarly, a number of studies published in the last 5 years have reported favorable outcomes for caffeine ingestion prior to resistance exercise, leading to improvements in maximal strength, maximal repetitions completed, and drive to exercise, as well as reductions in soreness and muscle pain [85–87]. Collectively, supplementation with caffeine leads to significant reductions in muscle pain, improvements in mood, improvements in maximal strength, and improvements in the maximal number of repetitions performed. Outside of the Ryan study, a key discussion point for all research highlighted involving caffeine is that none of the studies were developed to examine a question of timing. These studies are included because the nature in which caffeine operates results in a situation where preexercise administration is needed to fully take advantage of its stimulatory effects, particularly as they would work toward enhancing performance. In this respect, providing caffeine after a bout of resistance exercise would not make any pharmacological, physiological, or theoretical sense. For these reasons, caffeine use prior to both endurance and resistance exercise has a strong potential to exert favorable performance and metabolic outcomes. One final thought on caffeine and timing relates to the work of Pedersen et al., whereby the authors reported that postexercise ingestion of caffeine at a dose of 8 mg per kilogram of body mass, when combined with carbohydrate feedings, resulted in the fastest published rates of glycogen resynthesis that have ever been reported [88]. Again, this study did not examine caffeine timing per se, but demonstrated that providing it in a postexercise window with carbohydrate feedings can result in enhanced rates of muscle glycogen resynthesis. The efficacy of doing so prior to exercise and its impact on performance, glycogen storage, or utilization remains to be seen.

Another popular non-nutritive dietary supplement with demonstrated ergogenic benefit, creatine monohydrate, has also been shown through several research projects to merit involvement in the nutrient timing discussion. In one of the seminal studies on supplement timing and performance, Cribb and Hayes (2006) provided matched groups of resistance-trained males with a supplement containing protein, carbohydrate, and creatine monohydrate throughout a structured 10-week training period [61]. Subjects consumed the supplement either immediately before and after four weekly resistance training workouts or in the early morning and late evening of training days in a randomized, single-blind fashion. A number of timing-specific effects were observed by the researchers, including significantly greater improvements in lean body mass and muscular strength for the group receiving supplementation immediately before and after training. Most importantly for creatine users, after the training period, researchers found significantly

greater phosphocreatine and creatine concentrations in muscle biopsies from the group supplementing before and after exercise, indicating an enhanced effect of creatine use dependent on intake timing.

This conclusion was refined in a subsequent project performed by Antonio and Ciccone (2013). These researchers randomly assigned a group of 19 recreational male bodybuilders to receive 5 g of creatine monohydrate either immediately before or after a structured, 4-week resistance training regimen [89]. Though trends in the resulting data failed to reach significance, perhaps due to the small sample size utilized and the relatively short duration of the resistance training program, the authors used a magnitude-based inference analysis approach to conclude that postexercise supplementation was potentially superior in producing beneficial changes to fat-free mass, fat mass, and 1-RM bench press.

These somewhat tenuous results were then confounded by another recent study conducted by Candow et al. (2014). This project also compared pre- versus postexercise creatine supplementation, this time in a group of 22 untrained older adults of mixed gender. In a double-blind design, these subjects were randomized into groups receiving 0.1 g of creatine per kilogram body weight, supplied either immediately before or after structured resistance training sessions performed three times per week over 12 weeks. The authors found no significant difference between groups in the ensuing adaptations to resistance training, with both groups experiencing similar significant increases in lean tissue mass, muscle thickness, and muscle strength [90].

While the authors of these two projects reached disparate conclusions, there are a variety of important physiological considerations impacting these studies that can help highlight the level of nuance able to effect research of this nature. First and foremost, earlier work on creatine estimates that approximately 20–30 % of individuals fail to respond to creatine supplementation [91]. In light of the relatively small subject samples employed by both of these projects, any imbalance in the grouping of nonresponders during randomization could have significantly affected the subsequent results. Moreover, previous studies have reported male subjects as responding more favorably to creatine supplementation than females [92], so that the use of a mixed-sex sample by Candow et al. (2014) may have been nontrivial. Other inherent differences between these two projects, including absolute versus relative creatine dosage strategies, as well as subject age, training status, and the duration of the training program, could each have plausibly differentiated the eventual results. Altogether, the potential impact of these minor disparities points to the need for carefully conducted future research in order to distinguish any potential timing effect for creatine and other dietary supplements hitherto unconsidered.

Indeed, beyond augmenting the ergogenic benefit of these compounds, intake timing may also play a role in moderating any negative side effects accompanying these products. A straightforward and effective timing strategy is often used to mitigate the paresthesia associated with effective doses of beta-alanine, in simply breaking the dosage into smaller quantities consumed throughout the day [93]. Similarly, a recent project conducted by Siegler, Marshall, Bray, and Towlson (2012) exploring timing strategies for sodium bicarbonate supplementation found that intake timing impacted subsequent reports of gastrointestinal upset. Using a randomized, counterbalanced design, these researchers provided a group of eight male sprinters with 0.3 g of sodium bicarbonate per kilogram body weight at 60, 120, or 180 min prior to repeated bouts of sprinting. The authors found that the subjects performed similarly under all supplemental conditions, yet reports of gastrointestinal discomfort were significantly elevated for only those subjects receiving sodium bicarbonate at 60 and 120 min prior to exercise [94].

13.5 Meal Patterns and Time-of-Day Considerations

While it is true that the entire concept of nutrient timing, particularly as it relates to sports and exercise, has overwhelmingly involved timing

considerations closely surrounding some form of workout or competition, the strategy itself and the potential advantages it may offer can also apply to timing strategies for other scenarios such as health and weight loss. An early study published in 1997 by Keim and investigators required study participants to complete two 6-week diet periods. Similar diet compositions and caloric contents (~1,950 kcals) were consumed, but in one pattern, approximately 70 % of the prescribed kcals were consumed during the morning, while in the other group 70 % of the prescribed kcals were consumed with evening meals. Changes in weight loss and body composition were compared, and slightly greater weight loss occurred when the majority of kcals were consumed in the morning. While this is a seemingly positive outcome for consuming more kcals in the morning, greater amounts of fat-free mass were lost as well, leading to questions surrounding the long-term efficacy of this strategy regarding weight management and metabolic activity [95]. Observational research by investigators at the University of Texas-El Paso examined the food intake of 867 free-living individuals (375 males and 492 females) and reported that the timing of food consumption is correlated to the overall amount of kcals consumed each day, with consumption early in the day being negatively correlated with total food intake ($r=-0.13$, $p<0.01$), while late in the day consumption was positively correlated ($r=0.14$, $p<0.01$) [96]. A more detailed, follow-up analysis from the same study revealed that when carbohydrates, fats, and proteins were consumed in greater amounts earlier in the day, then reduced amounts were consumed later in the day. Conversely, when proportionally greater amounts were consumed later in the day, overall energy intakes tended to be higher [68].

In addition to changes in food intake, research in both animals and humans shows that the timing of food consumption may impact changes in body fat accumulation and production. Wu and investigators reported in laboratory animals that the first daily meal helps to program the circadian phase of peripheral clocks, while the last meal leads to increased rates of lipogenesis and adipose tissue accumulation [97]. Human research supports these findings, in that people who skip breakfast have been shown to display a delayed activation of lipolysis along with an increase in the production of adipose tissue [98, 99].

A more recent study conducted by Jakubowicz et al. in 2013 required overweight and obese women to consume a weight loss diet that provided approximately 1,400 kcals each day for a 12-week period. In this study, a portion of the study participants consumed 700 kcals during breakfast, 500 kcals during lunch, and 200 kcals during dinner, while the other portion of study participants consumed the exact opposite distribution (200 kcals for breakfast, 500 kcals for lunch, and 700 kcals for dinner) [100]. Approximately 2.5 times more weight was lost when the majority of kcals were consumed at breakfast, as compared to the opposing feeding pattern. In addition, significantly greater changes in waist circumference and overall body mass index were observed when the majority of kcals were consumed at the breakfast meal. Equally impressive findings from this study were that average triglyceride levels decreased by 34 % in the breakfast consumption group, as compared to a 15 % change in the dinner group, while greater improvements in serum glucose and insulin dynamics as well as improved feelings of satiety were also found in the group that consumed the majority of their kcals at breakfast [100].

Overall, the results of the Jakubowicz study provide additional empirical support for a number of other previously published reports. In both human and animal research, the practice of skipping breakfast and altering the macronutrient content of certain meals has been repeatedly shown to impact appetite, feelings of fullness, and overall food intake. For example, Leidy and colleagues in two separate published studies concluded that increasing the protein content of the breakfast meal can improve appetite control, food intake, and feelings of fullness [101, 102]. In closing, the Jakubowicz study offers an excellent extension of these findings and helps to illustrate that meal timing and the temporal distribution of kcal consumption may indeed impact weight loss, body composition, and various parameters of metabolic and cardiovascular health [100].

13.6 Meal Frequency

Meal frequency, or the number of occasions throughout the day in which a feeding episode takes place, is a function of meal patterns. For years, the impact of meal frequency on health and weight loss was widely thought to favorably impact changes in weight loss, weight maintenance, and body composition. The initial research supporting this strategy was reported by Fabry and coworkers. Using an epidemiological, cross-sectional study approach, they reported that in a population of 379 overweight individuals aged 60–64 years, the mean skinfold thickness was inversely related to the frequency of meals [103]. Follow-up investigations by this research group reported similar outcomes in a sample of 80 subjects aged 30–50 years of age [104]. Finally, Metzner and colleagues reported that in a very large sample of 2,000 men and women aged 35–60 years of age, meal frequency and adiposity were inversely related [105]. While consistent findings of this kind are encouraging, the observational nature of the underlying studies, and the reliance upon food records in determining how many kcals were consumed, creates an unsatisfactory combination of bias and error inextricable from the reported outcomes. Using a well-controlled, experimental approach, Cameron and colleagues had 16 obese men and women reduce their energy intake by 700 kcals per day and follow one of two different meal patterns. In an isocaloric fashion, one group was instructed to consume six meals per day (three traditional meals and three snacks), while the other group was instructed to consume three meals per day for an 8-week period. Changes in body mass, obesity indices, appetite, and ghrelin were measured at the end of the 8-week study, and no significant differences in any of the measured endpoints were found [106].

Kulovitz-Alencar and investigators at the University of New Mexico have recently presented research to further examine, in a controlled fashion, the impact of meal frequency on changes in body mass, body composition, and ghrelin, as well as glucose and insulin. This yet-to-be-published research was the first to use commercially available food products (i.e., Nutrisystem) as part of a greater regimen to examine the impact of meal frequency. In this study, a crossover approach was used whereby each group consumed either two meals per day or six meals per day for a 2-week period. No significant changes in body mass or body composition were observed, in addition to no change being found in glucose, insulin, and ghrelin changes [107]. Interestingly, a 2005 study by Farshchi required individuals to either consume a regular, consistent pattern of six daily meals over a 14-day period or eat anywhere from three to nine meals per day [108]. Regular meal patterns resulted in lower energy intake while also supporting greater levels of thermogenesis and improvements in a number of health markers found in the blood. Although both of these studies were identical in duration, the number of feeding episodes was different, and the combined results seem to indicate that a chaotic meal pattern may challenge the ability of the body to regulate the levels of various markers of health and appetite when compared to a regular meal pattern, irrespective of the total number of meals consumed per day. The Farshchi findings supported a previous 1997 review article by Bellisle [109], as well as a more recent review article by Kulovitz [110], indicating that when total energy intake is controlled, and when caloric restriction is employed, the impact of meal frequency takes a backseat to total daily caloric intake. Overall, the findings from these authors also support the conclusion of the International Society of Sports Nutrition in their position stand on meal frequency that [111]:

- Increasing meal frequency does not appear to favorably change body composition in sedentary populations.
- Altering meal frequency may positively impact various blood markers of health, particularly LDL and total cholesterol, as well as insulin.
- Increasing meal frequency appears to decrease hunger and improve appetite control.

13.7 Protein Patterns

In addition to the pattern and/or frequency in which meals are consumed, the pattern of protein feedings has also been explored in some preliminary research. In 2012, Moore and colleagues had eight participants complete three experimental trials which compared the impact of consuming the same total dose of protein (80 g) with three distinct feeding patterns over the same 12-h measurement window after an identical bout of lower body resistance exercise [112]. For example, one condition had participants consume two 40-g doses of whey protein isolate approximately 6 h apart. The next condition required the participants to consume four 20-g doses of whey protein isolate every 3 h. The final condition required the participants to consume eight 10-g doses of whey protein isolate every 90 min. Using stable isotope tracer technology, rates of muscle protein turnover, synthesis, and breakdown were compared between all three feeding patterns, and the authors concluded that protein turnover and synthesis rates were greatest when more frequent ingestion of smaller doses of whey protein isolate was consumed. From this study, the authors concluded that the pattern of ingested protein, and not only the total daily amount of protein, can impact whole-body protein metabolism.

Additional analysis from the same research study examined the changes in myofibrillar protein synthesis, a more specific measurement that reflects muscle protein as opposed to whole-body rates of protein metabolism [113]. Reports from this publication first indicated that myofibrillar protein synthesis rates increased in all three groups, irrespective of how the total protein dose was consumed. Second, the authors found that when four 20-g doses of whey protein isolate were consumed every 3 h over a 12-h postexercise period, significantly greater rates of myofibrillar protein synthesis occurred as compared with the other two ingestion patterns. In conclusion, the results from this study provide important information, namely, that intermediate protein doses (20 g vs. 40 g or 10 g) consumed every 3 h create more favorable changes in both whole-body as well as myofibrillar protein synthesis. While this study did not incorporate more than one exercise bout or one feeding period, the results do indicate that the timing or pattern in which high-quality protein is ingested may favorably impact net protein balance and in turn could go on to more favorably impact changes in strength and fat-free mass.

13.8 Conclusions and Perspective

As outlined throughout the chapter, nutrient timing is an exciting area of research that continues to gather interest from both researchers and consumers. Probably two of the most important things for readers to realize are that all nutrient timing information must be considered in the correct context and that many areas of research in this area are still underexplored. For example, it is clear that increasing carbohydrate intake to very high daily intake levels (7–10 g/kg/day) facilitates optimal restoration of muscle glycogen, yet unless the need is present for immediate or rapid restoration of these energy stores, "loading" regimens may not be necessary (though they should not be considered to be harmful or useless). However, this says nothing definitive about the importance of "carbohydrate loading" prior to a prolonged exercise bout, the impact this strategy can have on substrate utilization, perceptions of effort and fatigue, or frankly its influence on performance.

In a similar light, recent well-conducted reviews and systematic analyses have indicated that increased protein intake is important for promotion of favorable training adaptations [5], but that specific timing strategies may not be needed as long as protein intake reaches adequate levels [64, 65]. Finally, recent exciting work with various non-nutrients (e.g., caffeine and creatine) provides data to indicate that timed availability may impart favorable responses to acute exercise or prolonged training [82, 89]. As stated previously, limited studies are currently available that have examined over the course of several weeks of training equal doses of protein ingestion before

a workout in comparison to identical protein ingestion after a workout. This is somewhat surprising, but it underlines the point that much more research needs to be conducted.

Another consideration worth mentioning, which also highlights the lack of consistent reports, goes back to various aspects related to research design and statistical analysis. Put simply, many studies, by virtue of their complexity and invasiveness, find it necessary to employ small numbers of research participants. In addition, in many situations, the sizes of potential effects are quite small: fractions of a fraction. Put simply, a resistance training program is responsible for a great deal of the change in muscle mass that would typically occur after several weeks of following a well-developed resistance training program. The potential to invoke further change in these variables when comparing a carbohydrate or a protein-laden diet is much smaller than the potential impact of exercise itself. As such, one must consider that a timing-specific question is then seeking to determine whether changing "when" something is consumed makes an impact on the already comparatively diminutive effect of the nutrient itself. As a result, potential effects are quite small, and when combined with study designs that necessitate small numbers of study participants, the potential for statistical significance remains low. Nonetheless, this consideration remains important because it underscores the need for more research and continued investigation into understanding both the group and individual changes that can be expected from various strategies manipulating timing of intake.

13.9 Practical Applications

- The importance of adequate intake of energy, carbohydrate, and protein cannot be understated to help fuel athletes for optimal performance and adaptations to intense, high volumes of exercise training and recovery. Athletes and coaches must make sure these needs are being met.
- Prolonged exercise (>60–90 min) of moderate-to-high-intensity exercise relies heavily upon internal stores of energy, and timing strategies are one approach to facilitate recovery and offset these changes.
- High-intensity exercise requires energy and leads to fluid loss. Developing a following hydration strategy (1.5–2 cups of 6–8 % CHO solution [6–8 g CHO/100 mL fluid]) that involves regular and ongoing consumption of a carbohydrate-electrolyte solution can help to replace fluid, sustain blood glucose levels, and promote performance.
- Ingestion of a minimum of 6 g of the essential amino acid, leucine (approximately 20–25 groups of isolated versions of intact protein), appears to be a critical threshold to activate mechanisms of protein synthesis.
- Rapid ingestion of high amounts of carbohydrates (1.2 g of CHO per kilogram of body mass per hour) for 4–6 h starting soon after exhausting exercise is needed to rapidly stimulate replenishment of lost muscle glycogen.
- The addition of protein (0.2–0.5 g of protein per kilogram of body mass per day) to carbohydrate at a ratio of 3:1 (CHO: PRO) can further stimulate glycogen resynthesis when adequate carbohydrate cannot be delivered. Further, adding protein may help to attenuate muscle and accelerate recovery from intense exercise.
- In the absence of timing strategies, daily consumption of high amounts of dietary carbohydrate (>8 g of CHO per kilogram body mass per day) can encourage maintenance of high levels of muscle and liver glycogen.
- Timing of protein or appropriate amounts of the essential amino acids remains as a strategy that can potentially impact how an athlete responds and adapt to their training, in cases where adequate protein intake is provided across the day (1.2–1.8 g of protein per kilogram of body mass per day).
- Research examining the timing of certain non-nutrients has begun, and preliminary research indicates the timing of caffeine may impact endurance performance and timing of creatine may favorably impact resistance training adaptations in young people.
- In the face of restricting caloric intake for weight loss, altering meal frequency does not

appear to invoke any favorable influence, but may help with controlling hunger, appetite, and satiety, particularly if higher doses of protein are delivered within each feeding episode.

- Nutrient timing strategies that involve altering meal patterns and distribution of pattern indicate that intermediate-sized protein doses (20–30 g) every 3–4 h best support increased rates of muscle protein synthesis across the day.
- Nutrient timing strategies that involve altering when proportions of total caloric intake are consumed indicate improved weight loss, body composition, and health-related markers in the blood for people who consumed a greater proportion of their calories during the breakfast meal and when this meal provides higher amounts of dietary protein.

References

1. Sherman WM, Costill DL, Fink WJ, Miller JM. Effect of exercise-diet manipulation on muscle glycogen and its subsequent utilization during performance. Int J Sports Med. 1981;2(2):114–8.
2. Karlsson J, Saltin B. Diet, muscle glycogen, and endurance performance. J Appl Physiol. 1971;31(2):203–6.
3. Ivy JL, Katz AL, Cutler CL, Sherman WM, Coyle EF. Muscle glycogen synthesis after exercise: effect of time of carbohydrate ingestion. J Appl Physiol. 1988;64(4):1480–5.
4. Kerksick C, Stout J, Campbell B, Wilborn C, Kreider R, Kalman D, et al. International Society of Sports Nutrition position stand: nutrient timing. J Int Soc Sports Nutr. 2008;5(1):17.
5. Cermak NM, Res PT, de Groot LC, Saris WH, van Loon LJ. Protein supplementation augments the adaptive response of skeletal muscle to resistance-type exercise training: a meta-analysis. Am J Clin Nutr. 2012;96(6):1454–64.
6. Dennis SC, Noakes TD, Hawley JA. Nutritional strategies to minimize fatigue during prolonged exercise: fluid, electrolyte and energy replacement. J Sports Sci. 1997;15(3):305–13.
7. Rodriguez NR, Di Marco NM, Langley S. American College of Sports Medicine position stand. Nutrition and athletic performance. Med Sci Sports Exerc. 2009;41(3):709–31.
8. Burke LM, Cox GR, Culmmings NK, Desbrow B. Guidelines for daily carbohydrate intake: do athletes achieve them? Sports Med. 2001;31(4):267–99.
9. Sherman WM, Costill DL, Fink WJ, Hagerman FC, Armstrong LE, Murray TF. Effect of a 42.2-km footrace and subsequent rest or exercise on muscle glycogen and enzymes. J Appl Physiol. 1983;55:1219–24.
10. Bussau VA, Fairchild TJ, Rao A, Steele P, Fournier PA. Carbohydrate loading in human muscle: an improved 1 day protocol. Eur J Appl Physiol. 2002;87(3):290–5.
11. Coyle EF, Coggan AR, Hemmert MK, Lowe RC, Walters TJ. Substrate usage during prolonged exercise following a preexercise meal. J Appl Physiol. 1985;59(2):429–33.
12. Wright DA, Sherman WM, Dernbach AR. Carbohydrate feedings before, during, or in combination improve cycling endurance performance. J Appl Physiol. 1991;71(3):1082–8.
13. Neufer PD, Costill DL, Flynn MG, Kirwan JP, Mitchell JB, Houmard J. Improvements in exercise performance: effects of carbohydrate feedings and diet. J Appl Physiol. 1987;62(3):983–8.
14. Sherman WM, Brodowicz G, Wright DA, Allen WK, Simonsen J, Dernbach A. Effects of 4 h preexercise carbohydrate feedings on cycling performance. Med Sci Sports Exerc. 1989;21(5):598–604.
15. Tarnopolsky MA, Gibala M, Jeukendrup AE, Phillips SM. Nutritional needs of elite endurance athletes. Part I: carbohydrate and fluid requirements. Eur J Sport Sci. 2005;5(1):3–14.
16. Foster C, Costill DL, Fink WJ. Effects of preexercise feedings on endurance performance. Med Sci Sports Exerc. 1979;11:1–5.
17. Hawley JA, Burke LM. Effect of meal frequency and timing on physical performance. Br J Nutr. 1997;77 Suppl 1:S91–103.
18. Galloway SD, Lott MJ, Toulouse LC. Pre-exercise carbohydrate feeding and high-intensity exercise capacity: effects of timing of intake and carbohydrate concentration. Int J Sport Nutr Exerc Metab. 2014;24(3):258–66.
19. Fielding RA, Costill DL, Fink WJ, King DS, Hargreaves M, Kovaleski JE. Effect of carbohydrate feeding frequencies and dosage on muscle glycogen use during exercise. Med Sci Sports Exerc. 1985;17(4):472–6.
20. Febbraio MA, Chiu A, Angus DJ, Arkinstall MJ, Hawley JA. Effects of carbohydrate ingestion before and during exercise on glucose kinetics and performance. J Appl Physiol. 2000;89(6):2220–6.
21. Widrick JJ, Costill DL, Fink WJ, Hickey MS, McConell GK, Tanaka H. Carbohydrate feedings and exercise performance: effect of initial muscle glycogen concentration. J Appl Physiol. 1993;74(6):2998–3005.
22. Ivy JL. Glycogen resynthesis after exercise: effect of carbohydrate intake. Int J Sports Med. 1998;19 Suppl 2:S142–5.
23. Jentjens R, Jeukendrup AE. Determinants of post-exercise glycogen synthesis during short-term recovery. Sports Med. 2003;33:117–44.
24. Jentjens R, van Loon L, Mann CH, Wagenmakers AJM, Jeukendrup AE. Addition of protein and amino acids to carbohydrates does not enhance

postexercise muscle glycogen synthesis. J Appl Physiol. 2001;91:839–46.
25. van Loon L, Saris WH, Kruijshoop M. Maximizing postexercise muscle glycogen synthesis: carbohydrate supplementation and the application of amino acid or protein hydrolysate mixtures. Am J Clin Nutr. 2000;72:106–11.
26. Keizer H, Kuipers H, van Kranenburg G. Influence of liquid and solid meals on muscle glycogen resynthesis, plasma fuel hormone response, and maximal physical working capacity. Int J Sports Med. 1987; 8:99–104.
27. Nicholas CW, Green PA, Hawkins RD. Carbohydrate intake and recovery of intermittent running capacity. Int J Sport Nutr. 1997;7:251–60.
28. Ivy JL, Res PT, Sprague RC, Widzer MO. Effect of a carbohydrate-protein supplement on endurance performance during exercise of varying intensity. Int J Sport Nutr Exerc Metab. 2003;13(3):382–95.
29. Saunders MJ, Kane MD, Todd MK. Effects of a carbohydrate-protein beverage on cycling endurance and muscle damage. Med Sci Sports Exerc. 2004; 36(7):1233–8.
30. Koopman R, Pannemans DL, Jeukendrup AE, Gijsen AP, Senden JM, Halliday D, et al. Combined ingestion of protein and carbohydrate improves protein balance during ultra-endurance exercise. Am J Physiol Endocrinol Metab. 2004;287(4):E712–20.
31. Ivy JL, Goforth HW, Jr., Damon BM, McCauley TR, Parsons EC, Price TB. Early postexercise muscle glycogen recovery is enhanced with a carbohydrate-protein supplement. Journal of applied physiology (Bethesda, MD : 1985). 2002;93(4):1337–44.
32. Zawadzki KM, Yaspelkis 3rd BB, Ivy JL. Carbohydrate-protein complex increases the rate of muscle glycogen storage after exercise. J Appl Physiol. 1992;72(5):1854–9.
33. Berardi JM, Noreen EE, Lemon PW. Recovery from a cycling time trial is enhanced with carbohydrate-protein supplementation vs. isoenergetic carbohydrate supplementation. J Int Soc Sports Nutr. 2008;5:24.
34. Berardi JM, Price TB, Noreen EE, Lemon PW. Postexercise muscle glycogen recovery enhanced with a carbohydrate-protein supplement. Med Sci Sports Exerc. 2006;38(6):1106–13.
35. Howarth KR, Moreau NA, Phillips SM, Gibala MJ. Co-ingestion of protein with carbohydrate during recovery from endurance exercise stimulates skeletal muscle protein synthesis in humans. J Appl Physiol. 2009;106:1394–402.
36. Hawley JA, Burke LM, Phillips SM, Spriet LL. Nutritional modulation of training-induced skeletal muscle adaptations. J Appl Physiol (Bethesda, MD: 1985). 2011;110(3):834–45.
37. Margolis LM, Pasiakos SM. Optimizing intramuscular adaptations to aerobic exercise: effects of carbohydrate restriction and protein supplementation on mitochondrial biogenesis. Adv Nutr. 2013;4(6): 657–64.
38. Tipton KD, Rasmussen BB, Miller SL, Wolf SE, Owens-Stovall SK, Petrini BE, et al. Timing of amino acid-carbohydrate ingestion alters anabolic response of muscle to resistance exercise. Am J Physiol Endocrinol Metab. 2001;281(2):E197–206.
39. Fujita S, Dreyer HC, Drummond MJ, Glynn EL, Volpi E, Rasmussen BB. Essential amino acid and carbohydrate ingestion before resistance exercise does not enhance postexercise muscle protein synthesis. J Appl Physiol (Bethesda, MD: 1985). 2009;106(5):1730–9.
40. Gonzalez AM, Walsh AL, Ratamess NA, Kang J, Hoffman JR. Effect of a pre-workout energy supplement on acute multi-joint resistance exercise. J Sports Sci Med. 2011;10(2):261–6.
41. Ormsbee MJ, Mandler WK, Thomas DD, Ward EG, Kinsey AW, Simonavice E, et al. The effects of six weeks of supplementation with multi-ingredient performance supplements and resistance training on anabolic hormones, body composition, strength, and power in resistance-trained men. J Int Soc Sports Nutr. 2012;9(1):49.
42. Ormsbee MJ, Thomas DD, Mandler WK, Ward EG, Kinsey AW, Panton LB, et al. The effects of pre- and post-exercise consumption of multi-ingredient performance supplements on cardiovascular health and body fat in trained men after six weeks of resistance training: a stratified, randomized, double-blind study. Nutr Metab (Lond). 2013;10(1):39.
43. Lowery RP, Joy JM, Dudeck JE, Oliveira de Souza E, McCleary SA, Wells S, et al. Effects of 8 weeks of Xpand(R) 2X pre workout supplementation on skeletal muscle hypertrophy, lean body mass, and strength in resistance trained males. J Int Soc Sports Nutr. 2013;10(1):44.
44. Spradley BD, Crowley KR, Tai CY, Kendall KL, Fukuda DH, Esposito EN, et al. Ingesting a pre-workout supplement containing caffeine, B-vitamins, amino acids, creatine, and beta-alanine before exercise delays fatigue while improving reaction time and muscular endurance. Nutr Metab (Lond). 2012;9:28.
45. Hackney KJ, Bruenger AJ, Lemmer JT. Timing protein intake increases energy expenditure 24 h after resistance training. Med Sci Sports Exerc. 2010; 42(5):998–1003.
46. Haff GG, Koch AJ, Potteiger JA, Kuphal KE, Magee LM, Green SB, et al. Carbohydrate supplementation attenuates muscle glycogen loss during acute bouts of resistance exercise. Int J Sport Nutr Exerc Metab. 2000;10(3):326–39.
47. Bird SP, Tarpenning KM, Marino FE. Effects of liquid carbohydrate/essential amino acid ingestion on acute hormonal response during a single bout of resistance exercise in untrained men. Nutrition. 2006;22(4):367–75.
48. Bird SP, Tarpenning KM, Marino FE. Liquid carbohydrate/essential amino acid ingestion during a short-term bout of resistance exercise suppresses myofibrillar protein degradation. Metabolism. 2006; 55(5):570–7.

49. Beelen M, Koopman R, Gijsen AP, Vandereyt H, Kies AK, Kuipers H, et al. Protein coingestion stimulates muscle protein synthesis during resistance-type exercise. Am J Physiol Endocrinol Metab. 2008;295(1):E70–7.
50. Esmarck B, Anderson JL, Olsen S, Richter EA, Mizuno M, Kjaer M. Timing postexercise protein intake is important for muscle hypertrophy with resistance training in elderly humans. J Physiol. 2001;535:301–11.
51. Cribb PJ, Williams AD, Carey MF, Hayes A. The effect of whey isolate and resistance training on strength, body composition, and plasma glutamine. Int J Sport Nutr Exerc Metab. 2006;16(5):494–509.
52. Hartman JW, Tang JE, Wilkinson SB, Tarnopolsky MA, Lawrence RL, Fullerton AV, et al. Consumption of fat-free fluid milk after resistance exercise promotes greater lean mass accretion than does consumption of soy or carbohydrate in young, novice, male weightlifters. Am J Clin Nutr. 2007;86(2):373–81.
53. Phillips SM, Tang JE, Moore DR. The role of milk- and soy-based protein in support of muscle protein synthesis and muscle protein accretion in young and elderly persons. J Am Coll Nutr. 2009;28(4):343–54.
54. Kerksick CM, Rasmussen CJ, Lancaster SL, Magu B, Smith P, Melton C, et al. The effects of protein and amino acid supplementation on performance and training adaptations during ten weeks of resistance training. J Strength Cond Res. 2006;20(3):643–53.
55. Willoughby DS, Stout JR, Wilborn CD. Effects of resistance training and protein plus amino acid supplementation on muscle anabolism, mass, and strength. Amino Acids. 2007;32(4):467–77.
56. Borsheim E, Tipton KD, Wolf SE, Wolfe RR. Essential amino acids and muscle protein recovery from resistance exercise. Am J Physiol Endocrinol Metab. 2002;283(4):E648–57.
57. Miller SL, Tipton KD, Chinkes DL, Wolf SE, Wolfe RR. Independent and combined effects of amino acids and glucose after resistance exercise. Med Sci Sports Exerc. 2003;35(3):449–55.
58. Pitkanen HT, Nykanen T, Knuutinen J, Lahti K, Keinanen O, Alen M, et al. Free amino acid pool and muscle protein balance after resistance exercise. Med Sci Sports Exerc. 2003;35(5):784–92.
59. Tipton KD, Ferrando AA, Phillips SM, Doyle DJ, Wolfe RR. Postexercise net protein synthesis in human muscle from orally administered amino acids. Am J Physiol. 1999;276(4 Pt 1):E628–34.
60. Tipton KD, Wolfe RR. Exercise, protein metabolism, and muscle growth. Int J Sport Nutr Exerc Metab. 2001;11(1):109–32.
61. Cribb PJ, Hayes A. Effects of supplement timing and resistance exercise on skeletal muscle hypertrophy. Med Sci Sports Exerc. 2006;38(11):1918–25.
62. Hoffman JR, Ratamess NA, Tranchina CP, Rashti SL, Kang J, Faigenbaum AD. Effect of protein-supplement timing on strength, power, and body-composition changes in resistance-trained men. Int J Sport Nutr Exerc Metab. 2009;19(2):172–85.
63. Campbell B, Kreider RB, Ziegenfuss T, La Bounty P, Roberts M, Burke D, et al. International Society of Sports Nutrition position stand: protein and exercise. J Int Soc Sports Nutr. 2007;4:8.
64. Aragon AA, Schoenfeld BJ. Nutrient timing revisited: is there a post-exercise anabolic window? J Int Soc Sports Nutr. 2013;10(1):5.
65. Schoenfeld BJ, Aragon AA, Krieger JW. The effect of protein timing on muscle strength and hypertrophy: a meta-analysis. J Int Soc Sports Nutr. 2013;10(1):53.
66. Arble DM, Bass J, Laposky AD, Vitaterna MH, Turek FW. Circadian timing of food intake contributes to weight gain. Obesity (Silver Spring). 2009;17(11):2100–2.
67. Bray MS, Tsai JY, Villegas-Montoya C, Boland BB, Blasier Z, Egbejimi O, et al. Time-of-day-dependent dietary fat consumption influences multiple cardiometabolic syndrome parameters in mice. Int J Obes (Lond). 2010;34(11):1589–98.
68. de Castro JM. The time of day and the proportions of macronutrients eaten are related to total daily food intake. Br J Nutr. 2007;98(5):1077–83.
69. Genton L, Melzer K, Pichard C. Energy and macronutrient requirements for physical fitness in exercising subjects. Clin Nutr. 2010;29(4):413–23.
70. Lambert EV, Speechly DP, Dennis SC, Noakes TD. Enhanced endurance in trained cyclists during moderate intensity exercise following 2 weeks adaptation to a high fat diet. Eur J Appl Physiol Occup Physiol. 1994;69(4):287–93.
71. Phinney SD, Bistrian BR, Evans WJ, Gervino E, Blackburn GL. The human metabolic response to chronic ketosis without caloric restriction: preservation of submaximal exercise capability with reduced carbohydrate oxidation. Metabolism. 1983;32(8):769–76.
72. Johnson NA, Stannard SR, Thompson MW. Muscle triglyceride and glycogen in endurance exercise: implications for performance. Sports Med. 2004;34(3):151–64.
73. Burke LM, Kiens B. "Fat adaptation" for athletic performance: the nail in the coffin? J Appl Physiol. 2006;100(1):7–8.
74. Burke LM, Hawley JA, Angus DJ, Cox GR, Clark SA, Cummings NK, et al. Adaptations to short-term high-fat diet persist during exercise despite high carbohydrate availability. Med Sci Sports Exerc. 2002;34(1):83–91.
75. Havemann L, West SJ, Goedecke JH, Macdonald IA, St Clair Gibson A, Noakes TD, et al. Fat adaptation followed by carbohydrate loading compromises high-intensity sprint performance. J Appl Physiol (Bethesda, MD: 1985). 2006;100(1):194–202.
76. Barry DW, Hansen KC, van Pelt RE, Witten M, Wolfe P, Kohrt WM. Acute calcium ingestion attenuates exercise-induced disruption of calcium homeostasis. Med Sci Sports Exerc. 2011;43(4):617–23.

77. Sherk VD, Barry DW, Villalon KL, Hansen KC, Wolfe P, Kohrt WM, editors. Timing of calcium supplementation relative to exercise alters the calcium homeostatic response to vigorous exercise. Endocrine's Society Annual Meeting; 2013 June 18, 2013; San Francisco, CA.
78. Shea KL, Barry DW, Sherk VD, Hansen KC, Wolfe P, Kohrt WM. Calcium supplementation and PTH response to vigorous walking in postmenopausal women. Med Sci Sports Exerc. 2014;46(10): 2007–13.
79. Fujii T, Matsuo T, Okamura K. The effects of resistance exercise and post-exercise meal timing on the iron status in iron-deficient rats. Biol Trace Elem Res. 2012;147(1–3):200–5.
80. Matsuo T, Kang HS, Suzuki H, Suzuki M. Voluntary resistance exercise improves blood hemoglobin concentration in severely iron-deficient rats. J Nutr Sci Vitaminol. 2002;48(2):161–4.
81. Goldstein ER, Ziegenfuss T, Kalman D, Kreider R, Campbell B, Wilborn C, et al. International society of sports nutrition position stand: caffeine and performance. J Int Soc Sports Nutr. 2010;7(1):5.
82. Ryan EJ, Kim CH, Fickes EJ, Williamson M, Muller MD, Barkley JE, et al. Caffeine gum and cycling performance: a timing study. J Strength Cond Res. 2013;27(1):259–64.
83. Glade MJ. Caffeine-not just a stimulant. Nutrition. 2010;26(10):932–8.
84. Graham TE, Spriet LL. Performance and metabolic responses to a high caffeine dose during prolonged exercise. J Appl Physiol. 1991;71(6):2292–8.
85. Duncan MJ, Oxford SW. The effect of caffeine ingestion on mood state and bench press performance to failure. J Strength Cond Res. 2011;25(1):178–85.
86. Duncan MJ, Stanley M, Parkhouse N, Cook K, Smith M. Acute caffeine ingestion enhances strength performance and reduces perceived exertion and muscle pain perception during resistance exercise. Eur J Sport Sci. 2013;13(4):392–9.
87. Goldstein ER, Jacobs PL, Whitehurst M, Penhollow T, Antonio J. Caffeine enhances upper body strength in resistance-trained women. J Int Soc Sports Nutr. 2010;7(1):18.
88. Pedersen DJ, Lessard SJ, Coffey VG, Churchley EG, Wootton AM, Ng T, et al. High rates of muscle glycogen resynthesis after exhaustive exercise when carbohydrate is coingested with caffeine. J Appl Physiol (Bethesda, MD: 1985). 2008;105(1):7–13.
89. Antonio J, Ciccone V. The effects of pre versus post workout supplementation of creatine monohydrate on body composition and strength. J Int Soc Sports Nutr. 2013;10(1):36.
90. Candow DG, Zello GA, Ling B, Farthing JP, Chilibeck PD, McLeod K, et al. Comparison of creatine supplementation before versus after supervised resistance training in healthy older adults. Res Sports Med. 2014;22(1):61–74.
91. Syrotuik DG, Bell GJ. Acute creatine monohydrate supplementation: a descriptive physiological profile of responders vs. nonresponders. J Strength Cond Res. 2004;18(3):610–7.
92. Chilibeck PD, Stride D, Farthing JP, Burke DG. Effect of creatine ingestion after exercise on muscle thickness in males and females. Med Sci Sports Exerc. 2004;36(10):1781–8.
93. Helms ER, Aragon AA, Fitschen PJ. Evidence-based recommendations for natural bodybuilding contest preparation: nutrition and supplementation. J Int Soc Sports Nutr. 2014;11:20.
94. Siegler JC, Marshall PW, Bray J, Towlson C. Sodium bicarbonate supplementation and ingestion timing: does it matter? J Strength Cond Res. 2012;26(7): 1953–8.
95. Keim NL, Van Loan MD, Horn WF, Barbieri TF, Mayclin PL. Weight loss is greater with consumption of large morning meals and fat-free mass is preserved with large evening meals in women on a controlled weight reduction regimen. J Nutr. 1997; 127(1):75–82.
96. de Castro JM. The time of day of food intake influences overall intake in humans. J Nutr. 2004;134(1): 104–11.
97. Wu T, Sun L, ZhuGe F, Guo X, Zhao Z, Tang R, et al. Differential roles of breakfast and supper in rats of a daily three-meal schedule upon circadian regulation and physiology. Chronobiol Int. 2011; 28(10):890–903.
98. Loboda A, Kraft WK, Fine B, Joseph J, Nebozhyn M, Zhang C, et al. Diurnal variation of the human adipose transcriptome and the link to metabolic disease. BMC Med Genomics. 2009;2:7.
99. Ma Y, Bertone ER, Stanek 3rd EJ, Reed GW, Hebert JR, Cohen NL, et al. Association between eating patterns and obesity in a free-living US adult population. Am J Epidemiol. 2003;158(1):85–92.
100. Jakubowicz D, Barnea M, Wainstein J, Froy O. High caloric intake at breakfast vs. dinner differentially influences weight loss of overweight and obese women. Obesity (Silver Spring). 2013;21(12): 2504–12.
101. Leidy HJ, Bossingham MJ, Mattes RD, Campbell WW. Increased dietary protein consumed at breakfast leads to an initial and sustained feeling of fullness during energy restriction compared to other meal times. Br J Nutr. 2009;101(6):798–803.
102. Leidy HJ, Racki EM. The addition of a protein-rich breakfast and its effects on acute appetite control and food intake in 'breakfast-skipping' adolescents. Int J Obes (Lond). 2010;34(7):1125–33.
103. Fabry P, Hejl Z, Fodor J, Braun T, Zvolankova K. The frequency of meals. Its relation to overweight, hypercholesterolaemia, and decreased glucose-tolerance. Lancet. 1964;2(7360):614–5.
104. Hejda S, Fabry P. Frequency of food intake in relation to some parameters of the nutritional status. Nutr Dieta Eur Rev Nutr Diet. 1964;64:216–28.
105. Metzner HL, Lamphiear DE, Wheeler NC, Larkin FA. The relationship between frequency of eating and adiposity in adult men and women in the

Tecumseh Community Health Study. Am J Clin Nutr. 1977;30(5):712–5.
106. Cameron JD, Cyr MJ, Doucet E. Increased meal frequency does not promote greater weight loss in subjects who were prescribed an 8-week equi-energetic energy-restricted diet. Br J Nutr. 2010;103(8): 1098–101.
107. Alencar MK, Kerksick CM, Beam J, McCormick J, White A, Salgado R, et al., editors. Influence of meal frequency on insulin, glucose, and appetite control in obese women undergoing a portion-controlled weight-loss intervention. American College of Sports Medicine; 2014 Wednesday, May 28th, 2014.; Orlando, FL.
108. Farshchi HR, Taylor MA, Macdonald IA. Beneficial metabolic effects of regular meal frequency on dietary thermogenesis, insulin sensitivity, and fasting lipid profiles in healthy obese women. Am J Clin Nutr. 2005;81(1):16–24.
109. Bellisle F, McDevitt R, Prentice AM. Meal frequency and energy balance. Br J Nutr. 1997;77 Suppl 1:S57–70.
110. Kulovitz MG, Kravitz LR, Mermier C, Gibson AL, Conn CA, Kolkmeyer D, et al. Potential role of meal frequency as a strategy for weight loss and health in overweight or obese adults. Nutrition. 2014;30(4): 386–92.
111. La Bounty PM, Campbell BI, Wilson J, Galvan E, Berardi J, Kleiner SM, et al. International Society of Sports Nutrition position stand: meal frequency. J Int Soc Sports Nutr. 2011;8:4.
112. Moore DR, Areta J, Coffey VG, Stellingwerff T, Phillips SM, Burke LM, et al. Daytime pattern of post-exercise protein intake affects whole-body protein turnover in resistance-trained males. Nutr Metab (Lond). 2012;9(1):91.
113. Areta JL, Burke LM, Ross ML, Camera DM, West DW, Broad EM, et al. Timing and distribution of protein ingestion during prolonged recovery from resistance exercise alters myofibrillar protein synthesis. J Physiol. 2013;591(Pt 9):2319–31.
114. Weisgarber KD, Candow DG, Vogt ES. Whey protein before and during resistance exercise has no effect on muscle mass and strength in untrained young adults. Int J Sport Nutr Exerc Metab. 2012; 22(6):463–9.
115. Mamerow MM, Mettler JA, English KL, Casperson SL, Arentson-Lantz E, Sheffield-Moore M, et al. Dietary protein distribution positively influences 24-h muscle protein synthesis in healthy adults. J Nutr. 2014;144(6):876–80.
116. Res PT, Groen B, Pennings B, Beelen M, Wallis GA, Gijsen AP, et al. Protein ingestion before sleep improves postexercise overnight recovery. Med Sci Sports Exerc. 2012;44(8):1560–9.
117. Minor BD, Heusinger DE, Melanson EL, Hamilton KL, Miller BF. Energy balance changes the anabolic effect of postexercise feeding in older individuals. J Gerontol A Biol Sci Med Sci. 2012;67(11):1161–9.
118. Jordan LY, Melanson EL, Melby CL, Hickey MS, Miller BF. Nitrogen balance in older individuals in energy balance depends on timing of protein intake. J Gerontol A Biol Sci Med Sci. 2010;65(10): 1068–76.
119. Greer BK, Price A, Jones B. Timing influence of carbohydrate-protein ingestion on muscle soreness and next-day running performance. J Diet Suppl. 2014;11(2):166–74.
120. Heesch MW, Mieras ME, Slivka DR. The performance effect of early versus late carbohydrate feedings during prolonged exercise. Appl Physiol Nutr Metab. 2014;39(1):58–63.
121. Trabelsi K, Stannard SR, Maughan RJ, Jammoussi K, Zeghal K, Hakim A. Effect of resistance training during Ramadan on body composition and markers of renal function, metabolism, inflammation, and immunity in recreational bodybuilders. Int J Sport Nutr Exerc Metab. 2012;22(4):267–75.

14 Carbohydrate Utilization and Disposal in Strength/Power Training and Sports: Examining the Underexamined

Anthony L. Almada and David Barr

Abstract

Since the seminal work of Bergström and Hultman almost 50 years ago, a plethora of studies have focused upon carbohydrate utilization and disposal, predominantly in the context of endurance training and competition. Surprisingly, despite carbohydrate (primarily glycogen) being a predominant fuel substrate in strength/power training and sports, a relative paucity of data exists. The advent of low carbohydrate, "keto," "paleo," and "train low, compete high" diets has ushered in a widely held belief that even moderate carbohydrate intake is unwarranted and may promote excessive lipogenesis among intensively training individuals. A perusal of the literature wherein muscle glycogen is inaccessible (e.g., McArdle's disease) or quantified throughout exercise reveals substantial glycogenolysis during intense strength/power and high-intensity intermittent training, contrasted to a dearth of data regarding direct carbohydrate oxidation *rates* during such types of exercise. A greater understanding of carbohydrate flux and demands during strength/power training and sports may foster new investigations and applications, as well as accelerate training adaptations and performance.

Keywords

Glycogen • Carbohydrate • Lactate • Ketogenic • Resistance exercise • McArdle's disease • Intermittent exercise • High intensity • Intramuscular triglycerides

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Religion is like a pair of shoes…Find one that fits for you, but don't make me wear your shoes.

— George Carlin, comedian

And faith, by its very definition, tends to be impervious to intellectual argument or academic criticism.

— Jon Krakauer, author

14.1 Introduction

Matching the metabolic fuel demand rate with fuel selection/availability is what enables an athlete to perform six sets of squats for 8–10 repetitions at 75 % of 1 rep maximum (1RM) with 2 min of rest between sets, then run on a treadmill for 45 min at 50 % of maximal oxygen uptake (V_{O2max}), and then climb a 15 % grade of stairs over a distance of 100 m, in any order. The metabolic promiscuity of skeletal muscle, in its selection and utilization of substrates, is defined by the rate of ATP provision from available fuels. The major fuels available to muscle are lipid, carbohydrate, protein, and phosphocreatine (PCr). The relative abundance (capacity, in weight) of body lipid as a fuel substrate is offset by its reduced adenosine triphosphate (ATP) yield under training conditions marked by limited oxygen supply to working muscle. Indeed, energy yield from carbohydrate (CHO) oxidation during the performance of high-intensity work exceeds that obtained from lipid oxidation, both in rate and magnitude [1]. The superior kinetics of energy provision from CHO oxidation (via glycogenolysis and glycolysis) during intense exercise are contrasted to the relatively modest amount of carbohydrate stores (as glycogen, in the liver and muscle). Amino acids, primarily as branched chain amino acids (leucine, valine, and isoleucine; BCAAs), and predominantly leucine, are *trivial* fuels during intense exercise, e.g., resistance exercise [2, 3], yet skeletal muscle is the primary site of whole body leucine oxidation at rest [4]. Despite the abundance of body protein stores, it would seem counterproductive (from a teleological perspective) to the human organism to have even a modest reliance upon this potential fuel source, given that proteins exhibit essential structural, transport, catalytic (enzymatic), and locomotive roles, and abundant "storage" proteins remain *undiscovered*.

The immediate high-force generation (ATP) demands of high-intensity strength and power exercise are met by the integration of glycolysis and glycogen and phosphocreatine (PCr) breakdown (together comprising substrate-level phosphorylation) to support the obligate ATP resynthesis rates. The intramuscular glycogen reductions and lactate accumulation (from anaerobic glycolysis) that ensue from this type of muscular work can be seen within seconds after the onset of exercise [5–7]. The bioenergetic "power" liberated from substrate-level phosphorylation (of ADP to ATP) is offset by its low capacity (duration), rendering such high output *unsustainable* beyond a few minutes. In this context, it is intriguing to speculate that individuals exhibiting lower circulating and muscle PCr concentrations [8–10] may exhibit a relatively higher reliance upon anaerobic glycolysis, as has been demonstrated in mice with reduced muscle PCr under skeletal muscle ischemic (anaerobic glycolysis) conditions [11]. Recent genome-wide association studies in humans have described a link between single nucleotide polymorphisms in the gene encoding L-arginine:glycine amidinotransferase (AGAT), a rate limiting enzyme in de novo creatine biosynthesis, and blood concentrations of one of its direct products, homoarginine [12]. This suggests that muscle creatine and PCr concentrations in humans may be governed, in

part, by AGAT expression/activity. Collectively, these findings intimate a spectrum of ATP provision derived from the variable and integrated interplay between glycolysis/glycogenolysis and PCr hydrolysis, based upon resting muscle PCr content.

It is beyond the scope of this chapter to address PCr as a substrate. The reader is referred to some excellent reviews that include supplementation with creatine monohydrate to increase intramuscular PCr content and work capacity [13–17].

14.2 Substrate Utilization: Intramuscular Carbohydrate and Lipid

Skeletal muscle displays metabolic plasticity, enabling it to adapt to its state of fuel reserves and the diverse metabolic demands the human organism encounters. Among the two abundant, exercise-centric substrates supplied by diet and stored in muscle (lipid and carbohydrate), carbohydrate is unique in that it (1) is produced de novo (via gluconeogenesis); (2) is capable of acutely influencing performance when delivered from exogenous sources, e.g., intravenous and oral; *and* (3) can hyperaccumulate over a short time interval (glycogen supercompensation).

14.2.1 McArdle's Disease: Human "Knockout" Model of Glycogen-Free Exercise

Seminal studies by Hermansen et al. [18] and Tesch et al. [19] illuminated the substantial role of muscle glycogen in intermittent and continuous high-intensity (71–87 % of V_{O2max}) cycling and resistance training, respectively. Additional insights can be gleaned from assessing exercise performance and fuel utilization among persons living with McArdle's disease (MCD). In 1951, British physician Brian McArdle published his landmark case report of a patient presenting with idiopathic exercise intolerance [20]. McArdle had the patient perform an ischemic exercise test and noted their inability to display an increase in venous lactate (or pyruvate), which he inferred was due to a block in glycogenolysis.

MCD remains the most common muscle metabolic disease, defined by a lack of myophosphorylase, the skeletal muscle-specific isoform of glycogen phosphorylase. Myophosphorylase is the obligate enzyme in glycogenolysis [21]. Accordingly, persons with MCD chronically exhibit "supraphysiological" muscle glycogen concentrations, exceeding up to double that of persons without MCD, and do not display an increase or can even display a *decrease* in circulating lactate during exercise, the latter due to intramuscular lactate oxidation [20–23]. When a person with MCD commences moderate to vigorous exercise, the obligatory role of muscle glycogen is unveiled. Within several minutes after the onset of exercise, they experience an intolerance to further exercise, fatigue, tachycardia, and/or severe muscle pain, with no or only modest changes in muscle pH and lactate.

The genotypic hallmark of MCD is a mutation in the gene encoding for myophosphorylase and a frank absence of both the gene product and associated enzyme activity (among the majority of those with MCD [23]). The phenotypic trademark of MCD is a "second wind" [24], defined as an improved tolerability to exercise that manifests after a reduction in exercise intensity, after a brief rest, or abruptly after 8–10 min of sustained exercise. The lag period after initial exercise onset provides an opportunity for blood-borne (extramuscular) fuels (free fatty acids, hepatic-derived glucose, and, possibly, circulating lactate [24, 25]) to make pace with the substrate demands of exercise. Collectively, this results in a precipitous fall in heart rate and improved exercise tolerance. This reduced capacity at exercise onset underscores the critical role of glycogenolysis in the rest to exercise transition and the contribution of glycogenolysis to substrate-level phosphorylation. Indeed, in the index subject where the "second wind phenomenon" was first characterized [24], the subject reported performing a sprint race of approximately 200 yards, wherein he initially took the lead but at 50 yards began to fatigue and had to stop at 100 yards, due to a complete inability to move.

This suggests substrate-level phosphorylation relying solely upon PCr hydrolysis.

Provision of BCAAs to persons with MCD further underscores the insignificant role these amino acids exert vis-à-vis substrate utilization of exercising muscle: one open-label study with three MCD subjects provided 0.3 grams/kilogram body mass (g/kg bm) of a non-descript blend of BCAAs, 45–60 min before consecutive strength and endurance exercise bouts, with no enhancement over fasting or dextrose solution (provided 45 min pre-exercise) [26]. A single-blind design with six MCD subjects administered 77 mg BCAAs/kg bm (44 % leucine, 30 % valine, 26 % isoleucine) in a beverage 30 min before a 20-min bout of cycle ergometry at a maximum tolerable capacity [27]. Despite plasma individual BCAAs increasing 2.3–4.3-fold (3.8× higher for leucine) near the onset of exercise, the BCAA supplement was associated with an *ergolytic* effect in five of the six subjects, compared to a noncaloric placebo beverage.

Acute increases in lipid availability (via lipid infusion 30 min pre-exercise) do not improve exercise tolerance in MCD (defined by heart rate response) [28, 29], despite significant increases in whole body fat oxidation aligned with the onset of the second wind [30]. This suggests a "ceiling" effect of lipid oxidation and oxidative phosphorylation, perhaps due to reduced glycolytic flux and the attendant reduction in anaplerotic intermediates [31], e.g., pyruvate.

Distinctively, there do not appear to be any controlled, systematic dietary intervention studies employing long-term adaptation to a *low-carbohydrate/high-fat* diet in MCD, to assess the impact of an acquired shift in substrate selection [32]. The longest and largest open-label longitudinal study followed four persons (one female, three males) with MCD, undertaking a macronutrient shift to 70 % dietary fat and 20 % protein, for 18 months [33]. After 2 months, one male withdrew from the diet, while the remaining subjects persisted through 18 months. Despite blood creatine kinase concentration falling by 40 %, strength and endurance testing showed no improvement, and none of the subjects elected to continue with the diet.

A subset of patients with MCD display fractional (1–3 %) myophosphorylase activity and, thus, partial glycogenolytic capacity [23, 31]. These subjects with "atypical" MCD show markedly higher peak work rates in the initial first minutes of exercise onset, show a milder second wind phenomenon, and do *not* display a glucose-infusion-mediated second wind response. They also exhibit V_{O2max} and peak workloads (both during cycle ergometry) nearly double that of MCD with total myophosphorylase deficiency. Still, the V_{O2max} values are 55–65 % of age- and gender-matched controls [23]. In contradistinction, persons with atypical MCD display an anaerobic work capacity (ischemic maximal handgrip exercise) that is identical to that of MCD with frank myophosphorylase deficiency, being approximately one-third of control subjects [23].

Collectively, MCD, in both the severe and milder phenotypic forms, illustrates the axial role of muscle glycogen as a fuel substrate and of glycolytic flux for anaplerotic support of oxidative phosphorylation, in both low-moderate- and high-intensity exercises. This is further illustrated by the inability of acute increases in available lipid or oxidizable amino acid (BCAAs) substrate to compensate for the compromised availability of glucose substrate. The unavailability of glycogen's glucose reserves translates into significant reductions in absolute exercise tolerance and relative exercise performance.

14.2.2 Resistance Exercise

Studies that have examined carbohydrate utilization during exercise appear to be heavily skewed toward *endurance* training. Whether this reflects the personal interests of researchers, the preferences of granting agencies, or other variables is irrelevant, but it does illuminate the relatively small body of evidence supporting resistance training and substrate utilization. Notably, there appear to be a lack of studies that have systematically examined, with quantitative measurements (e.g., stable isotopes), glucose and lipid oxidation *during* resistance training (RT), the challenging nature of RT being an *intermittent* exercise not

being unrecognized [34]. Nevertheless, several studies have examined muscle glycogen utilization during intensive RT bouts. The germane, pioneering work of Tesch and colleagues was first evidenced in a study with nine experienced male bodybuilders (five were competitive) who performed an array of resistance training exercises to failure, targeting the upper legs, after consuming a light breakfast (composition not described) [35]. Following the completion of 20 sets (five sets for each of four exercises; repetitions to self-determined failure on every set; approximately 30-min duration), muscle glycogen in the left vastus lateralis had declined by 26 % (the paper described a *40* % decrease).

In a follow-up report 4 years later from Tesch's laboratory [36], using the same experimental data as in [35], they reported a 28 % fall in glycogen. Additionally, they also described changes in intramuscular triglyceride content IMTG. Four of the nine subjects showed very low IMTG, while the intersubject range at rest varied greater than sixfold (muscle glycogen content varied by *1.6-fold* between subjects). Among the five subjects with pre-exercise IMTG greater than 20 mmol/kg dry weight (dw) of muscle, post-exercise IMTG had declined, the group (inclusive of the other four subjects) showing a mean 30 % decrease. Complementing the intramuscular substrate change, halfway through the training session, the concentration of plasma free fatty acids (FFA) had increased modestly (≈15 %), while plasma glycerol rose nearly eightfold by the end of the session, attaining its zenith in the first 10 min after finishing the bout. The authors asserted that a higher resting IMTG fostered a greater utilization of this fuel substrate during the training session, irrespective of the resting muscle glycogen content, with both substrates being used but a higher resting IMTG exerting an apparent glycogen "sparing" effect. However, this study did not systematically assess if IMTG was *utilized as a fuel substrate* (by whole body or working muscle) during RT, only their disappearance.

Other studies have shown reductions in both muscle glycogen and IMTG after a *single* bout of leg RT, under acute low- and high-carbohydrate diet/glycogen deplete and replete conditions, respectively (*endurance*-trained cyclists/triathletes; [37]), and in untrained lean males [38] and overweight females [39]. A recent study employed a supervised, 6-week RT program with lean (22.9 % body fat), sedentary males [40]. Before and after completion of the RT program, the subjects performed a single bout of 1 h of cycle ergometry at ≈ 65 % of V_{O2max} (for the post-RT cycling bout, the subjects cycled at ≈ 65 % of *pre*-RT V_{O2max}). No post-training changes in carbohydrate or fat oxidation rates nor respiratory exchange ratio (RER) manifested, while heart rate (after completion of the training program) was significantly lower. Remarkably, IMTG in type I muscle fibers (post-RT program; at rest) *increased* significantly (+52 %; $P=0.01$) and by 46 % ($P=0.10$) in type II fibers. After the pre-RT cycle bout, type I fiber IMTG declined by 30 % ($P=0.04$) yet did not appear to change in type II fibers. Subsequent to 6 weeks of RT, the cycle bout induced a drop of IMTG within both type I (43 %; $P<0.01$) and type II (37 %; $P=0.01$) fibers. The greater magnitude of disappearance of IMTG from the endurance exercise bout, after a 6-week RT program, coupled with the absence of a change in whole body fat oxidation rates, strongly suggests that lipid substrate shifted from FFA of plasma origin to IMTG. The overt demonstration of increased whole body utilization of IMTG [41] during *resistance training* remains to be validated.

A study by Robergs et al. evaluated eight resistance-trained males who performed two different, RT regimens with equal work amounts but differing intensities, on consecutive days [42]. On the first day, all subjects performed six sets of six repetitions of single leg extensions at 70 % of one repetition maximum (1RM). The next day, subjects completed six sets of leg extensions with the contralateral leg, but at 35 % of 1RM. Muscle biopsies (vastus lateralis) were taken immediately before each exercise, after completion of the third and sixth sets, and 2 h post exercise (no caloric intake was allowed during the recovery period). Muscle glycogen fell similarly in each treatment (39 % for 70 % 1RM and 38 % for 35 % 1RM). Correspondingly, the

rate of glycogenolysis during the 70 % 1RM bout was approximately double that observed during 35 % 1RM, with the time to completion and repetitions/set during the 35 % 1RM exercise being approximately twice that of 70 % 1RM. Lacking from this design was a crossover component, to assess the impact of an order effect, i.e., would the 35 % 1RM bout performed on day *1* have altered the glycogen utilization rate relative to day 2, at 70 % 1RM?

An investigation by MacDougall (first reported in 1988 as a meeting abstract; [43]) and collaborators assessed muscle glycogen utilization in a prized, but rarely biopsied, muscle group—the *biceps brachii*. Eight experienced, bodybuilding-type RT men performed one or three sets of single arm, seated bicep curls at 80 % 1RM to failure [44]. Muscle biopsies were obtained from the control arm prior to the exercise and from the exercising arm after finishing either set. A statistically nonsignificant (12 %) decline in muscle glycogen was noted after the single set exercise. After completion of the three sets, a significant (24 %; $P<0.05$) decline was measured.

As part of a carbohydrate supplementation crossover intervention, Haff and colleagues [45] engaged eight resistance-trained males to perform a series of three RT bouts: (1) a warm-up set and then three higher-intensity (2.09 rad/s) sets of 10 reps of isokinetic leg extensions/flexions (ISO1) (3-min rest between sets); (2) 5 min after finishing the isokinetic bout, three sets of ten reps of each of three different squat exercises (3-min rest between sets; SQ); and (3) after 5 min of rest after the squat exercises, the subjects repeated the isokinetic test (ISO2). Muscle (vastus lateralis) biopsies were procured prior to and immediately after ISO1 and SQ. After ISO, muscle glycogen had decreased by 15.2–19.2 %. After SQ, it had declined by 40.7 % compared to baseline/pre-ISO and by 26.7 % between post-ISO and post-SQ.

Dietary manipulation combined with strategic glycogen-depleting exercise has been utilized to assess differences in separate limbs within the same subjects. In a study from John Hawley's lab, Churchley et al. enrolled seven, resistance-trained males and implemented acute diet and exercise treatments to produce a glycogen-adequate ("Normal") leg and a glycogen-reduced ("Low"), contralateral leg [46]. Subjects performed eight sets of five repetitions of single leg presses at 80 % 1RM, for each leg. The exercise began with the Low leg, with 60 s of rest before the Normal leg completed the same set. Weight was dropped by 5 % in sets where the Low leg could not perform five repetitions. Muscle biopsies (vastus lateralis) were harvested prior to the exercise and after the last (eighth) set for each leg. Despite resting glycogen in Low being significantly lesser (−44 %; $P<0.01$) than Normal, net glycogen utilization (in mmol/kg dw) was similar between legs. However, the markedly lesser pre-bout glycogen in the Low leg led to 47 % of baseline glycogen being utilized, contrasted to 28 % of the pre-RT bout glycogen measured in the Normal leg. Distinctively, work capacity of the Low leg was impaired, relative to the Normal leg (JA Hawley, personal communication).

Resistance exercise has an obligate requirement for glycogen in a variety of muscle groups, evidenced by significant utilization even after the performance of three sets. It appears that the moderate to substantial disappearance (likely utilization) of intramuscular/intramyocellular lipid during resistance training is widely unappreciated. Its metabolic role in this type of training remains to be revealed.

14.2.3 Power/High-Intensity Intermittent Exercise

High power output/supramaximal exercise has been used to ascertain the magnitude and kinetics of glycogen utilization. The use of a bicycle ergometer, over a non-motorized treadmill, allows for the optimization of a load defined by the applied resistance, with a treadmill's resistance being the inertial elements of the belt and bearings and only the *propulsive* aspect of total power generated by running being captured [47]. Gollnick et al. had six endurance-trained males. perform six, one minute bouts at ≈ 150 % V_{O2max} on a bicycle ergometer, with a 10-min rest period

intervening between each bout [48]. Muscle biopsies (vastus lateralis) were taken before the first bout and after the first, third, and sixth bouts. After bout 1, glycogen had fallen by 20 % and continued to decline in a linear fashion such that after bout 6, it had reached a value 62.8 % less than baseline (pre-bout 1). After the final bout, the subjects reported being unable to continue, associated with glycogen depletion in fast twitch muscle fibers.

A group comprised of two well-trained (oarsmen/rowers) and four recreationally active males performed high-intensity cycle ergometry (≈140 % V_{O2max}) for 1-min intervals, with 3-min rest periods, until they were unable to sustain 30 s of cycling. MacDougall and colleagues [49] demonstrated that this high-intensity intermittent exercise protocol elicited a variable decrement in muscle glycogen (pre vs. post exercise), ranging from 41.3 to 82.9 % (one of the oarsmen displayed the smallest decline while the other the greatest drop in glycogen content, within the group; the oarsmen also displayed the shortest times to exhaustion: ≈ 6–7 min). As a group, the mean decline in glycogen was 46 %. Because the supramaximal effort defined by ≈ 140 % V_{O2max} is relative, the two oarsmen undertook workloads that were dramatically greater, on an absolute scale, relative to the other four subjects. The authors thus ascribed the shorter times to exhaustion to this factor. No explanation was given for the variance in glycogen utilization rates between the oarsmen, although work and power output were not measured.

High-intensity intermittent training (HIIT) has been associated with a progressive impairment in glycogenolysis. In 1986, McCartney and collaborators had eight active but untrained males perform four 30-s maximal isokinetic cycling bouts, with an intervening 4-min rest period [50]. After the first bout, leg muscle (vastus lateralis) glycogen was reduced by 21.2 % (relative to baseline), fell another 21.8 % after bout 2 (equal to a 38.5 % decrease from baseline), and then ceased declining through bouts 3 and 4. Peak and average power fell by an additional ≈ 21 % in bout 3 and did not change further in bout 4. The arrested glycogenolysis seen after bouts 3 and 4 was marked by no further increase in plasma lactate and a dramatic, fivefold rise in plasma glycerol, unattended by a rise in plasma fatty acids. Two of the subjects had intramuscular ATP and PCr content measured just before the *beginning* of bouts 2 and 4, displaying significant rephosphorylation recovery (ATP, 95 and 90 % of baseline, respectively; PCr, 76 and 78 % of baseline, respectively). The authors speculated that the glycerol-specific rise was indicative of significant lipolysis of IMTG, the liberated FFA undergoing intramuscular oxidation and thus not appearing in the circulation, although no data were collected to support this hypothesis.

Eight physical education students undertook an HIIT protocol, involving ten maximal cycle ergometer sprints of 6-s duration, with a 30-s recovery between each sprint [6]. Muscle (vastus lateralis) biopsies obtained at baseline and after the first bout revealed a 13.7 % decline ($P<0.01$). Muscle glycogen fell by 13.7 % after bout 1 ($P<0.01$), by 19.1 % ($P<0.01$) between the end of bout 1 and *prior* to bout 10, and 8.8 % ($P<0.01$) from pre-bout 10 to post-bout 10. The total decline from baseline, after ten bouts, was 36.4 % ($P<0.01$). The calculated drop in the glycogenolytic rate seen in the first sprint and the last (tenth) was tenfold. In contrast, PCr hydrolysis was calculated to provide 80 % of the ATP generation during the tenth sprint. Gaitanos et al. asserted that the 30-s rest interval was adequate to support bioenergetically significant rephosphorylation of creatine to PCr and thus contribute to power output in the face of a large decline in glycogenolysis.

In another HIIT protocol, apparently untrained young males undertook three, 30-s maximal isokinetic cycling bouts with 4-min rest periods [51], and muscle (vastus lateralis) biopsies were taken at rest and at 6, 15, and 30 s of bouts 1 and 3. Average power output during bout 1 was 35.5 % greater than bout 3. After bout 1, muscle glycogen was reduced by ≈ 19 % yet did not undergo further change, even after bout 3. Muscle lactate concentration increased dramatically (numerical values not provided) by the end of bout 1 and had climbed even higher by the *beginning* of bout 3 yet did not change thereafter.

Muscle PCr content fell significantly (91.4 %; $P<0.05$) from rest to the end of bout 1. However, although bout 3 PCr content was significantly reduced ($P<0.05$) relative to the same time point in bout 1, the concentration was 78 % of that measured *before* bout 1.

These power/HIIT studies support the notion that substrate-level phosphorylation relying ***primarily*** *upon PCr hydrolysis (as described above in McArdle's disease—with absent or greatly compromised glycogenolysis and glycolytic flux) may be insufficient to sustain maximal power generation. Muscular work requiring substantial power outputs, as seen in HIIT, has an essential reliance upon substrate-level phosphorylation (both glycogen-fueled glycolysis* ***and*** *PCr) to meet the metabolic ATP demands. The repeated performance of this type of training results in dramatic reductions in the rate of glycogen utilization, with power output being supported, albeit with a progressive, temporal decrement, by phosphocreatine-dependent ATP resynthesis.*

14.2.4 Manipulation of Muscle Glycogen I. Acute Low-Carbohydrate Diet

Short-term (1–7 days) restriction of dietary carbohydrate, in combination with specific exercises that promote glycogen depletion and reductions in glycogenic substrate, offers insight into the contribution of muscle (and liver) glycogen to fuel provision and muscular performance. In 1989, Symons and Jacobs published what may be the first paper assessing resistance exercise performance in a reduced muscle glycogen state [52]. They enrolled eight male subjects "accustomed" to (training state not defined) leg RT exercises and had them perform a battery of exercise: electrical stimulation of the leg extensors to determine isometric force; determination of maximal, voluntary isometric contraction (leg extension); and a muscle fatigue test (MFT) via 50 isokinetic maximal single leg extension repetitions. Glycogen depletion was achieved through cycling (ergometer) at varying intensities and durations and maximal unilateral leg extensions. Subjects performed the same tests, once with a 2.5-day period of low-carbohydrate (meals provided; 60–80 g/day; ≈ 8–10 % CHO) intake and the other experimental period where the subjects ate their "normal" diet (carbohydrate content not described). Muscle biopsies (vastus lateralis) revealed a mean 64.2 % reduction in glycogen after the low-carbohydrate diet (153 mmol/kg dw) relative to the control diet (427 mmol/kg dw). Despite this change, the performance measures, and whole blood (earlobe) lactate concentrations, did not differ between treatments.

A decade later, Balsom and colleagues [53] had seven trained physical education students (type of training not described) perform an exhaustive cycling protocol (variable intensity and duration, to achieve muscle glycogen depletion). Twenty-four hours later, they performed an HIIT session comprised of fifteen 6-s bouts on a cycle ergometer with a target pedaling frequency (140 rpm), with 30-s rest intervals ("Short"). This was then followed 24 h later by a different HIIT protocol, employing the same exercise and rest intervals but to a predetermined fatigue point ("Long") rather than a specific number of bouts, with ≈ 20 % lesser resistance applied to the ergometer's flywheel (relative to Short). Each subject performed this entire protocol twice, differing by adherence to a low-carbohydrate (meals supplied; ≈ 30 g/day; 4 % CHO, 64 % fat, and 32 % protein) or high-carbohydrate (meals supplied; ≈ 500 g CHO/day; ≈ 67 % CHO, 20 % fat, and 13 % protein) diet over the 48-h period between the glycogen depletion exercise session and the Long HIIT protocol. Muscle (vastus lateralis) glycogen in the low-CHO diet, prior to Short, was 54.7 % lower ($P<0.05$) than after high-CHO diet. Glycogen utilization during the Short HIIT bout did not significantly differ between diet treatments. Glycogen concentrations in the low-CHO treatment prior to Long (which afforded an additional day of dietary intervention) were not different than before Short, but a further increase in high-CHO diet led to a 66.5 % difference ($P<0.05$). During the first 3 s of each of the 15 bouts, pedaling frequency did not differ between diets, yet the decline in frequency seen in the final 3 s of the last four

bouts was significantly greater in low CHO ($P<0.05$). After Long, the low-CHO treatment utilized 117 mmol/kg dw glycogen (a 64.6 % decline from pre-Long), while high-CHO treatment consumed 389 mmol/kg dw (a 72 % decline from pre-Long). The number of 6-s bouts completed during Long under low-CHO diet was 111, while high-CHO diet completed 294 bouts, a 265 % difference. Whole blood (fingertip) lactate values at the end of Short and Long were not different, irrespective of diet treatment, whereas plasma FFA were 64.4 % higher ($P<0.05$) *prior* to Long but were similar between groups after Long.

Using a design modified from Phinney et al. [54], Lambert [55] and colleagues enrolled five trained cyclists, who were randomly assigned to two diet treatments of 2-week duration, followed by a 2-week washout period (ad libitum/"normal" diet), and then a crossover to the other diet. The high-fat ("FAT") diet provided 7.1 % CHO, 67.3 % fat, and 25.5 % protein. The high-CHO ("CHO") diet afforded 73.6 % CHO, 12.0 % fat, and 13.5 % protein. Although the diets were isocaloric, total caloric intake was not described. Exercise tests were performed at the end each diet treatment. In a fasted state, subjects performed a series of 5-s tests on a cycle ergometer at maximal cadence, with randomly varying intensities, to determine maximum pedaling velocity and force of contraction. Each subject then performed a single 30-s Wingate test on the ergometer to assess peak power output. Thirty minutes of rest followed the Wingate test and then subjects were biopsied (vastus lateralis). Glycogen content was 77.1 % greater ($P<0.01$) with CHO diet over FAT, yet no differences were seen between groups for any of the performance measures. Immediately after the biopsy, the subjects performed a high-intensity cycling bout (85 % of peak power output; ≈ 90 % V_{O2max}) until exhaustion, and then another biopsy was obtained. Muscle glycogen utilization rates did not differ between CHO and FAT, with CHO glycogen at *exhaustion* being similar to the pre-exercise, *starting* glycogen value for FAT. The mean time to exhaustion for CHO (12.5 min) was 50.6 % greater than FAT (8.3 min) but was not statistically significant (likely attributable to the small sample size: $n=5$). It is noteworthy that the subjects were described as being nonketotic, defined by no differences in plasma ß-hydroxybutyrate (BHB) concentrations.

In a follow-up study with Lambert and Noakes from [55], Havemann and associates employed a 6-day high-fat diet (FAT; 68.2 % fat, 16.8 % CHO [150 g/day], and 15.0 % protein; 3,560 kcalories/day), followed by a single day of CHO loading (≈90 % of total calorie intake and providing 8–10 g CHO/kg bm) [56]. Subjects (eight endurance-trained male cyclists) also crossed over to a high-CHO diet for 6 days (CHO; 17.1 % fat, 67.8 % CHO [602 g/day], and 15.1 % protein; 3,550 kcalories/day). A 2-week washout separated the diet treatments, with subjects randomly assigned in a single-blind manner. All meals were provided to the subjects. On the eighth day after each diet treatment, subjects performed a 100-km, varying intensity time trial on a cycle ergometer, with four, 1-km, high-intensity sprints (>90 % of peak power output; W_{peak}) and four, 4-km sprints (≈78–84 % W_{peak}) interspersed through the distance. At periodic intervals, subjects ingested a 10 % maltodextrin solution (200 ml every 20 min) to maintain plasma glucose concentrations. This type of time trial was intended to mimic real-world, road-racing conditions. Mean power output during the 1-km sprints was significantly lower ($P<0.05$) after FAT, compared to CHO (≈55V less), evidenced during the first three sprints (the fourth and final sprint was at 99 km, *1 km before finishing the bout*, possibly influencing motivation for a higher power output, which was virtually identical to the CHO diet condition). Blood lactate, FFA, and glucose did not differ during any time period. *Unfortunately, muscle glycogen was not measured*. On days 3 and/or 5 of the diet, wherein steady-state cycling (≈70 % V_{O2max}) was performed, six of the eight subjects during the FAT diet period complained of "tired" and "burning" legs and a difficulty in maintaining the training cadence at the defined workload, with two subjects unable to complete the 60-min session. This is likely reflective of the high-fat/low-CHO *maladapted* metabolic state of the subjects.

14.2.5 Manipulation of Muscle Glycogen II. Chronic Low-Carbohydrate Diet

Aggressive and sustained exclusion of carbohydrate intake in individuals fosters the genesis of ketone bodies (BHB, acetoacetate) in metabolically significant quantities. Because of the protracted intervention period warranted, to achieve metabolic *adaptation* during a ketogenic diet [32], these studies are typically designed over periods of at least 2–4 weeks of continuous diet alteration. Fleming and colleagues within Jeff Volek's laboratory enrolled 20 moderately active, noncompetitive athlete males engaged in regular endurance and resistance training [57]. An earlier report [58], not cited in [57], provides more detailed information on the subjects and body composition changes in the same study. Twelve subjects were randomized to a high-fat/low-CHO diet (FAT; 61 % fat [157 g/day], 8 % CHO [46 g/day], and 15.1 % protein [176 g/day]; 2,335 kcalories/day [all are mean values]). The remaining eight maintained their habitual diet (NORM; 26 % fat [56 g/day], 58 % CHO [283 g/day], and 16 % protein [80 g/day]; 1,950 kcalories/day). The FAT diet provided ≈ 2.2–2.3 g protein/kg/day whereas NORM provided 0.9 g/kg/day. Serum BHB concentrations were significantly elevated ($P \leq 0.05$) at weeks three and six of FAT, to which the authors ascribed dietary compliance with the ketogenic, FAT diet. After 6 weeks, FAT diet subjects had achieved significant changes in body composition ($P \leq 0.05$) relative to baseline: 1.1-kg lean body mass increase and 3.3-kg reduction in fat mass. The NORM diet was not associated with any alterations in body composition. Despite the favorable changes in body composition, several high-intensity performance measures were impaired after FAT. V_{O2max} fell significantly (6.6 %; $P \leq 0.05$) from baseline values, while peak and mean power during the first of two 30-s Wingate tests declined by 10.5 % and 20.7 % ($P \leq 0.05$), respectively. No significant performance changes were seen after NORM.

Compared to road or off-road cycling, cycle ergometry *lacks* a propulsion component (stationary state; absence of rolling resistance against the contact surface). Following the FAT diet intervention, the subjects lost an average of 2.2 kg body mass, including ostensibly significant ($P \leq 0.05$) and favorable changes of body composition in the legs and trunk (and the aforementioned whole body shifts). After expressing peak power in the first Wingate test as a function of the post-diet body weight, the FAT treatment still yielded a significant decrement (8.9 %; $P \leq 0.05$).

Several studies have shown that ideal dietary protein intakes for athletes range between 1.3 and 1.8 g/kg (reviewed in [59]). In light of this, one could assert that the NORM diet was inadequate in *daily* protein intake (0.9 g/kg) while the FAT diet provided a surfeit (2.2–2.3 g/kg) [57, 58]. Approximately half of the subjects engaged in regular RT. The absence of muscle glycogen and blood substrate (lactate, FFA, glycerol) measurements, before and during exercise, render these findings challenging to explain beyond a chronic, low-carbohydrate/high-fat/high-protein diet producing impairments in high-intensity exercise performance, juxtaposed to what many athletes would consider desirable shifts in body composition.

In another 2003 study where muscle biopsies *were* performed, Vogt et al. randomized 11 male, competitive duathletes/triathletes (mean of 5 years' experience) into a crossover design with two, 5-week dietary intervention periods [60]. The two diets were the following: FAT was comprised of 52.9 % fat (192 g/day), 31.4 % CHO (246 g/day), and 14.4 % protein (112 g/day), 3,268 kcalories/day, and CHO was comprised of 16.5 % fat (53 g/day), 68.2 % CHO (475 g/day), and 14.3 % protein (100 g/day), 2,905 kcalories/day (all are mean values). In random order, the subjects were assigned to one diet and then switched to the other diet, uniquely *without* a washout period. Body weight and composition did not change throughout the study. The kcalorie intake during FAT was significantly greater than CHO (12.5 %, $P < 0.05$). Pre-diet muscle (vastus lateralis) glycogen values did not differ from either dietary treatment. The authors commented that 4 of the 11 subjects displayed increased

muscle glycogen during the FAT diet (data not described in the paper). The IMTG change after FAT was significantly greater after FAT, compared to CHO (223.1 %; $P<0.01$). Maximal power output during a V_{O2max} test performed at baseline and at the end of each dietary period did not differ nor did maximal blood lactate (capillary; collection site not described) concentrations. The absence of an impact of the FAT diet on muscle glycogen concentrations (487.8 mmol/kg dw) is not surprising with an average 31 %/246 g carbohydrate intake/day, in conjunction with a 12 % greater energy intake relative to CHO, which may explain the lack of performance differences between interventions.

In toto, these diverse studies that attempted to manipulate muscle glycogen concentrations suggest that moderate-intensity exercise may be sustainable under conditions of reduced muscle glycogen or moderate reductions in dietary carbohydrate. However, near-maximal and supramaximal high-intensity exercise performance can be compromised, even after acute glycogen loading following CHO restriction. The need for more rigorous studies that employ serial primary endpoint measures (muscle glycogen, IMTG, and direct substrate utilization, e.g., stable isotopes of glucose and palmitate), and the provision of adequate protein intakes, is patently clear.

14.3 Exogenous Substrate Provision: Pre- and Intra-exercise Carbohydrate Supplementation

Given that glycolytic flux is augmented by strength and power exercise bouts, it is of interest to systematically determine the impact of providing exogenous carbohydrate prior to, and during, the performance of these types of exercise. Abundant studies have been performed with CHO supplementation before and during *endurance* exercise (reviewed in [61, 62]). Although a number of pre- and intra-high-intensity exercise carbohydrate supplementation studies have been undertaken [63–70], with a variety of carbohydrate sources and yielding equivocal results, there appears to be only *one* report in which muscle glycogen measurements were performed.

In 2000, Haff and his colleagues ([45]; vide supra) evaluated the influence of providing carbohydrate to eight resistance-trained males. Subjects entered the laboratory in a 3-h fasted state, and baseline muscle (vastus lateralis) biopsies were obtained. On each of the two testing days, a CHO drink (Gatorlode®, Quaker Oats; 20 % maltodextrin and dextrose) or flavor-, color-, and *volume*-matched, noncaloric placebo (aspartame sweetened) was administered both after the isokinetic leg extension/flexion session and 10 min prior to the commencement of the leg RT session (1.0 g CHO/kg bm; mean dose of 86.0 g CHO). Thereafter, every 10 min during the RT bout, subjects ingested 0.3 g CHO/kg bm (mean dose of 25.8 g), administered three times during the session. The CHO drink significantly reduced glycogen utilization during the RT bout relative to placebo (48.0 %; $P<0.01$). After the RT bout, the subjects performed another bout of isokinetic exercise (three sets of ten reps, with 3-min rest between sets). None of the performance variables were altered by CHO supplementation.

It is unfortunate that a dearth of studies exists that employ direct measures of muscle substrate utilization/disappearance during strength and power exercise. As mentioned in Chap. 16, *Beyond the Obvious: Future Innovation in Sports Nutrition*, of this book (note: also previously mentioned above, in this chapter), the financial, ethical, and recruitment challenges associated with *muscle biopsies* have proven an enduring deterrent to include this pivotal substrate measure in studies where fuel selection, utilization, and resynthesis are being explored. Thus, the true role and impact of pre- and intra-exercise supplementation around high-intensity power and strength training remain enigmatic.

14.4 Conclusion

The plasticity of the skeletal muscle to select fuel substrate [71] is an intriguing facet of exercise biochemistry across the intensity spectrum.

Among healthy individuals, muscle glycogen is *always* utilized to a variable yet metabolically significant degree, irrespective of the work intensity. This axiom of muscle metabolism is magnified by metabolic diseases wherein muscle glycogen is biologically unavailable as a substrate, e.g., McArdle's disease and among persons living with McArdle that have a modicum of residual myophosphorylase activity. The current enchantment with low or reduced carbohydrate diets among athletes engaging in high-intensity/intermittent training does not appear to align with an evidence base and indeed may be misguided. In fact, dietary strategies focused upon reduced dietary carbohydrate intakes among these exercising/competing individuals may indeed *compromise* performance. Clearly, more systematic studies with primary endpoint measures (muscle glycogen, lipid, and direct assessments of whole body substrate oxidation, i.e., stable isotopic measures) are earnestly needed to provide enlightened guidance. Moreover, the critical question as to the *nutritional state* of subjects in such studies, immediately prior to performance and substrate assessments, remains ignored. Is it prudent and relevant that a *carbohydrate-adapted* subject be fed a low-carbohydrate, high-fat meal before [57], or a high fat/low carb, partially adapted subject be given a carbohydrate drink [56] during, the capturing of exercise performance and metabolic data? What is the difference in outcome measures if adapted subjects have assessments undertaken in a *fasted versus fed* (feeding *aligned* with their prior diet composition) state? As the pace of science continues, it is hoped that emerging, rigorous evidence will displace the rampant evangelism that defines this topic.

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References

1. Brooks GA. Bioenergetics of exercising humans. Compr Physiol. 2012;2:537–62.
2. Tarnopolsky MA, Atkinson SA, MacDougall JD, Senor BB, Lemon PW, Schwarcz H. Whole-body leucine metabolism during and after resistance exercise in fed humans. Med Sci Sports Exerc. 1991; 23:326–33.
3. Moore DR, Del Bel NC, Nizi KI, Hartman JW, Tang JE, Armstrong D, et al. Resistance training reduces fasted- and fed-state leucine turnover and increases dietary nitrogen retention in previously untrained young men. J Nutr. 1997;137:985–91.
4. Tessari P, Garibotto G, Inchiostro S, Robaudo C, Saffioti S, Vettore M, et al. Kidney, splanchnic, and leg protein turnover in humans. J Clin Invest. 1996;98:1481–92.
5. Hultman E, Greenhaff PL, Ren JM, Söderlund K. Energy metabolism and fatigue during intense muscle contraction. Biochem Soc Trans. 1991;19:347–53.
6. Gaitanos GC, Williams C, Boobis LH, Brooks S. Human muscle metabolism during intermittent maximal exercise. J Appl Physiol. 1993;75:712–9.
7. Sahlin K, Tonkonogi M, Söderlund K. Energy supply and muscle fatigue in humans. Acta Physiol Scand. 1998;162:261–6.
8. Delanghe J, De Slypere JP, De Buyzere M, Robbrecht J, Wieme R, Vermeulen A. Normal reference values for creatine, creatinine, and carnitine are lower in vegetarians. Clin Chem. 1989;35:1802–3.
9. Watt KK, Garnham AP, Snow RJ. Skeletal muscle total creatine content and creatine transporter gene expression in vegetarians prior to and following creatine supplementation. Int J Sport Nutr Exerc Metab. 2004;14:517–31.
10. Burke DG, Chilibeck PD, Parise G, Candow DG, Mahoney D, Tarnopolsky M. Effect of creatine and weight training on muscle creatine and performance in vegetarians. Med Sci Sports Exerc. 2003;35: 1946–55.
11. Nabuurs CI, Choe CU, Veltien A, Kan HE, van Loon LJC, Rodenburg RJT, et al. Disturbed energy metabolism and muscular dystrophy caused by pure creatine deficiency are reversible by creatine intake. J Physiol. 2013;591:571–92.
12. Choe CU, Atzler D, Wild PS, Carter AM, Böger RH, Ojeda F, et al. Homoarginine levels are regulated by L-arginine:glycine amidinotransferase and affect stroke outcome: results from human and murine studies. Circulation. 2013;128:1451–61.
13. Wallimann T, Wyss M, Brdiczka D, Nicolay K, Eppenberger HM. Intracellular compartmentation, structure and function of creatine kinase isoenzymes in tissues with high and fluctuating energy demands: the 'phosphocreatine circuit' for cellular energy homeostasis. Biochem J. 1992;281:21–40.
14. Harris R, Söderlund K, Hultman E. Elevation of creatine in resting and exercised muscle of normal subjects by creatine supplementation. Clin Sci. 1992;83:367–74.
15. Sahlin K, Harris RC. The creatine kinase reaction: a simple reaction with functional complexity. Amino Acids. 2011;405:1363–7.
16. Wyss M, Kaddurah-Daouk R. Creatine and creatinine metabolism. Physiol Rev. 2000;80:1107–213.

17. Maughan RJ, Greenhaff PL, Hespel P. Dietary supplements for athletes: emerging trends and recurring themes. J Sports Sci. 2011;29(Suppl1):S57–66.
18. Hermansen L, Hultman E, Saltin B. Muscle glycogen during prolonged severe exercise. Acta Physiol Scand. 1967;71:129–39.
19. Tesch PA, Colliander EB, Kaiser P. Muscle metabolism during intense, heavy-resistance exercise. Eur J Appl Physiol Occup Physiol. 1986;55:362–6.
20. McArdle B. Myopathy due to a defect in muscle glycogen breakdown. Clin Sci. 1951;10:13–33.
21. Beynon RJ, Bartram C, Hopkins P, Toescu V, Gibson H, Phoenix J, et al. McArdle's disease: molecular genetics and metabolic consequences of the phenotype. Muscle Nerve. 1995;3:S18–22.
22. Nielsen JN, Vissing J, Wojtaszewski JFP, Haller RG, Begum N, Richter EA. Decreased insulin action in skeletal muscle from patients with McArdle's disease. Am J Physiol Endocrinol Metab. 2002;282: E1267–75.
23. Vissing J, Duno M, Schwartz M, Haller RG. Splice mutations preserve myophosphorylase activity that ameliorates the phenotype in McArdle disease. Brain. 2009;132:1545–52.
24. Pearson CM, Rimer DG, Mommaerts WF. A metabolic myopathy due to absence of muscle phosphorylase. Am J Med. 1961;30:502–17.
25. Kitaoka Y, Ogborn DI, Mocellin NJ, Schlattner U, Tarnopolsky M. Monocarboxylate transporters and mitochondrial creatine kinase protein content in McArdle disease. Mol Genet Metab. 2013;108: 259–62.
26. Kushner RF, Berman SA. Are high-protein diets effective in McArdle's disease? Arch Neurol. 1990;47:383–4.
27. MacLean D, Vissing J, Vissing SF, Haller RG. Oral branched-chain amino acids do not improve exercise capacity in McArdle disease. Neurology. 1998;51: 1456–9.
28. Andersen ST, Vissing J. Carbohydrate- and protein-rich diets in McArdle disease: effects on exercise capacity. J Neurol Neurosurg Psychiatry. 2008;79: 1359–63.
29. Andersen ST, Jeppesen TD, Taivassalo T, Sveen ML, Heinicke K, Haller RG, et al. Effect of changes in fat availability on exercise capacity in McArdle disease. Arch Neurol. 2009;66:762–6.
30. Ørngreen MC, Jeppesen TD, Tvede Andersen S, Taivassalo T, Hauerslev S, Preisler N, et al. Fat metabolism during exercise in patients with McArdle disease. Neurology. 2009;72:718–24.
31. Haller RG, Vissing J. Spontaneous "second wind" and glucose-induced second "second wind" in McArdle disease: oxidative mechanisms. Arch Neurol. 2002;59: 1395–402.
32. Phinney SD. Ketogenic diets and physical performance. Nutr Metab. 2004;1:2.
33. Quinlivan R, Martinuzzi A, Schoser B. Pharmacological and nutritional treatment for McArdle disease (Glycogen Storage Disease type V). Cochrane Database Syst Rev. 2010;12, CD003458.
34. Vezina JW, Der Ananian CA, Campbell KD, Meckes N, Ainsworth BE. An examination of the differences between two methods of estimating energy expenditure in resistance training activities. J Strength Cond Res. 2014;28:1026–31.
35. Tesch PA, Colliander EB, Kaiser P. Muscle metabolism during intense, heavy-resistance exercise. Eur J Appl Physiol Occup Physiol. 1986;55:262–6.
36. Essén-Gustavsson B, Tesch PA. Glycogen and triglyceride utilization in relation to muscle metabolic characteristics in men performing heavy-resistance exercise. Eur J Appl Physiol Occup Physiol. 1990; 61:5–10.
37. Creer A, Gallagher P, Slivka D, Jemiolo B, Fink W, Trappe S. Influence of muscle glycogen availability on ERK1/2 and Akt signaling after resistance exercise in human skeletal muscle. J Appl Physiol. 2005;99: 950–6.
38. Koopman R, Manders RJ, Jonkers RA, Hul GB, Kuipers H, van Loon LJ. Intramyocellular lipid and glycogen content are reduced following resistance exercise in untrained healthy males. Eur J Appl Physiol. 2006;96:525–34.
39. Harber MP, Crane JD, Douglass MD, Weindel KD, Trappe TA, Trappe SW, et al. Resistance exercise reduces muscular substrates in women. Int J Sports Med. 2008;29:719–25.
40. Shepherd SO, Cocks M, Tipton KD, Witard OC, Ranasinghe AM, Barker TA, et al. Resistance training increases skeletal muscle oxidative capacity and net intramuscular triglyceride breakdown in type I and II fibres of sedentary males. Exp Physiol. 2014;99: 894–908.
41. Stellingwerff T, Boon H, Jonkers RA, Senden JM, Spriet LL, Koopman R, et al. Significant intramyocellular lipid use during prolonged cycling in endurance-trained males as assessed by three different methodologies. Am J Physiol Endocrinol Metab. 2007;292:E1715–23.
42. Robergs RA, Pearson DR, Costill DL, Fink WJ, Pascoe DD, Benedict MA, et al. Muscle glycogenolysis during differing intensities of weight-resistance exercise. J Appl Physiol. 1991;70:1700–6.
43. MacDougall JD, Ray S, McCartney N, Sale D, Lee P, Garner S. Substrate utilization during weightlifting. Med Sci Sports Exerc. 1988;20:S66.
44. MacDougall JD, Ray S, Sale DG, McCartney N, Lee P, Garner S. Muscle substrate utilization and lactate production. Can J Appl Physiol. 1999;24:209–15.
45. Haff GG, Koch AJ, Potteiger JA, Kuphal KE, Magee LM, Green SB, et al. Carbohydrate supplementation attenuates muscle glycogen loss during acute bouts of resistance exercise. Int J Sport Nutr Exerc Metab. 2000;10:326–39.
46. Churchley EG, Coffey VG, Pedersen DJ, Shield A, Carey KA, Cameron-Smith D, et al. Influence of preexercise muscle glycogen content on transcriptional

activity of metabolic and myogenic genes in well-trained humans. J Appl Physiol. 2007;102:1604–11.
47. Lakomy HKA. The use of a non-motorised treadmill for analyzing sprint performance. Ergonomics. 1987; 3:627–37.
48. Gollnick PD, Armstrong RB, Sembrowich WL, Shepherd RE, Saltin B. Glycogen depletion pattern in human skeletal muscle fibers after heavy exercise. J Appl Physiol. 1973;34:615–8.
49. MacDougall JD, Ward GR, Sutton JR. Muscle glycogen repletion after high-intensity intermittent exercise. J Appl Physiol. 1977;42:129–32.
50. McCartney N, Spriet LL, Heigenhauser GJ, Kowalchuk JM, Sutton JR, Jones NL. Muscle power and metabolism in maximal intermittent exercise. J Appl Physiol. 1986;60:1164–9.
51. Parolin ML, Chesley A, Matsos MP, Spriet LL, Jones NL, Heigenhauser GJF. Regulation of skeletal muscle glycogen phosphorylase and PDH during maximal intermittent exercise. Am J Physiol Endocrinol Metab. 1999;277:E890–900.
52. Symons JD, Jacobs I. High-intensity exercise performance is not impaired by low intramuscular glycogen. Med Sci Sports Exerc. 1989;21:550–7.
53. Balsom PD, Gaitanos GC, Soderlund K, Ekblom B. High-intensity exercise and muscle glycogen availability in humans. Acta Physiol Scand. 1999;165: 337–45.
54. Phinney SD, Bistrian BR, Evans WJ, Gervino E, Blackburn GL. The human metabolic response to chronic ketosis without caloric restriction: preservation of submaximal exercise capability with reduced carbohydrate oxidation. Metabolism. 1983;32:769–76.
55. Lambert EV, Speechly DP, Dennis SC, Noakes TD. Enhanced endurance in trained cyclists during moderate intensity exercise following 2 weeks adaptation to a high fat diet. Eur J Appl Physiol Occup Physiol. 1994;69:287–93.
56. Havemann L, West SJ, Goedecke JH, Macdonald IA, St Clair Gibson A, Noakes TD, et al. Fat adaptation followed by carbohydrate loading compromised high-intensity sprint performance. J Appl Physiol. 2006; 100:194–202.
57. Fleming J, Sharman MJ, Avery NG, Love DM, Gomez AL, Scheett TP, et al. Endurance capacity and high-intensity exercise performance responses to a high fat diet. Int J Sport Nutr Exerc Metab. 2003;13:466–78.
58. Volek JS, Sharman MJ, Love DM, Avery NG, Gomez AL, Scheett TP, et al. Body composition and hormonal responses to a carbohydrate-restricted diet. Metabolism. 2002;51:864–70.
59. Phillips SM, van Loon LJ. Dietary protein for athletes: from requirements to optimum adaptation. J Sports Sci. 2011;29 Suppl 1:S29–38.
60. Vogt M, Puntschart A, Howald H, Mueller B, Mannhart C, Gfeller-Tuescher L, et al. Effects of dietary fat on muscle substrates, metabolism, and performance in athletes. Med Sci Sports Exerc. 2003;35:952–60.
61. Karelis AD, Smith JW, Passe DH, Peronnet F. Carbohydrate administration and exercise performance: what are the potential mechanisms involved? Sports Med. 2010;40:747–63.
62. Jeukendrup A. A step towards personalized sports nutrition: carbohydrate intake during exercise. Sports Med. 2014;44 Suppl 1:S25–33.
63. Lambert CP, Flynn MG, Boone JB, Michaud TJ, Rodriguez-Zayas J. Effects of carbohydrate feeding on multiple-bout resistance exercise. J Appl Sport Sci Res. 1991;5:192–7.
64. Anantaraman R, Carmines AA, Gaesser GA, Weltman A. Effects of carbohydrate supplementation on performance during 1 hour of high-intensity exercise. Int J Sports Med. 1995;16:461–5.
65. Haff GG, Stone MH, Warren BJ, Keith R, Johnson RL, Nieman DC, et al. The effect of carbohydrate supplementation on multiple sessions and bouts of resistance exercise. J Strength Cond Res. 1999;13: 111–7.
66. Haff GG, Schroeder CA, Koch AJ, Kuphal KE, Comeau MJ, Potteiger JA. The effects of supplemental carbohydrate ingestion on intermittent isokinetic leg exercise. J Sports Med Phys Fitness. 2001;41: 216–22.
67. Kulik JR, Touchberry CD, Kawamori N, Blumert PA, Crum AJ, Haff GG. Supplemental carbohydrate ingestion does not improve performance of high-intensity resistance exercise. J Strength Cond Res. 2008;22:1101–7.
68. Wax B, Brown SP, Webb HE, Kavazis AN. Effects of carbohydrate supplementation on force output and time to exhaustion during static leg contractions superimposed with electromyostimulation. J Strength Cond Res. 2012;26:1717–23.
69. Sousa M, Simões HG, Castro CC, Otaduy MC, Negrão CE, Pereira RM, et al. Carbohydrate supplementation increases intramyocellular lipid stores in elite runners. Metabolism. 2012;61:1189–96.
70. Wax B, Kavazis AN, Brown SP. Effects of supplemental carbohydrate ingestion during superimposed electromyostimulation exercise in elite weightlifters. J Strength Cond Res. 2013;27:3084–90.
71. Yoshida Y, Jain SS, McFarlan JT, Snook LA, Chabowski A, Bonen A. Exercise- and training-induced upregulation of skeletal muscle fatty acid oxidation are not solely dependent on mitochondrial machinery and biogenesis. J Physiol. 2013;591: 4415–26.

Exercise for Athletes with Diabetes

15

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Abstract

Physical activity has long been considered to be beneficial to individuals with all forms of diabetes mellitus. Regular exercise improves glucose control and a variety of metabolic risk factors associated with the disease. In addition, exercise may decrease the risk for developing diabetes in individuals at risk. Most of the benefits of physical activity are related to improved insulin sensitivity and glucose uptake resulting in changes in body weight and composition. Athletes with diabetes mellitus need education and guidance regarding concerns with athletic activity in patients with diabetes including hypoglycemia and hyperglycemia in an attempt to maintain their overall health status. In addition the effects of exercise are often altered by many of the medications in common use in this population. With appropriate prescreening for relevant complications and proper understanding of diet and drug interactions, most athletes with diabetes mellitus can enjoy the benefits of physical activity safely.

Keywords

Diabetes mellitus • Hypoglycemia • Hyperglycemia • Neuropathy • Insulin • Glycemic load

15.1 Chapter Introduction

Diabetes mellitus can be found in over 20 million individuals in the United States. At least twice those numbers have various forms of "pre"-diabetes. Both overt diabetes and milder forms of glucose intolerance are major predisposing factors for premature coronary artery disease. Also diabetes is the major cause of blindness and

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is the number one cause of renal failure and nontraumatic limb amputation.

Two major types of diabetes mellitus have been recognized [1]. The most prevalent form of the disease, type 2 diabetes mellitus, accounts for almost 90 % of cases and results from a combination of resistance to the effects of insulin and a progressive decrease in the function of the beta cells of the pancreas which produce that hormone. Insulin resistance, a hyperinsulinemic state, along with subtle abnormalities of beta cell function can precede the onset of type 2 diabetes mellitus by many decades. These individuals are at high risk for premature coronary artery disease associated with the cluster of cardiovascular risk factors including dyslipidemia, impaired fibrinolytic activity, and hypertension, which has been given the name of "metabolic syndrome."

Type 1 diabetes mellitus, which tends to occur more often but not exclusively in children, is the result of progressive immunologic destruction of the beta cells that results in absolute insulin deficiency. There are a number of other subtypes of diabetes mellitus. One of the increasing importance tends to occur in young teenagers, mostly in Black and Hispanic ethnic groups, and consists of a relatively acute onset of severe insulin deficiency in morbidly obese individuals. While the etiology of this form of diabetes is unclear, it is not associated with an autoimmune response.

The therapeutic value of regular exercise in patients with diabetes has been recognized since at least the eighteenth century [2]. Exercise, diet, and medication represent the three cardinal elements in the management of the disease [3–5]. Exercise not only improves insulin sensitivity and blood glucose control, but it diminishes the cluster of cardiovascular risk factors that occur in patients with even milder forms of glucose intolerance [6]. Physically active patients with diabetes may have to deal with long-term complications that require assessments, preparations, and restraints that may not apply to the general population. In addition, they often find themselves requiring medications which may complicate their ability to exercise safely. In addition to the use of exercise in the therapy of overt diabetes, the large and growing population of individuals with metabolic syndrome needs to be enabled to safely participate in recreational and competitive athletic activities.

15.2 Exercise Capacity in Individuals with Diabetes

Individuals with uncomplicated type 1 diabetes mellitus appear to have a normal capacity for exercise and physical training. The situation in type 2 diabetes mellitus is more complicated. Studies suggest a small decrease in maximal aerobic exercise capacity in not only individuals with type 2 diabetes mellitus but also in those at high risk for the disease, even when controlled for physical activity. In addition, patients with type 2 diabetes mellitus tend to have a higher ratio of type II to type I muscle fibers and a lower muscle density of capillaries and mitochondria. Despite these findings, individuals with type 2 diabetes mellitus do display significant training effects with aerobic exercise.

15.3 Effects of Exercise on Glycemic Control

Regular exercise has been shown to reduce the insulin resistance in patients with prediabetes and type 2 diabetes mellitus [7]. Mechanisms include an increase in capillary and mitochondrial density [8], activation of glucose transport by glycogen depletion, activation of AMP kinase, and depletion of intracellular lipid metabolites which are known to contribute to insulin resistance in the liver and muscle [9]. The most important of these effects appears to be related to the summed subacute effects of individual exercise bouts, which may persist for as long as 48–72 h. Physical training and improvements in insulin sensitivity in patients predisposed to type 2 diabetes mellitus have been shown to delay progression to overt disease in a number of populations including individuals with the metabolic syndrome and women with a history of gestational diabetes and polycystic ovarian syndrome.

In individuals with overt type 2 diabetes mellitus, studies have confirmed that regular exercise results in improved metabolic control [10]. Most of these studies have utilized largely aerobic exercise programs, but recent studies suggest the addition of a component of high-volume resistance exercise may potentiate the beneficial metabolic effects [11, 12]. Exercise intensities and durations adequate to cause significant depletion of intracellular glycogen and perhaps free fatty acid intermediates appear to be necessary for substantial subacute effects. Bouts with duration of at least 30 min at 50 % or more of an individual's maximal aerobic exercise capacity are recommended. In addition, frequency of exercise appears to be a key factor requiring a minimum of 3 or 4 exercise sessions per week. Studies utilizing the same total workload per week with greater intensity and less frequency have yielded lesser improvements in metabolic control. Typically, an improvement of 0.5 % or greater in levels of hemoglobin A-1-C can be anticipated. The improvements tend to be greatest in individuals with mild type 2 diabetes mellitus who still retain significant capacity to secrete insulin. It has been more difficult to demonstrate improvement in HGBA1C in individuals with type 1 although associated cardiovascular risk factors may be beneficially affected [13]. This is largely a result of a major confounding factor, the hypoglycemic effects of exercise bouts.

15.4 Regulation of Glucose Levels During Exercise

A number of redundant systems exist in the body to protect against the development of hypoglycemia [14]. As glucose levels begin to fall, alpha-adrenergic input to the pancreas decreases insulin secretion. A further drop in glucose results in a release of glucagon, enhancing hepatic glucose output. Finally, if glucose levels continued to fall, the release of epinephrine results in further enhancement of glucose production by the liver and an increase in the availability of free fatty acids to the peripheral muscle which limits the rate of glucose utilization.

Patients with uncomplicated mild type 2 diabetes mellitus rarely have problems with hypoglycemia during physical activity. Individuals with type 1 diabetes mellitus as well as those individuals with type 2 diabetes mellitus who have developed significant insulin deficiency often find that the risks of hypoglycemia limit their ability to participate in physical activity. When insulin is injected in a subcutaneous depot, the body has no capacity to downregulate insulin levels during exercise. In addition, the majority of patients with type 1 diabetes mellitus that have had their disease for more than 5 years develop glucagon deficiency. Finally, long-standing diabetes may result in autonomic dysfunction and inability to produce catecholamines. It should be noted that the usual warning symptoms of hypoglycemia are often not appreciated during physical activity as the adrenergic activation of both hypoglycemia and exercise causes symptoms that overlap. The frequent occurrence of difficult to predict hypoglycemic episodes often results in the need to decrease insulin doses and increase carbohydrate intake in a way that negates otherwise beneficial effects on glucose control [15–17].

In addition to hypoglycemia occurring at the end of an exercise bout, many individuals are predisposed to a second wave of sometimes very significant hypoglycemic episodes occurring 6–10 h after intense physical activity as a result of the subsequent improvement in insulin sensitivity. For those who exercise late in the day, these episodes often occur during sleep and may be particularly dangerous. Some general recommendations for avoiding exercise-related hypoglycemia follow that may provide useful starting points:

1. The most common way of avoiding hypoglycemia is the consumption of additional readily absorbable carbohydrate. In general 15–30 g carbohydrate can be consumed at the initiation of exercise and every 30 min during moderately intense physical activity. Consumption of much larger amounts of carbohydrate or use of hyperosmolar solutions may actually result in delayed gastric emptying with gastric distention, which may impair high-level physical activity.

2. For those individuals who exercise in the evening and suffer from delayed hypoglycemia at night, snacks of slowly absorbed carbohydrate and protein at bedtime may be helpful in preventing these episodes. For some individuals, a snack in conjunction with a sucrose inhibitor, such as acarbose, may be helpful.
3. Timing of exercise to follow a meal may result in both a lower incidence of hypoglycemia and a blunting of post-meal glucose excursions. On the other hand, the additional strain on the cardiovascular system in individuals at high risk for coronary artery disease limits this approach.

15.4.1 For Athletes Who Require Insulin Therapy

1. Avoid injecting short- or rapid-acting insulin immediately over an area of exercising muscle as this may enhance the rate of insulin absorption and result in hypoglycemia (e.g., avoid injection into the thigh if bicycling).
2. Consider reducing the dose of insulin in anticipation of exercise. Such reductions need to be worked out on a highly individualized basis. The effects of exercise may vary depending on time of day, recent food intake, ambient temperature, and state of hydration. In general, a dose reduction of 30–50 % of the insulin acting during the time of the exercise and up to several hours postexercise may be appropriate for activity of greater than 30 min.
3. For patients on basal-bolus insulin therapy, a reduction in the rapid- or short-acting insulin injected prior to exercise by as much as 50 % may be necessary. For example, exercise occurring 1–2 h after a meal may require a reduction in mealtime insulin. The use of newer rapid-acting insulin has been helpful in avoiding periods of relative hyperinsulinemia between meals; therefore, it may not be necessary to reduce the dose of rapid-acting insulin given with the meal if exercise occurs more than 2 h after eating. However, a reduction in basal insulin may be required.
4. For individuals on insulin pump therapy, the basal rate can be decreased by 20–50 % starting 1–2 h prior to exercise. This reduction in basal rate may be needed for one or more hours following the cessation of the exercise. This temporary reduction in basal insulin is best accomplished using the insulin pump's temporary basal rate feature. For individuals exercising intensely, it may be necessary to suspend or disconnect the insulin pump at the beginning of exercise, but this should never be done for more than 60 min in individuals with type I diabetes in order to avoid ketoacidosis.
5. It may also be necessary to decrease subsequent overnight basal rates on days of moderate to intense exercise; however, the degree of reduction needs to be worked out on an individual basis and will vary based upon the duration of the exercise and how late in the day the exercise occurs.
6. If hypoglycemia does occur, it should be treated by consumption of 15–30 g of readily absorbable carbohydrate. Blood glucose level should be monitored every 15–20 min accompanied by ingestion of 15 g of rapidly digested carbohydrate until the blood glucose stabilizes above 70–100 mg/dL.
7. For athletes who find themselves in a position where carbohydrate is not immediately available, a 10 s intense sprint has been shown to result in an acute transient increase in glucose levels to allow time for more definitive treatment [18].
8. Continuous glucose monitoring (CGM) during physical exercise may be highly useful in selected patients with insulin-treated diabetes. Recent studies to assess the accuracy of CGM [19–21] confirm that decreases in glucose during intensive effort can be tracked by a subcutaneous sensor. Available data suggested that CGM tends to overestimate glucose levels during exercise compared with blood glucose concentrations, especially when glucose is falling rapidly to low levels. From a practical point of view, athletes can consider the information on

glucose trends provided by the sensing system as useful but should view the absolute value of the displayed glucose level with some caution.

15.5 Hyperglycemia and Exercise

In contrast to unanticipated hypoglycemia, some patients will find themselves dealing with unanticipated hyperglycemia after their workouts and the following recommendations provide helpful approaches to avoid such occurrences:

1. Individuals who exercise at near-maximal exertion often experience a transient rise in plasma glucose levels. This results from the rapid release of glucose from the liver secondary to glycogenolysis with a minimal increase in peripheral glucose utilization. Treatment of this transient and self-limited hyperglycemia with insulin should be avoided.
2. A more difficult problem is the increase of plasma glucose and occasionally ketones during brisk exercise in patients with severe insulin deficiency and very poor metabolic control. Here unrestrained hepatic glucose and ketone production outstrips peripheral utilization. Competing in a hyperglycemic state places the athlete at risk for dehydration, reduced athletic performance, and possible ketosis. Such situations are often identified by fasting plasma glucose >300 mg/dl. Such patients should first be adequately insulinized and hydrated prior to exercise. In addition, athletes should check their fasting blood glucose prior to exercise to stimulate the recommended insulin levels.
3. If the clients *fasting* blood glucose is >250 mg/dl and ketones are present in the urine and/or blood, exercise is contraindicated. If the *fasting* blood glucose value is >300 mg/dl and ketones are not present, exercise should be done with caution after rehydration, and blood glucose levels should be monitored. The underlying reason for the hyperglycemia should be identified and treated before sustained athletic activity [22].

15.6 Evaluation of Athletes Before Exercise

Before beginning an exercise program, the individual with diabetes mellitus should undergo a detailed medical evaluation with appropriate diagnostic studies [23]. This examination should carefully screen for the presence of macro- and microvascular complications which may be worsened by the exercise program. Identification of areas of concern will allow the design of an individualized exercise prescription which can minimize risk to the patient.

15.6.1 Cardiovascular Disease

Myocardial infarction is the leading cause of death in the United States. Although usually accompanied by typical symptoms, myocardial ischemia in patients with long-standing diabetes mellitus is often asymptomatic or associated with atypical symptoms. Some studies have shown that 50 % of ischemic episodes are not recognized in this population [24].

A graded exercise test may be helpful if a patient, about to embark on a moderate- to high-intensity exercise program (maximal heart rate >55 %), is at high risk for underlying cardiovascular disease, based on one of the following criteria [25]:

- Age >35 years with type 1 diabetes mellitus.
- Type 2 diabetes mellitus of >10-year duration.
- Type 1 diabetes mellitus of >15-year duration.
- The presence of multiple additional risk factors for coronary artery disease.
- Level of activity planned is greater than routine daily activities.
- The presence of microvascular disease (retinopathy or nephropathy, including microalbuminuria).
- Peripheral vascular disease.
- Autonomic neuropathy.

In some patients who exhibit nonspecific electrocardiographic changes in response to exercise

or who have nonspecific ST and T wave changes on the resting EKG, alternative tests such as radionuclide stress testing may be performed. Patients with known coronary artery disease should undergo a supervised evaluation of the ischemic response to exercise, ischemic threshold, and the propensity to arrhythmia during exercise. In many cases, left ventricular systolic function at rest and during its response to exercise should be assessed. In patients with diabetes planning to participate in low-intensity forms of exercise (<60 % of maximal heart rate) such as walking, the physician should use clinical judgment in deciding whether to recommend an exercise stress test.

15.6.2 Peripheral Neuropathy

Peripheral neuropathy (PN) may result in the loss of protective sensation in the feet. Significant PN is an indication to limit weight-bearing exercise. Repetitive exercise on insensitive feet can ultimately lead to ulceration and fractures [26]. Evaluation of PN can be made by checking the deep tendon reflexes, vibratory sense, and position sense. The inability to detect sensation using the 5.07 (10 g) monofilament is indicative of the loss of protective sensation. Athletes with neuropathy need to pay special attention to adequate footwear and may sometimes require orthotics. The use of silica gel or air midsoles as well as polyester or blend (cotton polyester) socks to prevent blisters and keeping the feet dry is important for minimizing trauma to the feet. Careful inspection of the feel on a daily basis is important. Individuals must be taught to monitor closely for blisters and other potential damages to their feet. A diabetes identification bracelet or shoe tag should be clearly visible when exercising.

If the neuropathy is severe or is associated with a loss of proprioception or if it occurs in the presence of peripheral vascular disease, certain activities like long-distance running should be discouraged. Table 15.1 was created by the authors of this chapter that lists contraindicated and recommended exercises for patients with loss of protective sensation in the feet.

Table 15.1 Exercises for diabetic patients with loss of protective sensation

Contraindicated exercise	Recommended exercise
	Swimming
Treadmill	Bicycling
Prolonged walking	Rowing
Jogging	Chair exercises
Step exercises	Arm exercises
	Other non-weight-bearing exercises

15.6.3 Autonomic Neuropathy

The presence of autonomic neuropathy may limit an individual's exercise capacity and increase the risk of an adverse cardiovascular event during or after exercise. Cardiac autonomic neuropathy (CAN) may be indicated by resting tachycardia (>100 beats per minute), orthostasis (lowering of systolic blood pressure >20 mmHg upon standing), or other disturbances in autonomic nervous system function involving the skin, pupils, or gastrointestinal or genitourinary systems. Sudden death and silent myocardial ischemia have been attributed to CAN in diabetes [27]. Resting or stress thallium myocardial scintigraphy is an appropriate noninvasive test for the presence and extent of macrovascular coronary artery disease in these individuals. Hypotension and hypertension after vigorous exercise are more likely to develop in patients with autonomic neuropathy, particularly when starting an exercise program. Because these individuals may have difficulty with thermoregulation, they should be advised to avoid exercise in hot or cold environments and to be vigilant about adequate hydration. Adequate hydration prior to exercise is recommended (e.g., 17 oz of fluid consumed 2 h before exercise). During exercise fluids should be taken early and frequently in an amount sufficient to compensate for losses in sweat. The reader is referred to Chap. 6 of this textbook for specific detailed scientific base research regarding adequate hydration recommendations.

15.6.4 Peripheral Arterial Disease

Evaluation of PAD is based on signs and symptoms, including intermittent claudication, cold feet, decreased or absent pulses, atrophy of subcutaneous tissue, and hair loss.

15.6.5 Retinopathy

The eye examination schedule should follow the American Diabetes Association's Clinical Practice Guidelines [28]. For patients who have proliferative diabetic retinopathy (PDR) that is active, strenuous activity may precipitate vitreous hemorrhage or traction retinal detachment. High-volume moderate-resistance exercise has been shown to result in fluctuation in systolic blood pressure to generally less than 180 mm and is probably safe. However, athletes with proliferative retinopathy should exercise caution when attempting exercises that involve Valsalva maneuvers or sudden jarring motions.

On the basis of Joslin Clinic experience, the degree of diabetic retinopathy has been used to stratify the risk of exercise and to individually tailor the exercise recommendations. Table 15.2 noted below provides viable considerations for activity limitations in diabetic retinopathy clients.

Table 15.2 Considerations for activity limitation in diabetic retinopathy (DR)

Mild nonproliferative diabetic retinopathy reevaluation suggested in 6–12 months	
Moderate nonproliferative diabetic retinopathy reevaluation in 4–6 months	Discourage activities that dramatically elevate blood pressure – Power lifting – Heavy Valsalva
Severe nonproliferative diabetic retinopathy reevaluation in 2–4 months	Discourage activities that substantially increase systolic blood pressure, Valsalva maneuvers, and active jarring: – Boxing – Heavy competitive sports
Proliferative diabetic retinopathy-acceptable activities: – Low-impact cardiovascular conditioning – Swimming (not diving) – Walking – Low-impact aerobics – Stationary cycling – Endurance exercises Reevaluation in 1–2 months (may require laser surgery)	Discourage strenuous activities, Valsalva maneuvers, pounding, or jarring: – Weight lifting – Jogging – High-impact aerobics – Racket sports – Strenuous trumpet playing

15.6.6 Nephropathy

Many patients with long-standing diabetes mellitus and no proteinuria at rest will develop significant proteinuria after an intensive exercise session. Active individuals should be instructed not to engage in intensive activity prior to assessment for proteinuria. The predictive value for such exercise-related increments of urinary protein on the subsequent development of renal disease is still undetermined.

Athletes with diabetes do not have a higher incidence of end-stage renal disease in cross-sectional studies. Specific exercise recommendations have not been developed for patients with incipient (microalbuminuria >20 albumin excretion) or overt nephropathy (>200 mg/min) [29]. Patients with overt nephropathy often have a reduced capacity for exercise which leads to self-limitation in activity level. Although there is no clear reason to limit low to moderate intensity forms of activity, very high-intensity or strenuous exercises should probably be discouraged as the hemodynamic consequences are likely to be detrimental. Many athletes use dietary supplements very high in protein and these should be avoided in the presence of renal disease as high protein intake may accelerate loss of renal function.

15.7 Preparing for Exercise

A standard recommendation for athletes with diabetes is that exercises include a proper warm-up and cooldown period. A warm-up should

consist of 5–10 min of aerobic activity (walking, cycling, etc.) at low-intensity level.

After a short warm-up, muscles should be gently stretched for another 5–10 min. Following the activity session, a cooldown should be structured similarly to the warm-up. The cooldown should last about 5–10 min and gradually bring the heart rate down to its pre-exercise level. Many exercise-related arrhythmias occur during the postexercise recovery period and it has been suggested the high levels of FFA that occur when exercise is abruptly terminated may contribute. A cooldown period will blunt this response.

There are several considerations that are particularly important and specific for the individuals with diabetes.

- High-resistance exercise using weights may be acceptable for young individuals with diabetes, but not for older individuals or those with long-standing diabetes. Moderate weight training programs that utilize light weights and high repetitions can be used for maintaining or enhancing muscle strength in nearly all patients with diabetes.
- Readily digestible, well-tolerated foods and suitable timing prevent exercising with a full stomach. Meals should contain complex carbohydrates and proteins for satiety. Hypertonic drinks (high carbohydrates) reduce gastric emptying speed leading to gastric dilatation. This can cause nausea and impair performance in athletic activity. These drinks also cause a sharp spike in blood glucose level. Instead isotonic drinks with 5–8 g of carbohydrates/100 ml are more advisable for rehydration.

15.8 Exercise Prescription

The recommendations given below may be useful for previously sedentary patients with diabetes who wish to initiate serious programs of physical activity. These exercise prescription categories include the following considerations:

15.8.1 Type of Exercise

Aerobic-type activities, for example, swimming, cycling, and brisk walking, are usually recommended to patients with diabetes mellitus. These exercises result in improved insulin sensitivity and enhanced glucose disposal per unit of muscle mass. Recent studies [11] suggest that a single bout of resistance-type exercise reduced the prevalence of hyperglycemia by as much as 35 ± 7 % during the 24 h postexercise period when compared with the control (no-exercise) experiment. A similar 33 ± 11 % reduction in the prevalence of hyperglycemia was observed following a corresponding 45 min bout of endurance-type exercise. Previously, the benefits of resistance-type exercise training on glycemic control have often been ascribed to an increase in muscle mass over time and concomitant expansion of glucose disposal capacity [12]. However, recent studies have shown that a single bout of resistance-type exercise improves glycemic control for up to 24 h following exercise, without changes in muscle mass.

Studies [30] have shown that athletes with type 1 diabetes mellitus might benefit from resistance exercise. Resistance exercise is associated with improvements in muscular strength [31], improved lipid profiles, lower insulin needs, and lower self-monitored blood glucose levels in individuals with type 1 diabetes mellitus. More exercise-associated glycemic fluctuations were observed with aerobic exercise compared with resistance exercise. Resistance exercise may be more beneficial as far as glucose stability is concerned. Meanwhile, it should also be noted that postexercise hypoglycemia might occur more frequently in individuals who have changed their exercise routine to incorporate resistance training or for patients unaccustomed to exercise.

To summarize, a single session of resistance- or endurance-type exercise substantially reduces the prevalence of hyperglycemia and improves glycemic control during the subsequent 24 h period.

15.8.2 Intensity and Duration of Exercise

There have been few studies regarding the optimal duration of exercise necessary to maximize beneficial metabolic effects. Exercise of less than 15–20 min duration generally results in poor training effect, whereas sessions of greater than 45 min are associated with an increased incidence of musculoskeletal injuries. Interestingly, rest periods of up to 90 s every 5 min have little effect on improved fitness for a given total amount of exercise, and frequent brief rest periods are probably a good strategy for older and more sedentary patients who cannot tolerate sustained exercise of even low intensity [32].

Optimization of a specific physiological or metabolic effect may require different levels of exercise intensity. In terms of glucose disposal, exercise of 30 % of their maximum aerobic capacity or less has been associated with little benefit. At exercise intensities of greater than 50 % of maximum aerobic capacity, improvements in glucose disposal are related to the total work performed. Thus, a decrease in intensity can be compensated for to some degree by an increase in duration of exercise. Other metabolic parameters, e.g., lipid metabolism and coagulation parameters, may require workloads of different intensities and frequencies. At any rate, it appears reasonable to recommend an exercise intensity of 50–70 % of maximum aerobic capacity for most individuals. This can be prescribed in terms of heart rate, which can easily be monitored by patients.

An estimate of the target pulse can be obtained using the following formula [32]:

$$\text{Target pulse} = 0.5 \text{ to } 0.7 \left(\text{maximal heart rate} - \text{resting heart rate}\right) + \text{resting heart rate}.$$

Resting heart rate should be measured by the patient before getting out of bed in the morning. It should be kept in mind that estimates of maximal heart rate derived from standard tables based on normal populations correlate poorly with maximal heart rates of patients with diabetes. The exercise program can be initiated at a target pulse corresponding to about 50 % of maximum aerobic capacity and gradually increased to the desired range over a 3–4-week period.

15.8.3 Frequency of Exercise

The optimal frequency of exercise regimens is unknown. If transient effects of individual exercise bouts are of paramount importance, it is likely that exercise of greater frequency will result in maximal metabolic benefit. One cannot fully compensate for a decreased frequency of exercise by increasing the intensity of individual exercise sessions, and, in general, exercise frequencies of less than 3–4 times a week do not result in substantial benefits. For many type 1 diabetes mellitus patients, a daily exercise regimen will allow for more predictable insulin dosing and more stable metabolic control. For some patients brief, intense interval exercise bouts undertaken immediately before breakfast, lunch, and dinner had a greater impact on postprandial and subsequent 24 h glucose concentrations then a single bout of continuous exercise [33].

15.8.4 Time of Day

In general, patient convenience is the major determinant of time of exercise. However, insulin resistance is greater early in the day, and because of the relatively transient effects of exercise on glucose disposal, it is likely that exercise done in the morning will have the greatest impact on glycemic excursions throughout the day. Exercise sessions in the evening may be associated with a higher risk of unappreciated hypoglycemia overnight, and assessment of glucose in the early morning hours may be necessary.

15.8.5 Exercise and Cardiovascular Disease

Studies done in the past have uniformly shown that exercise training restores myocardial structure and performance, with increasing resistance to ischemia and favorable metabolic effects. A recent study showed that weight loss in patients enrolled in an exercise program may have a beneficial effect on myocardial function, but the relative roles of exercise and weight loss require further definition [34, 35].

15.8.6 Effects on the Components of the Metabolic Syndrome

15.8.6.1 Hypertension

Physical training is associated with a modest (5–10 mmHg) decrease in systolic and diastolic blood pressure and a modest decrease in the percentage of patients who go on to require antihypertensive medication. Benefits are at least as good and possibly better in older subjects and women. Improvements are most likely to be noted in the more insulin-resistant hyperinsulinemic patients.

15.8.6.2 Hyperlipidemia

The most consistent effect of regular exercise is a transient decrease in plasma triglyceride levels, which often fall by up to 30 %. Changes in LDL cholesterol have not been consistently demonstrated, but exercise does appear to diminish the concentration of a small, dense subclass of LDL that may be more strongly associated with atherosclerotic cardiovascular disease [36]. Effects are greatest in more insulin-resistant hypertriglyceridemic patients. Increases in HDL cholesterol can occur but this generally required exercise of an intensity and duration seen in athletes but rarely achieved by most patients.

15.8.7 Role of Exercise in Prevention of Type 2 Diabetes

Research studies have shown that exercise prevents the progression to overt type 2 diabetes mellitus [37, 38]. Analysis of select populations has shown that the occurrence of type 2 diabetes mellitus is higher in sedentary as compared to physically active men. Regular exercise improves insulin sensitivity and decreases visceral adiposity. Although obesity is generally regarded as the major risk factor for development of type 2 diabetes mellitus [39], decreased physical activity independent of obesity has also been identified as an important predictor of the disease. Several studies have shown that exercise, by reversing insulin resistance, might delay the progression to type 2 diabetes mellitus.

15.9 Exercise in Special Athlete Groups

15.9.1 Swimming

Principles outlined for other types of exercise apply for swimming. In addition, athletes should note that their insulin absorption might decrease when swimming in cooler water. Heat increases absorption of insulin while cold decreases absorption. Extreme ambient temperatures (<36 F or >86 F) can affect insulin housed within the pump and interfere with insulin action.

15.9.2 Scuba Diving

The effects of scuba diving on those with diabetes have not been well established. Diabetes is listed as a contraindication by many scuba diving certification agencies. This is apparently based on the risk and subsequent consequences of hypoglycemia while diving. The interplay of diabetic complications, e.g., micro/macrovascular diseases, with diving physiology has not been considered the major limiting factor to diving. People with diabetes need to be primarily concerned with the prevention of hypoglycemia while scuba diving (and be prepared for in-water treatment of hypoglycemia), the possible relationship between diabetic complications and diving physiology (pressure, circulatory, and respiratory), and adequate training to anticipate and treat diabetes-related problems during diving.

For further details, please refer to ADA recommendations in "The Health Professional's Guide to Diabetes and Exercise" [40].

15.10 Interaction of Commonly Used Drugs with Exercise

15.10.1 Alcohol

Some alcoholic beverages are used by athletes for hydration. Beer, for example, is a rich source of carbohydrate and can contribute to electrolyte replacement as well as water [41]. The contraindicated concerns with alcohol are as follows:

1. It has a diuretic effect and can lead to dehydration.
2. Alcohol is a glycogenolytic agent and initially causes a short-lived hyperglycemia. Subsequently, hypoglycemia is a more important consideration (due to exhaustion of glycogen stores and inhibition of hepatic glucose production). As little as two "shots" or two beers can inhibit gluconeogenesis by 80 %.

15.10.2 Beta Blockers

These agents have been reported to increase the incidence of hypoglycemia in some individuals. It is a rare side effect of the drug in type 2 diabetes mellitus where glucagon is preserved, but in long-standing type 1 diabetes mellitus or following pancreatectomy where there is a loss of glucagon, beta blockers may predispose to hypoglycemia and delay recovery from hypoglycemic events, especially in the presence of autonomic dysfunction. These agents need not be avoided but should be used with caution.

15.10.3 Sulfonylureas

Sulfonylureas work by stimulating the release of insulin from the beta cells of the pancreas and enhancing beta cell sensitivity to glucose. Sulfonylureas are effective in decreasing plasma glucose by 50–70 % and reducing HgA1c by 1.5–1.7. Sulfonylureas have the same general restrictions as insulin. They can cause hypoglycemia and weight gain. Dose reduction may be needed when starting exercise to prevent hypoglycemic episodes.

15.10.4 DPP-4 Inhibitors and GLP-1 Agonists

Both these classes of drug work by enhancing or mimicking the effects of GLP-1, a major gut incretin. DPP-4 inhibitors prevent the degradation of incretion, while GLP-1 agonists mimic the action of incretin. Due to their mechanism of action, the drugs help lower post-meal blood sugars. They have lesser propensity to cause hypoglycemia as compared to sulfonylureas. The average decrease in HgA1c after 24 weeks of therapy with DPP-4 inhibitors varies between 0.65 and 1.4 %. GLP-1 agonists have been shown to decrease HgA1c by 1.23 % in long-term studies.

15.10.5 Acarbose

Acarbose works by inhibiting alpha-glucosidase enzyme in the brush border of the small intestine and alpha amylase. These enzymes hydrolyze complex carbohydrates to glucose and other monosaccharides. Inhibition of the enzyme leads to slower and more prolonged glucose absorption. This helps lower the postprandial blood glucose levels. Since acarbose prevents the degradation of complex carbohydrates into glucose, some carbohydrates will be undigested and be delivered to the colon causing GI side effects like flatulence and diarrhea. While acarbose does not cause hypoglycemia, consumption of complex carbohydrates may fail to increase blood glucose levels when needed to prevent or treat hypoglycemia. Such patients should be instructed to use a simple glucose source such as glucose tablets or gel to treat hypoglycemic events.

15.10.6 Sodium Glucose Cotransporter-2 Inhibitors

Sodium glucose cotransporter-2 (SGLT-2) inhibitors are a new class of oral drugs for treatment of type 2 diabetes mellitus. They inhibit glucose reabsorption in the proximal renal tubules providing an insulin-independent mechanism of lowering blood glucose. Their use in clinical practice is associated with improved blood glucose and weight loss. These drugs lead to an increase in urinary output because of osmotic diuresis and there is a concern for dehydration. Adequate hydration is an important consideration with the use of these drugs in athletes.

15.11 Glycogen Loading

The initial level of stored glycogen in the muscle and liver has been shown to be an important determinant of the ability to engage in long-term endurance exercise. When glycogen is depleted and then carbohydrate is refed, a rebound in glycogen levels to well above basal transiently occurs which has been termed super compensation. A similar phenomenon may occur with depletion of intramuscular triglycerides. Various combinations of dietary CHO restriction and exercise to deplete glycogen stores along with high-carbohydrate refeeding regimens have been proposed over the years. It is important to note that while glycogen loading may improve endurance, it may cause edema and stiffening of muscles and could be associated with a higher incidence of myoglobinuria after events such as marathon running. Patients with diabetes develop an increase in insulin sensitivity with glycogen depletion in muscle and super compensation has been shown to cause peripheral insulin resistance. Athletes on intensive insulin regimens will have to closely monitor their insulin requirement throughout any such training regimen.

For many athletes, the risk of dropping too low in carbohydrates may outweigh the proposed benefits of glycogen loading. An alternative solution is to taper exercise while maintaining carbohydrate intake, which will support increased glycogen levels. It is important to understand that glycogen loading is primarily helpful for long-distance endurance athletes (marathon, triathlon) and not high-skill/power sports, such as baseball or sprinting. For glycogen loading, 8–12 g/kg of carbohydrates is recommended for a few days leading up to a long-distance event. The amount depends on the duration of the event and where an individual is starting with their carbohydrate intake prior to glycogen loading [1].

15.12 Practical Nutrition Applications

Not all carbohydrates are created equal. When it comes to carbohydrate quality, the timing and type of the carbohydrate, as well as the type and duration of exercise, will dramatically impact the best glycemic option for the athlete. This section will discuss the different types of carbohydrates, how to determine the quality of the carbohydrate on a daily basis, and when appropriate times are to have different types of carbohydrates.

15.12.1 Determining Carbohydrate Quality: Low- Versus High-Glycemic Carbohydrates

The glycemic index is a measure of how foods affect the blood glucose level, which directly impacts the risk of hypo- and hyperglycemia episodes. The speed of digestion of a carbohydrate is determined by multiple factors. Some of these factors include whether it is starchy versus sugary and whole grain versus refined and the dietary fiber content as well as its interaction with protein and fats, which will be discussed later. Starches are made of multiple units of sugar such as glucose. The longer and more complex the units of carbohydrates, the longer it takes to digest. This is in contrast to simple carbohydrates and sugars, which are single, di-, or shorter chains of carbohydrates that tend to digest quickly. When considering the complex carbohydrate chain length, the longer the chain length, the slower the glycemic response. Hence, the shorter

the carbohydrate chain length, the faster the glycemic response.

The next factor is the dietary fiber component. Dietary fibers are nondigestible carbohydrates that act to slow digestion and blunt the glycemic response to allow for a sustained release of blood glucose as well as insulin. Whole grains tend to have higher fiber and other nutrients to improve blood glucose relative to refined grains, which are stripped of the fiber-containing bran. The carbohydrate to dietary fiber ratio has become a stable recommendation to determine the quality of the carbohydrate consumed. The ideal ratio for providing sustained energy and blood glucose levels is a 5:1 ratio of total carbohydrates to fiber.

Low-glycemic carbohydrates provide more sustainable energy, with less spikes and dips in blood sugar and insulin. Low-glycemic carbohydrates tend to be higher in fiber and lower in sugar. As a result, they are slower to digest and help maintain muscle and brain fuel. For the majority of the day, these are the preferred choice of carbohydrate type to consume for maintaining steady blood sugar. Examples of low-glycemic carbohydrates include oatmeal, unflavored popcorn, leafy vegetables, and certain fruits, including apples with the skin and many different berries.

High-glycemic index carbohydrates are fast-digesting, quickly increasing blood glucose levels, and tend to be low in fiber and higher in sugar. These are tools that can be used with athletes but only at specific times of the day when quick bursts of energy or increases in blood glucoses are needed. Examples of high-glycemic carbohydrates include juices, white breads, white rice, corn, potatoes, and certain fruits, such as watermelon, banana, and grapes. Many of the most popular breakfast cereals have a total carbohydrate to fiber ratio as high as 50:1, reflecting a high glycemic index. It is important for athletes to take this into consideration when making their cereal choices, as choosing cereals with a lower carbohydrate to fiber ratio (ideally 5:1) will help stabilize blood glucose levels during the day. Please see Table 15.3 to determine viable low- and high-glycemic carbohydrate snack options accordingly.

Table 15.3 Low- and high-glycemic snacking foods

Low-glycemic carbohydrate snacks[a]
Whole grain bread
Whole wheat pasta
Oatmeal
Apples
Berries (any type)
Low-fat, low-sugar popcorn
High-fiber cereals (5:1 carb to fiber ratio)
Brown rice
Whole wheat tortillas
Beans
High-glycemic carbohydrate snacks
Melon
Bananas
Grapes
White bread
White rice
White potatoes
Cream of wheat
High-sugar, low-fiber cereals (>10:1 carb to fiber ratio)
White bagels
Sports drinks
Sports bars and candy bars
Potato chips and crackers

[a]Low-glycemic snacks should be chosen for the majority of the day. High-glycemic snacks should purely be used when a quick rise in energy or blood glucose is needed such as during or after exercise or to avoid hypoglycemia.

15.12.2 Interaction of Carbohydrates with Other Nutrients

Although we discussed the importance of carbohydrates on blood glucose, it is important to understand the interaction of other nutrients on blood glucose control. In particular, the following section will discuss the impact of proteins and fats for athletes with diabetes.

Proteins have an important role in regulating glycemic and insulin responses. Studies show that people who are trying to manage weight and blood glucose greatly benefit from higher protein diets [42]. When proteins are consumed, the body is able to use amino acids to produce its own supply of glucose in the liver. This helps to provide a sustained supply of glucose

to the body. Studies show that people on higher protein diets have more stable blood glucose and insulin levels when waking. While total protein requirements for athletes are greater, we recommend it is best to think of proteins on a per-meal basis, as proteins have important acute timing effects, and if the distribution of protein intake is suboptimal, then the glycemic benefits of proteins will not be achieved. Accordingly, research suggests that adults should aim for ~30 g of protein per meal from high-quality sources (i.e., animal proteins, dairy, etc.) will help support euglycemia as well as muscle building and recovery from exercise [43, 44]. Patients with diabetic or other renal diseases, on the other hand, may benefit from limiting protein intake to about 1 g per kilogram of IBW.

Fats also play a critical role in regulating glycemia. Dietary fats potently slow digestion, in part by stimulating release of the gut peptide cholecystokinin (CCK). Consuming fats with a meal can substantially lower the glycemic response and regulate blood glucose levels. This delay in carbohydrate absorption may be particularly useful at night to avoid delayed hypoglycemia.

15.12.3 Carbohydrate Counting

Carbohydrate counting has been shown to be an extremely effective method for managing diabetes when executed properly. Nutrition education and interventions demonstrate the impact that this can have for helping reduce risk of hyper- and hypoglycemia [45]. Through teaching individuals the portions of foods that reflect a standard 15 g of carbohydrates, an individual can effectively manage their blood glucose. The amount of insulin used to cover an individual's carbohydrate needs varies and is determined by the endocrinologist. During of stress, illness, and growth spurts, an individual's carbohydrate/insulin ratio can vary significantly.

15.12.4 Carbohydrate Type and Nutrient Timing

When it comes to the timing of carbohydrates, the primary times to consider different types of carbohydrates include meals during the day and before bed, as well as pre-exercise, during exercise, and postexercise. At breakfast and lunch and for most snacks, the majority of your carbohydrates should be low-glycemic and slow-digesting, aiming for the ratio of 5:1 for total carbohydrates to dietary fiber.

Intense exercise during the day or evening increases the risk for hypoglycemia up to a few hours following the completion of exercise. This is referred to as delayed-onset hypoglycemia (CITE). Accordingly, at night before sleeping, it is important that sufficient carbohydrates be consumed to minimize the risk of hypoglycemia. Too much insulin, insufficient carbohydrates, or consuming high-glycemic foods can increase risk of the hypoglycemia. In addition to a low-glycemic carbohydrate, the addition of protein, fats, and low-glycemic vegetables can help prevent low blood glucose.

Fast-digesting carbohydrates, which have a high glycemic index, are to be utilized if exercise is longer than 75 min to minimize hypoglycemia. Below is a recommended meal timeline for athletes around their workouts. For sample meal plans, see Appendix.

15.12.4.1 Pre-workout Nutrition

3–4 h prior: low-glycemic carbohydrates (5:1 ratio).

60 min prior: low glycemic, depending on the individual's digestion rates. This recommendation is very individualized and athletes must experiment on what works for their stomach and training needs. Some athletes can only eat meals 3 h prior to exercise, while others may have a moderate-glycemic index carbohydrate (8:1 carbohydrate to fiber ratio) at this time, such as a granola bar.

15 min before: high glycemic (oranges, grapes, watermelon).

15.12.4.2 During Workout Nutrition

<60 min training sessions: if the training session is short, then an electrolyte containing beverage with small amounts of carbohydrates may be sipped on during the training session (150–240 ml for 15–20 min of exercise).

>75 min long training sessions: high-glycemic sports drinks with electrolytes should be consumed for high-intensity sports, such as soccer and basketball. Approximately 30–60 g of carbohydrates is shown to improve athletic performance [46–49].

Power- and skill-based sports, such as baseball and golf, usually benefit from low- to moderate-glycemic carbohydrate snacks even during exercise. The use of high-glycemic carbohydrates in these sports is typically only in response to low blood glucose or when one is at risk for low blood glucose.

15.12.4.3 Postexercise Nutrition

1. High-glycemic carbohydrates should be consumed if athletes have more than one training session of the same body part within 24 h or if total carbs are limited throughout the day. However, if there is sufficient time to replenish glycogen stores between two training sessions or competitions, then focusing on high-glycemic carbohydrates after workouts is not as critical. If there are multiple training sessions of the same body part within 12–24 h of the workout completion, a fast-digesting carb will speed glycogen replenishment to allow for glycogen to be utilized in the following session for fuel. Combining a high-quality, rapidly digesting protein with carbs after a workout will even further speed glycogen replenishment. However, it is important to follow a fast-digesting carbohydrate containing meal with a low-glycemic index meal within 60–90 min to help stabilize blood glucose levels. For individuals whose goals are not performance-based, but rather body composition or overall health, appropriate recovery and spacing of training allow for consumption of low-glycemic carbohydrates following a workout. In this case, glycogen replenishment is not as critical as providing long-lasting fuel for the muscles. In addition, please see Table 15.3 for sample low-glycemic snack foods at bedtime.

15.13 Appendix

15.13.1 Sample Meal Plans

15.13.1.1 Endurance Athlete (Track, Soccer)

Note: Serving sizes will depend on the individual athlete needs and should be customized by their endocrinologist and dietitian.

15.13.2 Breakfast (3 h Pre-workout)

Omelet (3 eggs, ¼ cup of low-fat cheese, 2 slices of ham)
1 cup of oatmeal
½ cup of blueberries

15.13.3 Snack (1 h Pre-workout)

High-fiber granola bar (5:1 ratio) and an apple

15.13.4 During Workout

Every 15 min sip on 150–240 ml of 6–8 % carbohydrate containing sports beverage with electrolytes.

15.13.5 Post-workout (Within 60 min)

Fast-digesting protein (whey or eggs) combined with high-glycemic carbohydrate (sports drink, white rice, or white bread)

15.13.6 Post-workout Meal (Lunch) (Within 60–90 min Following Post-workout Shake)

4 oz. salmon
1 cup of brown rice
Mixed salad
Tbsp. olive oil

15.13.7 Snack

1 cup of Greek yogurt
2 cups of mixed berries
1 tbsp. peanut butter

15.13.8 Dinner

6 oz. flank steak
4 oz. broccoli
1 whole grain dinner roll
1 cup of brown rice

15.13.9 Presleep Snack

4 oz. low-fat Greek yogurt
1 cup of 1 % milk
2 pieces of whole grain bread
2 tbsp. peanut butter
1 tsp. jelly

15.13.9.1 Power/Skill Athlete (Baseball, Powerlifting)

Note: Serving sizes will depend on the individual athlete needs and should be customized by their endocrinologist and dietitian.

15.13.10 Breakfast (3 h Pre-workout)

Omelet (3 eggs, ¼ cup of low-fat cheese, 2 slices of ham)
1 cup of oatmeal
½ cup of blueberries

15.13.11 Snack (1 h Pre-workout)

High-fiber granola bar (5:1 ratio) and an apple

15.13.12 During Workout

Every 15 min sip on 150–240 ml of water with electrolytes or low-sugar sports drink. For long-duration games or matches >60 min, snack on moderate-glycemic index carbohydrates (7:1 ratio carbohydrates to fiber) such as granola bars and oranges.

15.13.13 Post-workout (Within 60 min)

Protein and low-glycemic carbohydrates—1 whole grain bagel, 1 apple, 8 oz. low-fat Greek yogurt

15.13.14 Post-workout Meal (Lunch) (Within 60–90 min Following Post-workout Shake)

4 oz. salmon
1 cup of brown rice
Mixed salad
Tbsp. olive oil

15.13.15 Snack

1 cup of Greek yogurt
2 cups of mixed berries
1 tbsp. peanut butter

15.13.16 Dinner

6 oz. steak
4 oz. broccoli
1 whole grain dinner roll
2 whole grain tortillas

15.13.17 Presleep Snack

20 g of whey protein mixed in water
2 pieces of whole grain bread
2 tbsp. peanut butter
1 tsp. jelly
1 cup of spinach

References

1. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2010;33 Suppl 1:S62–9.
2. Rollo J. Cases of Diabetes Mellitus: with the results of the trials of certain acids and other substances in the cure of the Lues Venera. 2nd ed. London: Dilly; 1798.
3. Praet SFE, van Loon LJ. Exercise: the brittle cornerstone of Type 2 diabetes treatment. Diabetologia. 2008;51(3):398–401.
4. Schneider SH, Elouzi EB. The role of exercise in Type 2 Diabetes Mellitus. Prev Cardiol. 2000;3(2):77–82.
5. Mikus CR, Oberlin DJ, Libla J, Boyle LJ, Thyfault JP. Glycaemic control is improved by 7 days of aerobic exercise training in patients with Type 2 Diabetes. Diabetologia. 2012;55(5):1417–23. doi:10.1007/s00125-012-2490-8.
6. Kohn HW, Gordon NF, Villegas JA, Blair SN. Cardiorespiratory fitness, glycemic status and mortality risk in men. Diabetes Care. 1992;184–192.
7. Devlin JT. Effects of exercise on insulin sensitivity in humans. Diabetes Care. 1992;15(11):1690–3.
8. Prior SJ, Blumenthal JB, Katzel LI, Goldberg AP, Ryan AS. Increased skeletal muscle capillarization after aerobic exercise training and weight loss improves insulin sensitivity in adults with IGT. Diabetes Care. 2014;37(5):1469–75.
9. Goodyear LJ, Smith RJ. Exercise and diabetes. In: Kahn CR, Weir GC, editors. Joslin's diabetes. 13th ed. Boston, MA: Lea and Febiger; 1994. p. 451–9.
10. Schneider SH. Long-term exercise programs. In: Ruderman N, Devlin JT, editors. The health professional's guide to diabetes and exercise. Alexandria, VA: American Diabetes Association; 1995. p. 125–32.
11. van Dijk JW, Manders RJF, Tummers K, Bonomi AG, Stehouwer CDA, Hartgens F, van Loon LJC. Both resistance- and endurance-type exercise reduce the prevalence of hyperglycaemia in individuals with impaired glucose tolerance and in insulin-treated and non-insulin-treated type 2 diabetic patients. Diabetologia. 2012;55(5):1273–82.
12. Eves ND, Plotnikoff RC. Resistance training and type 2 diabetes: considerations for implementation at the population level. Diabetes Care. 2006;29(8):1933–41.
13. Schneider SH, Amorosa LF, Khachadurian AK, Ruderman NB. Studies on the mechanism of improved glucose control during regular exercise in type2 (non-insulin dependent) Diabetes. Diabetologia. 1984;26(5):355–60.
14. Peterson CM, Jones RL, Dupuis A, Levine BS, Bernstein R, O'Shea M. Feasibility of improved blood glucose control in patients with insulin-dependent Diabetes mellitus. Diabetes Care. 1979;2(4):329–35.
15. Schneider SH, Kachadurian AK. Ten-year experience with an exercise-based outpatient life-style modification program in the treatment of diabetes mellitus. Diabetes Care. 1992;15(11):1800–10.
16. Tonoli C, Heyman E. Effects of different types of acute and chronic (training) exercise on glycemic control in Type 1 Diabetes Mellitus: a meta-analysis. Sports Med. 2012;42(12):1059–80.
17. Metcalf KM, Singhvi A. Effects of moderate to vigorous intensity physical activity on overnight and next-day hypoglycemia in active adolescents with Type 1 Diabetes. Diabetes Care. 2014;37(5):1272–8.
18. Davey RJ, Paramalingam N, Retterath A, Lim EM, Davis E, Jones TW, Fournier PAF. Antecedent hypoglycaemia does not diminish the glycaemia-increasing effect and glucoregulatory responses of a 10 s sprint in people with Type 1 Diabetes. Diabetologia. 2014;57:1111–8.
19. Figueira FR, Umpierre D, Ribeiro JP, Tetelbom PS, Henn NT, Esteves JF, Schaan BD. Accuracy of continuous glucose monitoring system during exercise in Type 2 Diabetes. Diabetes Res Clin Pract. 2012;98(3):e36–9.
20. Radermecker RP, Fayolle C, Brun JF, Bringer J, Renard E. Accuracy assessment of online glucose monitoring by a subcutaneous enzymatic glucose sensor during exercise in patients with Type 1 Diabetes treated by continuous subcutaneous insulin infusion. Diabetes Metab. 2013;39(3):258–62.
21. MacLeod SF, Terada T, Chahal BS, Boulé NG. Exercise lowers postprandial glucose but not fasting glucose in type 2 Diabetes: a meta-analysis of studies using continuous glucose monitoring. Diabetes Metab Res Rev. 2013;29(8):593–603.
22. Jimenez CC. National Athletic Trainers' Association Position Statement: management of the athlete with Type 1 Diabetes Mellitus. J Athl Train. 2007;42(4):536–45.
23. Burr JF, Shephard RJ, Riddell MC. Physical activity in Type 1 Diabetes Mellitus: assessing risks for physical activity clearance and prescription. Can Fam Physician. 2012;58(5):533–5.
24. Marwick TH, Hordern MD, Miller T, Chyun DA, Bertoni AG, Blumenthal RS, Philippides G, Rocchini A. Exercise training for Type 2 Diabetes Mellitus impact on cardiovascular risk: a scientific statement from the American Heart Association. Circulation. 2009;119:3244–62.
25. Schneider SH, Shindler D. Application of ADA guidelines for evaluation of the diabetic patient before recommending exercise program. In: Ruderman N,

Devlin JT, Schneider SH, Kriska A, editors. Handbook of exercise in diabetes. Alexandria, VA: ADA; 2002. p. 253–68.
26. Levin ME. The diabetic foot. In: Ruderman N, Devlin JT, editors. The health professional's guide to diabetes and exercise. Alexandria, VA: American Diabetes Association; 1995. p. 137–41.
27. Vinik AI. Neuropathy. In: Ruderman N, Devlin JT, editors. The health professional's guide to diabetes and exercise. Alexandria, VA: American Diabetes Association; 1995. p. 183–94.
28. Aiello LM, Cavallerano J. Retinopathy. In: Ruderman N, Devlin JT, editors. The health professional's guide to diabetes and exercise. Alexandria, VA: American Diabetes Association; 1995. p. 145–51.
29. Mogensen CE. Nephropathy. In: Ruderman N, Devlin JT, editors. The health professional's guide to diabetes and exercise. Alexandria, VA: American Diabetes Association; 1995. p. 165–71.
30. Yardley JY, Kenny GP, Perkins BA, Riddell MC, Balaa N, Malcolm J, Boulay P, Khandwala F, Sigal RJ. Resistance versus aerobic exercise acute effects on glycemia in type 1 diabetes. Diabetes Care. 2013; 36(3):537–42.
31. Durak EP, Jovanovic-Peterson L, Peterson CM. Randomized crossover study of effect of resistance training on glycemic control, muscular strength, and cholesterol in type I diabetic men. Diabetes Care. 1990;13(10):1039–43.
32. Kanj H, Schneider SH, Ruderman NB. Exercise and Diabetes Mellitus. In: Horton ES, Terjung RL, editors. Exercise, nutrition and energy metabolism. New York: Macmillan; 1988. p. 228–40.
33. Francois ME, Baldi JC, Manning PJ. Exercise snacks' before meals: a novel strategy to improve glycaemic control in individuals with insulin resistance. Diabetologia. 2014;57:1437–45.
34. Turcotte LP, Fisher JS. Skeletal muscle insulin resistance: roles of fatty acid metabolism and exercise. Phys Ther. 2008;88(11):1279–96.
35. Wong CY, Byrne NM, O'Moore-Sullivan T, Hills AP. Effect of weight loss due to lifestyle intervention on subclinical cardiovascular dysfunction in obesity (body mass index >30 kg/m2). Am J Cardiol. 2006; 98(12):1593–8.
36. Houmard JA, Bruno NJ, Bruner RK, McCammon MR, Israel RG, Barakat HA. Effects of exercise training on the chemical composition of plasma LDL. Arterioscler Thromb Vasc Biol. 1994;14:325–30.
37. Kriska AM, Blair SN, Pereira MA. The potential role of physical activity in the prevention of non-Insulin dependent Diabetes mellitus: the epidemiological evidence. Exerc Sport Sci Rev. 1991;22:121.
38. Eriksson KF, Lindgärde F. Prevention of Type 2 (non-insulin-dependent) Diabetes mellitus by diet and physical exercise. The 6-year Malmö feasibility study. Diabetologia. 1991;34(12):891–8.
39. Dowse GK, Zimmet PZ, Gareeboo H, George K, Alberti MM, Tuomilehto J, Finch CF, Chitson P, Tulsidas H. Abdominal obesity and physical inactivity as risk factors for NIDDM and impaired glucose tolerance in Indian, Creole, and Chinese Mauritians. Diabetes Care. 1991;14(4):271–82.
40. Graham C, Prosterman S. Scuba diving. In: Ruderman N, Devlin JT, editors. The health professional's guide to diabetes and exercise. Alexandria, VA: American Diabetes Association; 1995. p. 294–6.
41. Howard AA, Arnsten JH, Gourevitch MN. Effect of alcohol consumption on Diabetes Mellitus: a systematic review. Ann Intern Med. 2004;140(3): 211–9.
42. Layman DK. The role of leucine in weight loss diets and glucose homeostasis. J Nutr. 2003;133:261S–7.
43. Layman DK, Walker DA. Potential importance of leucine in treatment of obesity and the metabolic syndrome. J Nutr. 2006;136:319S–23.
44. Layman DK. Role of leucine in protein metabolism during exercise and recovery. Can J Appl Physiol. 2002;27:646–63. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/12501002.
45. Control TD, Trial C. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent Diabetes Mellitus. The Diabetes Control and Complications Trial Research Group. N Engl J Med. 1993;329:977–86. doi:10.1056/NEJM199309303291401.
46. Sugiura K, Kobayashi K. Effect of carbohydrate ingestion on sprint performance following continuous and intermittent exercise. Med Sci Sports Exerc. 1998;30(11):1624–30.
47. Jeukendrup AE, Brouns F, Wagenmakers AJ, Saris WH. Carbohydrate-electrolyte feedings improve 1 h time trial cycling performance. Int J Sports Med. 1997;18(2):125–9.
48. Nicholas CW, Williams C, Lakomy HK, Phillips G, Nowitz A. Influence of ingesting a carbohydrate-electrolyte solution on endurance capacity during intermittent, high-intensity shuttle running. J Sports Sci. 1995;13(4):283–90.
49. Coggan AR, Coyle EF. Carbohydrate ingestion during prolonged exercise: effects on metabolism and performance. Exerc Sport Sci Rev. 1991;19:1–40. Review.

Part IV

Present and Future Directions of Nutritional Supplements

Beyond the Obvious: Future Innovations in Sports Nutrition

16

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Abstract

The global proliferation of sports nutrition brands is emblematic of the size of consumers seeking enhancements through this class of ingestible products. However, a nearly ubiquitous theme of commonality is shared by these products: the compositions are often close to identical, differing only by amount and description, with ancillary alterations in flavor or packaging. How many branched chain amino acid or whey protein compositions can be birthed? The future of sports nutrition will continue to witness the penetration of multinational (food, beverage, and pharma) brands entering the fray through acquisition, and patent filings, which may foster a generic storm *or* heightened innovation. What remains most compelling is the opportunity for true innovation and pioneering to disrupt the highly duplicative sports nutrition product landscape. Such adventurous excursions may include systematic research/innovation programs that provide novelty, compelling proof of concept, and "real-world" utility; implementation of research methods that provide direct, inferential insights into the bioavailability and metabolism of bioactives; and novel protein/amino nitrogen sources that mimic the biological effects of whey protein.

Keywords

Innovation • Performance • Glycemic • Nutrition • Exercise • Creatine • L-Carnitine • Protein • Whey • Vegan

Absence of evidence is not evidence of absence [unless intensive investigations have beeyucted].

—Modified from Carl Sagan

For a successful technology, reality must take precedence over public relations, for Nature cannot be fooled.—Richard Feynman (Nobel laureate, Physics, 1965), from his report on the Challenger mission failure submitted to NASA

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16.1 Introduction

The enhancement of human muscular performance is likely a quest that has endured for millennia. Arguably, the longevity of the quest to enhance the human *physique*, a far more arbitrary and subjective pursuit, may be anchored back to the advent of the full or part length mirror, detailed anatomical drawings, or the camera. The emergence of governing or regulatory bodies that define what is "legal" or "allowed," e.g., the World Anti-Doping Agency (WADA) and Union Cycliste Internationale (UCI) have emerged as legislators of allowed and prohibited substances in competitive sports. The blurring of lines between "drugs" and ostensibly legal "sports/performance nutritionals" (SPNs) has led to numerous bioactives found in the latter category to be added to the prohibited list of the former.

It appears that the majority of SPNs marketed across the five major continents are not offered to consumers as *single* bioactive entities, e.g., creatine monohydrate and L-leucine, but as multi-ingredient cocktails. The fluid and geographically divergent regulatory bar of allowance—for novel bioactives for SPNs—coupled with the apparently constant consumer need for novelty and uniqueness, channels and drives new product creations and introductions. However, from the vantage of a scientist or academic, consumer or coach, parent or agent, and physician or physiotherapist comes the question, "Where do these ingredients come from?" A companion question, diverging from the chemistry of composition and pursuing the path of biology—safety and efficacy for the actual SPN—is, "Does this product work and is it safe?" Invoking an epidemiological measure, we have estimated that the "prevalence" of an "evidence based" [1] SPN is about 0.001 (or 0.1 %) [2]. I offer that an "evidence-based" *SPN* refers to an SPN that enjoys at least one reviewed journal publication *describing systematic research on the actual SPN*—the product offered for sale and marketed for specific utilities and benefits. Systematic research here refers to randomized controlled trials, performed in human subjects.

The premise that the majority of SPNs offered across the globe are NOT evidence based can lead one to infer that (1) consumers and purchase influencers do not assign any measurable value or inclusion criterion (for purchase of an SPN) to this feature, (2) consumers and purchase influencers are ignorant of this lacking attribute, or (3) they are persuaded to believe the contrary that a large number of SPNs are indeed evidence based. Thus, if an evidence base is not a purchase driver, and other factors are, what will shape the direction and destiny of SPNs of the future?

16.2 Claims Entropy

All SPNs are linked to claims—express or overt, or implied—*on* the actual SPN product *label* and "off label": *online* (the brand website, banner advertisements, social media posts), *on air* (Internet or broadcast radio live interviews or commercials, TV advertisements), *on demand* (YouTube video, podcast, archived webinars), *in person* (at a consumer or trade show, with claims made by employees or consultants representing an SPN brand, sponsored athletes/influencers at a competition, or giving a seminar), or *in print* (advertisements, collateral sales materials, e.g., brochures). Could an SPN that makes NO implied or express claims, on or off label, survive in the claim-laden market landscape?

Over the past several years in the course of our business, we have encouraged numerous individuals, comprised of elite athletes and their coaches or agents, retailers (owners, managers, and staff from nutrition, cycling, multisport/triathlon, and running), and management of gym/fitness/CrossFit® box/personal training centers, to place calls to a variety of SPN brand marketers and ask for evidence to support one or more of the claims associated with a specific SPN. Invariably, for those individuals that elected to perform claims due diligence—at least half did not follow through—they were both surprised and dismayed by the outcome, i.e., the absence of evidence to support any of the claims on the actual SPN. During the query, when the individuals pressed

the company for the justification of an absolute *lack* of independent evidence, these types of replies were most commonly offered:

- "Clinical studies cost millions of dollars" [cost prohibitive].
- "We have a lot of consumers who think our product really works" [testimonial-centric validation of efficacy].
- "We are planning to do some studies (at a later date)" [future promise of validation].
- "We don't need to do studies—we *know* our product works" [self-affirmation of efficacy].

A perusal of the world's leading website for SPNs, bodybuilding.com, or any print or digital magazine that features advertising and editorial about SPNs (e.g., bodybuilding, fitness, cycling, triathlon, running, stand up paddle) yields a diverse surfeit of product claims, often couched in superlatives: "ultimate endurance formula," "untouchable mass gains," "preeminent pre-workout," or "testosterone effects without the injection." As editorial content strives to incorporate more scientific evidence, the adoption of scientific jargon in SPN claims maintains step and extends beyond the arbitrary reader comprehension limits set by editors. Gene expression, molecular signaling pathways and molecules, pharmacokinetics/pharmacodynamics, receptor and transporter expression and translocation, metabolomics, and even gut microbiomics have been woven into SPN claims.

Over 20 years ago, a seismic shift occurred in the United States regulatory (and claims) landscape for SPNs, the Dietary Supplement Health and Education Act of 1994 (DSHEA) [3], which works closely with the Federal Trade Commission (FTC). Eight years later, the European Food Safety Authority (EFSA) was birthed [4], followed by a 2006 Regulation [5] that empowered EFSA to evaluate the scientific merit and authorize/deny claims made for food products within the European community, including food supplements and SPNs. In 2004, Health Canada annexed the Natural Health Products Act [6] to the 1985 Food and Drug Act [7], offering a claims authorization framework, which included monographed ("automatically allowed/approved") sport/performance nutrition ingredients with attendant strength/dosage and usage requirements.

These codified rules empower and enable governmental agencies to allow and restrict the claims for, and composition of, SPNs. A widely held and vociferously contested perception is that the global nutritional supplement industry (across the globe) is "unregulated" [7–10]. It is notable that the two main markets, North America and Europe, provide regulatory tools to police claims, yet sanctions on SPNs are as rare as full solar eclipses. Asserting that the claims for SPNs are "unregulated" is tantamount to stating that the highways, roads, and autobahns across the world have *no* speed limits. If speed cameras fitted with facial recognition resolution lenses—linked to a remote system that issued stout fines—or police cars were present at every 0.5 km distance, driving above the speed limit would very likely be a very rare occurrence. Similarly, if enforcement resource allocations (staff, funding) were augmented markedly, the SPN claims landscape would likely experience an ordering effect, abbreviating the entropic path that has been expanding since the advent of the progenitorial SPNs: desiccated liver and wheat germ oil.

16.3 SPN Research "Innovations"

Despite the relative dearth of evidence-based SPNs, an incremental number of original research investigations have been emerging over the past two decades. The existence of even a single study on an SPN can be noteworthy and distinguishing, but the study design and associated rigor can delineate between a value-adding and (consumer) cash-subtracting SPN.

16.3.1 Comparison Controls

One of the strongest categories (sales, product offerings) of SPNs is so-called "pre-workout" products. As the moniker implies, these SPNs are

intended to be ingested prior to a workout. The vast majority contains one or more stimulants—with caffeine being axial—almost invariably accompanied by several additional "accessory" ingredients. Many such products invoke the descriptor "synergistic" yet are devoid of any of such evidence (see below).

If one is attempting to demonstrate the performance enhancement potential of caffeine plus other bioactives, it would appear methodologically reasonable to compare the SPN to an equimolar dose of *caffeine alone* (a positive control), not only a wholly inert placebo control. However, many studies have not implemented a caffeine control and do not perform an unblinding assessment after conclusion of the trial, to ascertain the efficacy of masking subjects to their research arm assignment [11–16]. Indeed, several blinded studies have revealed discrimination of acute caffeine doses and significant stimulant responses, *as low as* 30–50 mg [17, 18]. Moreover, the irrational inclusion of ß-alanine (ß-Ala) in pre-workout SPNs (a nonprotein amino acid pioneered by Dr. Roger Harris), with a compelling ergogenic evidence base, albeit *after a few to several weeks of multi-gram daily dosing* [19], introduces a potentially greater confounding/unmasking element. ß-Ala elicits a temporary, dose-dependent, uncomfortable itching, "flushing" response, through activation of a G protein-coupled itch receptor present in sensory neurons [20], the clinical presentation sometimes referred to as "paresthesia" [21]. Unmasking of subjects through a perceptible stimulant effect or itching has the potential to dramatically alter the outcome of a study, while the *absence* of conditioned responses, e.g., stimulant/arousal or itch, may foster a fear-based neural response [22] with potentially *ergolytic* effects.

One of the reasons behind the preponderance of studies on pre-workout SPNs that lack a caffeine comparator is market/economic risk: if a company that markets SPNs (or energy drinks) sponsors an academic laboratory to undertake such a study, the likelihood of the data being made public (through presentation at a scientific conference and/or publication in a reviewed journal) is high. Thus, assuring a study outcome that is only favorable to an SPN is a critical element of protocol development for an SPN marketer to embrace. Drug studies often use a well-researched positive comparator against novel drugs, without an inert placebo control, thus obviating the argument that a three-group (pre-workout v. caffeine v. inert placebo) study would be economically untenable. *An innovation path for future SPNs would be the implementation of positive comparator allocation arms and unmasking assessments performed in the early phase of a study, after treatment randomization and after the conclusion of a study.*

16.3.2 Acting on Interactions: Favorable or Unfavorable

As stated above, many SPNs are comprised of more than one ingredient, "cocktails" that may have in excess of thirty labeled, presumed "bioactive" ingredients. In contradistinction, there is a nearly absolute lack of evidence exploring the interactions that follow ingestion, starting with bioavailability and pharmacokinetics. Protein-centric SPNs are exemplary, many combining two or more protein sources and asserting different pharmacokinetic and pharmacodynamic profiles, e.g., "slow" and "fast" proteins, derived from seminal studies conducted in subjects wherein *whole body*—not skeletal muscle—protein synthesis rate was assessed for 7 h postprandially [23]. Notably, there do not appear to be any studies that have implemented *chronic* supplementation, comparing isonitrogenous doses of differing "fast" and "slow" protein cocktails, and assessed changes in muscular performance and/or regional and whole body composition in trained athletes.

The nonprotein, ß-amino acid, L-carnitine, has been advocated as an SPN bioactive for over 30 years. Internet searches yield many pages claiming L-carnitine increases endurance, muscle mass gain, fat burning, and even promotion of body fat loss [24–26]. However, a review of the literature indicates the efficacy of L-carnitine in muscular performance is equivocal or non-efficacious and that supplementation does not

effect reductions in fat mass or increases in muscle mass among athletes [27–29]. Additionally, a single intravenous dose of L-carnitine, or chronic oral dosing, does not produce significant increases in intramuscular L-carnitine [27, 29]. Eight weeks of oral supplementation with 1 or 3 g/day of a modified form of L-carnitine, glycine propionyl-L-carnitine (GlycoCarn®, Sigma-Tau HealthScience, Inc.), also has been shown to have no impact on aerobic or anaerobic performance, body fatness, or intramuscular L-carnitine content [30].

An elegant example of SPN innovation is illustrated by the systematic research and development of a composition designed to increase intramuscular L-carnitine content and elicit shifts in substrate utilization at both rest and exercise. Through a proof of principle study involving acute insulin and L-carnitine infusion, Professor Paul Greenhaff and his colleagues demonstrated significant increases in intramuscular carnitine [31]. This was followed by a demonstration of increased muscle glycogen and carnitine content and reduced intramuscular lactate and pyruvate dehydrogenase complex (PDC) at rest, after a similar insulin and carnitine infusion protocol [32]. These intramuscular changes are indicative of alterations in substrate selection, specifically reduced glycolytic flux and possibly increased fatty acid oxidation.

In a follow-up study, acute and short-term oral carbohydrate supplementation (Lucozade®, GlaxoSmithKline; providing 94 g of sugars) with 4.5 g of L-carnitine L-tartrate (Carnipure®, Lonza AG) produced an apparent increase in whole body carnitine retention (as determined by reduced urinary carnitine excretion) compared to L-carnitine supplementation alone [33]. This investigation was succeeded by a 24-week period of supplementing endurance-trained athletes with 2.0 g of L-carnitine L-tartrate (Carnipure®, Lonza AG) combined with 80 g of a starch carbohydrate (Vitargo®, Swecarb) twice daily or the carbohydrate alone [34]. After 24 weeks, the carnitine + carbohydrate group displayed a 30 % greater muscle carnitine content than the carbohydrate control. Muscle glycogen utilization during a 30 min cycle ergometer bout at 50 % of maximal aerobic capacity (V_{O2max}) was 55 % less, and muscle lactate was significantly lesser after a successive 30 min 80 % V_{O2max} bout, in the carnitine + carbohydrate group. When the subjects then performed an all out, 30 min cycling bout, 35 % more work was done in the carnitine + carbohydrate group after 24 weeks of supplementation, compared to the carbohydrate control.

This compelling line of research, exploiting insulin-mediated increases in muscle carnitine, requires physiological hyperinsulinemia. As some individuals may not wish to ingest an additional 160 g of a highly insulinemic carbohydrate [35] as was used above [34], Greenhaff and colleagues chose an acute dose mixture of 40 g of carbohydrate and 40 g of whey protein, or 80 g of carbohydrate (Vitargo), consumed 1 h after ingestion of 3 g of L-carnitine (containing 0.1 % *deuterated* L-carnitine) [36]. The well-characterized insulinemic response that follows dietary protein ingestion, especially with whey protein [37, 38], can allow for a reduction in carbohydrate content by fostering a hyperinsulinemic response sufficient to activate muscle carnitine uptake. The use of the (stable) isotopically labeled carnitine permitted the assessment of apparent muscle carnitine uptake when coupled with arteriovenous measurements (across the forearm) of the tracer and unlabeled carnitine and blood flow [36]. The rate of carnitine disposal (presumably into skeletal muscle) was significantly greater with the carbohydrate drink compared to a flavor-matched, noncaloric control. However, despite similar insulinemic responses with the carbohydrate and carbohydrate + whey drinks (≈4–5 times greater area under the curve (AUC) over 3 h, relative to placebo), carnitine disposal with carbohydrate + protein was no greater than the placebo drink, and both were significantly less than the carbohydrate drink. Although the carnitine and drinks were not co-ingested, this suggests that whey protein antagonizes acute muscle carnitine uptake and/or promotes enteral or hepatic carnitine catabolism [38], when added to carbohydrate.

This research program, evolving since the early 2000s and still ongoing, resulted in patents and patent applications, a robust evidence base, revelation of a potential antagonistic interaction

that is highly relevant to SPN formulation, and a promising platform for SPN marketing and medical nutrition applications. The major challenges associated with this innovation are the substantial calorie intakes and the protracted supplementation duration needed to achieve performance enhancement. Although this program is time and resource intensive, future innovations in SPN could aspire to this methodical and sequential approach, while capturing intellectual property and incremental SPN product innovations in the process, to secure a magnified and enduring return on investment.

16.3.3 Misdirected: Indirect and Direct Measures

As the number of SPN scientific publications increases, budgetary constraints and methodological assumptions can reduce the quality of research produced. One example is illustrated by studies where inferences are made regarding muscle glycogen content, before, during, or after an intervention. Because of the costs associated with performing natural abundance ^{13}C nuclear magnetic resonance spectroscopy for glycogen quantitation [39], or muscle biopsies, and the associated challenges of obtaining ethical approval for multiple biopsies, muscle glycogen is routinely not measured. A cursory survey of recent studies (2014), wherein muscle glycogen and/or utilization was asserted to be altered or maintained, due to or in spite of diet and/or training alterations, respectively, reveals a common lack of glycogen measurements [40–43].

Glycogen The advent of a noninvasive, relatively low-cost method to quantify muscle glycogen, utilizing ultrasound technology (MuscleSound®, MuscleSound, LLC), may usher in a greater number of studies employing direct assessment of muscle glycogen throughout the exercise/competition cycle. It employs a portable device and cloud-based software. In a study funded by MuscleSound and led by the founder of the company, elite cyclists had muscle glycogen assessed before and after an intense bout of ergometer cycling [44]. The ultrasound value of muscle glycogen change compared favorably to that obtained with muscle biopsies ($r = 0.81$). At the time of writing, no independent studies comparing the method to muscle biopsy, or assessing muscle glycogen changes *during* (interrupted) exercise, have been published. With more rigorous independent validation, in a large cross section of athletes, genders, and metabolic extremes, e.g., McArdle's disease or type 1 diabetics pursuing a ketogenic diet, this innovation may prove invaluable to SPN innovation and validation.

Glycemic Index The glycemic index (GI), first described in 1981 by David Jenkins and colleagues [45], is a physiological measure of the change in blood glucose over a fixed period of time (usually 2 h) after ingestion of a test food, supplement, or beverage, relative to an "indexed" carbohydrate, e.g., dextrose or white bread providing an equal amount of digestible carbohydrates (usually 50 g). Thus, a "high" GI test substance would produce a greater and/or longer increase in glycemia relative to a "low" GI test substance.

Almost two decades ago, the misperception began to emerge, inferring that high GI substances displayed faster gut transit/digestion/absorption kinetics, while low GI substances provided slower kinetics, yet without direct evidence. Indeed, postprandial blood glucose concentration is governed by three factors: (1) rate of appearance of glucose from the intestines, (2) rate of appearance of glucose via de novo gluconeogenesis, and (3) rate of disappearance/disposal (primarily in skeletal muscle in nondiabetic, fit individuals). Not until 2003, in a study undertaken by Simon Schenk (while a masters' student in the laboratory of Dr. Eddie Coyle) were the kinetics of GI systematically addressed, in conventional foods [46]. Using endurance-trained male athletes, Schenk et al., performed a crossover GI test with All-Bran® cereal (Kellogg Company), a "classical" low GI cereal [45], and Kellogg's Corn Flakes® (Kellogg Company), a "classical" high GI cereal [45], coupled with a continuous infusion of a doubly labeled stable isotope of glucose: [6,6-$^{2}H_{2}$]glucose. The isotope

enabled the direct assessment of the rate of appearance (Ra) and rate of disappearance of glucose (Rd) (in and from the blood, respectively). As was shown in 1981 [45], the bran cereal elicited a low GI value, while the corn flakes a high GI value (2.4 times higher). Counterintuitively, this was *not* due to a blunted Ra with the bran cereal—the Ra was identical to that of corn flakes—but to a significantly greater Rd (bran cereal), via a *more robust early-phase insulin response* and subsequent glucose disposal (muscle glycogen was not measured).

Had the isotopic method not been implemented, a likely/common interpretation would have been that the bran "slowed" the rate of transit/digestion/absorption and thus produced a slower, lower GI, despite GI studies showing that fiber does not significantly influence GI values [45, 47]. It is not uncommon for interventions with high GI substances to assert that they exhibit more rapid absorption, in the absence of any direct, supportive kinetic data [48–50].

Creatine "Bioavailability" Like GI values, apparent absorption of creatine, indirectly inferred from blood concentration changes, can foster misguided interpretations. Several studies have demonstrated that apparent absorption of creatine after oral administration is around 80–90+ % [51, 52]. A study with single oral dosing of deuterated creatine in one subject revealed whole body uptake of 78 % [53]. More rigorous analysis, including fecal creatine and creatinine measurements, along with periodic urine collection, has shown apparent creatine absorption to approximate 100 %, with *trivial* conversion of creatine into creatinine [49] (significant creatine to creatinine conversion is often asserted by some creatine-centric SPN marketers [54]).

Interpretation that a higher AUC and or peak concentration of blood creatine is indicative of greater creatine absorption, in the absence of muscle creatine assessments, can lead to a spurious interpretation. The ingestion of 5 g of creatine monohydrate in a noncaloric solution or the same creatine solution followed 30 min later by a carbohydrate drink providing ≈92 g of sugars (Lucozade), each consumed four times daily for 5 days, was assessed in 24 young males in Greenhaff's laboratory [55]. Urinary creatine concentration (24 h collection) on day 1 of supplementation was markedly increased in both treatment groups, but was 1.8 times higher in the creatine alone beverage. However, muscle total creatine after 5 days of supplementation with the creatine solution and delayed carbohydrate drink *increased by an additional 60 %* compared to the increment seen in the creatine solution alone.

In a companion study with similar design, ingestion of a creatine only solution produced a nearly twofold higher maximum plasma creatine concentration (C_{max}) and a 2.5 times greater AUC (over a 4.5 h period) compared to creatine co-ingested with a drink providing 92 g of sugars (Lucozade) [56]. Moreover, 24 h urinary creatine concentrations were ≈twice as great in the creatine only solution treatment. A *prima facie* interpretation of this study is that more creatine was absorbed from the creatine only solution, based on notably higher blood and urine creatine concentrations. However, like blood glucose excursions seen in GI testing, increased blood creatine may also suggest reduced extraction or disposal by peripheral tissues, especially skeletal muscle, the major repository of creatine. As was evidenced in the previously described study [55], where muscle creatine concentration was measured via biopsy, muscle creatine content was dramatically greater, and urinary creatine was substantially lower with the creatine + carbohydrate drink relative to the creatine alone drink, the latter outcome also replicated in [56].

Taken together, reduced blood and urinary creatine values may indeed be indicative of comparable or greater absorption and superior muscle/whole body creatine retention, relative to higher blood and/or urinary creatine values [57]. Thus, studies comparing different creatine forms that assess blood concentrations and assign higher "bioavailability" or "absorption," based on greater AUC and/or C_{max} values *alone*, lack merit [58].

A compelling future for SPN innovations could be paved by a greater number of proof of principle and follow-up studies that implement direct assessments related to the presumed

benefit(s) of the SPN in question. Moreover, resolution of the *actual* effects and metabolic impact of candidate SPNs may foster the evolution of more effective products for consumers. Even initial, SPN-relevant "*n* of 1" [59] studies that incorporate highly *objective* assessment tools can be potent, value-adding instruments to accelerate the innovation of safe and effective SPNs that ultimately enjoy a strong evidence base.

16.4 Gut Reaction: Beyond a Tube Within a Tube

Classical textbook gastrointestinal physiology describes the gut as a system involved in the digestion, absorption, metabolism, and excretion of ingested materials, with an antimicrobial function (gastric acid) and a commensal microbial population—an inner "tube" within an outer "tube"—the extra-gastrointestinal compartment comprised of the systemic circulation and associated organs. Additionally, the major means in which the outer tube communicates back with the inner tube is via the enterohepatic circulation. The emergence of the gut microbiome—the microbial community and its associated genes residing within the human gut—as a functional, interactive "new" organ and focus of intense research [60–64], holds vast promise as a target for SPN innovations, inclusive of changes upon body composition.

Seminal work almost a decade ago began to reveal how common dietary elements can "imprint" human metabolism through the gut microbiome axis, with metabolic effects persisting for weeks after cessation of the introduced dietary element [65]. Perhaps the most SPN innovation-relevant aspect of the gut microbiome is how high-protein diets can transform the microbial population [66–68]. While the impact of chronic high-protein, high-fat, or high-carbohydrate diets in athletes, upon the function of the gut microbiome, remains enigmatic, it harbors massive promise in relation to strategic selection of probiotic strains that can offset or complement the impact of long-term dietary discretions.

A tangent related to gut function and SPNs is the body of evidence forming around splanchnic hypoperfusion of intense exercise and its impact upon gut function, as advanced by Dr. Kaatje Lenaerts and colleagues in the Netherlands [69]. Resistance-trained subjects performing a bout of resistance exercise manifest acute impairments in enterocyte function, resulting in compromised apparent and actual absorption of amino acids derived from protein-consumed postexercise [70]. A study by this group suggested that high-dose (10 g) ingestion of the nonprotein amino acid L-citrulline prior to endurance cycling preserved splanchnic perfusion [71], offering the enticing suggestion that pre-exercise L-citrulline ingestion (or other nitric oxide synthase influencing bioactives) may augment postexercise protein digestion kinetics and muscle protein synthesis rates.

16.5 SPN Bioactives: Manufacturing Shifts

The provision of adequate nutrition to the world's population continues to ascend in prominence and import. Arguably, SPNs could be considered "luxury nutrition," with their manufacturing subject to potential scrutiny, from both policy maker and stakeholder vantages. Relevant to SPNs that are manufactured in a ready to drink (RTD) format is a recent report by the World Economic Forum [72]. A survey conducted with over 700 members that comprise the multistakeholders community described *water crises* among the top three highest concern risks. The global proliferation of RTDs and their associated bottling facilities, all hyper-dependent on potable water supplies, may beget new innovations in capturing and purifying water, ranging from hyper-efficient moisture collection systems to waste stream recapture from adjacent facilities, e.g., creation of a zero water dairy facility that reclaims water extracted from the creation of milk powder [73].

Approximately one-third of human global protein consumption is derived from animal products [74] (including dairy proteins that are an axial component of many SPNs). The adaptive

capacity of the dairy protein producing global consortium to meet the demand for dairy proteins used in SPNs (especially whey protein), in light of greenhouse gas and ozone hole concerns, water shortages, population shifts, and climate insults [75, 76], provides some intriguing opportunities for innovation.

Once a nascent subcategory, vegan-centric SPNs are gaining a significant foothold among SPN consumers. Not surprisingly, there is a paucity of evidence supporting the chronic bioequivalence of a commercially available, vegan protein SPN finished good against a dairy/animal comparator, i.e., increases in muscle/fat-free lean mass, performance-centric adaptations to training, or both. One recent study out of Dr. Jacob Wilson's laboratory in Florida compared supplementation with *high-dose* protein from rice protein concentrate (Growing Naturals Rice Protein Isolate with Oryzatein® rice protein, Axiom Foods) versus *high-dose* protein from whey protein isolate (NutraBio 100 % Whey Protein Isolate, NutraBio), each consumed after an 8-week, hypertrophy-oriented resistance training program in resistance-trained individuals [77]. The high dose of protein was selected, in part, to deliver a higher leucine content, despite the absence of rigorous studies employing chronic supplementation with leucine or branched chain amino acids displaying increases in muscle mass [78, 79].

The paper described both "48 g of whey (or rice) protein *isolate*" and "48 g of protein in the form of whey (or rice) protein isolate," the former delivering ≈42 g of protein. Irrespective of the quantity, based upon several studies in *young*, resistance-training males consuming whey protein isolate (WPI) after a bout of resistance training, the dose was excessive/high, as noted by the authors [77]. Indeed, two recent studies with WPI have shown that single or multiple post-workout doses of WPI in excess of 20 g (among resistance-trained males less than ≈90 kg) elicit significant "wasting" of the protein excess, via amino acid oxidation and significant urea production, with no greater muscle fractional synthesis rate (mFSR) [80, 81]. "Young" is emphasized, as a recent analysis of dietary protein dose-response pharmacodynamics (as mFSR) comparing younger (18–37 years) to older (65–80 years) males suggests that the meal protein dose for younger males be 0.24 g protein/kg body mass and 0.40 g/kg for older males (based on 3 meals/day diet) [82].

Collectively, given the voluminous array of protein-centric SPNs available throughout the globe, a suite of innovation foci emerge:

- Development of RTDs that deliver their bioactive payloads in a palatable manner, with less water volume
- Innovation of vegan protein cocktails less reliant upon dairy proteins, which produce bioequivalent chronic outcomes in training athletes, e.g., a moderate dose pea + rice protein blend, enriched with select amino acids
- Introduction of evidence-based, protein-centric SPNs that target "silver" athletes/individuals engaged in intensive training programs and reversing or arresting age-related loss of muscle mass and function (sarcopenia)

16.6 Conclusion

The market, industrial, climatic, regulatory, and media forces continue to shape the direction of the SPN industry. Ultimately, the end user/consumer of any SPN is seeking a product that is safe and effective and (often) offers an enhancement over their current SPN or diet, beyond the offering of convenience. Remarkably, the vast majority of SPN marketers have sufficient revenues to sponsor independent studies conducted by experienced research teams with expertise in the outcome measures being considered, i.e., reviewed publications of original research. The highly competitive and increasingly regulatory body-enforced SPN landscape will continue to spur novelty and invention. What remains hopeful is the shift of the industry stakeholders to a greater allocation of revenues to innovation directives that result in the creation of evidence-based SPNs that offer both a competitive edge for the hyperopic, investing SPN company and SPN consumers.

References

1. Almada AL. Nutraceuticals and functional foods: aligning with the norm or preparing for the storm. In: Bagchi D, editor. Nutraceutical and functional food regulations in the United States and around the world. 2nd ed. London: Academic Press; 2014. p. 3–11.
2. Sackett DL, Rosenberg WMC, Gray JAM, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. BMJ. 1996;312:71–2.
3. Dietary Supplement Health and Education Act of 1994 Pub. L. No. 103–417, 108 Stat. 4325 (October 25, 1994).
4. http://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:2002R0178:20090807:EN:HTML
5. http://eur-lex.europa.eu/legal-content/en/ALL/?uri=CELEX:32006R1924
6. http://laws-lois.justice.gc.ca/eng/regulations/SOR-2003-196/page-1.html
7. Anon. Unregulated dietary supplements. 19 Sep 1998 [cited 2014 Nov 14] http://www.nytimes.com/1998/09/19/opinion/unregulated-dietary-supplements.html
8. Wallis L. The toxic truth about vitamin supplements: How health pills millions take with barely a second thought can do more harm than good 23 Aug 2010 [cited 2014 Nov 15] http://www.dailymail.co.uk/health/article-1305534/The-toxic-truth-vitamin-supplements-Health-pills-millions-barely-second-thought-harm-good.html
9. Anon. Sports nutrition sector hits back at "unregulated" charge. 18 Feb 2013 [cited 2014 Nov 15] http://www.naturalproductsonline.co.uk/sports-nutrition-sector-hits-back-at-unregulated-charge/
10. Anon. Supplementing your supplements. 14 August 2013 [cited 2014 Nov 15] www.spoor.com/articles/Supplementing_your_supplements-474.html
11. Candow DG, Kleisinger AK, Grenier S, Dorsch KD. Effect of sugar-free Red Bull energy drink on high-intensity run time-to-exhaustion in young adults. J Strength Cond Res. 2009;23:1271–5.
12. Spradley BD, Crowley KR, Tai CY, Kendall KL, Fukuda DH, Esposito EN, et al. Ingesting a pre-workout supplement containing caffeine, B-vitamins, amino acids, creatine, and beta-alanine before exercise delays fatigue while improving reaction time and muscular endurance. Nutr Metab. 2012;9:28.
13. Kendall KL, Moon JR, Fairman CM, Spradley BD, Tai CY, Falcone PH, et al. Ingesting a pre-workout supplement containing caffeine, creatine, beta-alanine, amino acids, and B-vitamins for 28 days is both safe and efficacious in recreationally active men. Nutr Res. 2014;34:442–9.
14. Gonzalez AM, Walsh AL, Ratamess NA, Kang J, Hoffman JR. Effect of a pre-workout energy supplement on acute multi-joint resistance exercise. J Sports Sci Med. 2011;10:261–6.
15. Fukuda DH, Smith AE, Kendall KL, Stout JR. The possible combinatory effects of acute consumption of caffeine, creatine, and amino acids on the improvement of anaerobic running performance in humans. Nutr Res. 2010;30:607–14.
16. Lee J, Kim HT, Solares GJ, Kim K, Ding Z, Ivy JL. Caffeinated nitric oxide-releasing lozenge improves cycling time trial performance. Int J Sports Med. 2015;36:107–12.
17. Griffiths RR, Evans SM, Heishman SJ, Preston KL, Sannerud CA, Wolf B, et al. Low-dose caffeine discrimination in humans. J Pharmacol Exp Ther. 1990;252:970–8.
18. Childs E, de Wit H. Subjective, behavioral, and physiological effects of acute caffeine in light, nondependent caffeine users. Psychopharmacology (Berl). 2006;185:514–23.
19. Hobson RM, Saunders B, Ball G, Harris RC, Sale C. Effects of ß-alanine supplementation on exercise performance: a meta-analysis. Amino Acids. 2012;43:25–37.
20. Liu Q, Sikand P, Ma C, Tang Z, Han L, Li Z, et al. Mechanisms of itch evoked by ß-alanine. J Neurosci. 2012;32:14532–7.
21. Decombaz J, Beaumont M, Vuichoud J, Bouisset F, Stellingwerff T. Effect of slow-release ß-alanine tablets on absorption kinetics and paresthesia. Amino Acids. 2012;43:67–76.
22. Jensen KB, Kaptchuk TJ, Chen X, Kirsch I, Ingvar M, Gollub RL, et al. A neural mechanism for nonconscious activation of conditioned placebo and nocebo responses. Cereb Cortex. 2014. doi:10.1093/cercor/bhu275.
23. Boirie Y, Dangin M, Gachon P, Vasson MP, Maubois JL, Beaufrère B. Slow and fast dietary proteins differently modulate postprandial protein accretion. Proc Natl Acad Sci U S A. 1997;94:14930–5.
24. Anon. L-Carnitine - Is it good or bad for your heart? Hammer Nutrition [cited 2014 Nov 21]; [about 3 screens]. Available from: http://www.hammernutrition.com/knowledge/l-carnitine-is-it-good-or-bad-for-your-heart.17139.html?sect=blog-section
25. Lockridge R. 11 side effects of L-carnitine. 18 Oct 2013 [cited 2014 Nov 21] http://www.bodybuilding.com/fun/11-super-side-effects-from-taking-l-carnitine.html
26. Poliquin Group editorial staff. Top 12 reasons to use carnitine. 31 December 2011 [cited 2014 Nov 21] http://www.poliquingroup.com/articlesmultimedia/articles/article/767/top_12_reasons_to_use_carnitine.aspx
27. Brass EP. Carnitine and sports medicine: use or abuse? Ann N Y Acad Sci. 2004;1033:67–78.
28. Karlic H, Lohninger A. Supplementation of L-carnitine in athletes: does it make sense? Nutrition. 2004;20:709–15.
29. Wächter S, Vogt M, Kreis R, Boesch C, Bigler P, Hoppeler H, et al. Long-term administration of L-carnitine to humans: effect on skeletal muscle carnitine content and physical performance. Clin Chim Acta. 2002;318:51–61.
30. Smith WA, Fry AC, Tschume LC, Bloomer RJ. Effect of glycine propionyl-l-carnitine on aerobic and

anaerobic exercise performance. Int J Sport Nutr Exerc Metab. 2008;18:19–36.
31. Stephens FB, Constantin-Teodosiu D, Laithwaite D, Simpson EJ, Greenhaff PL. Insulin stimulates L-carnitine accumulation in human skeletal muscle. FASEB J. 2005;20(2):377–9. doi:10.1096/fj.05-4985fje.
32. Stephens FB, Constantin-Teodosiu D, Laithwaite D, Simpson EJ, Greenhaff PL. An acute increase in skeletal muscle carnitine content alters fuel metabolism in resting human skeletal muscle. J Clin Endocrinol Metab. 2006;91:5013–8.
33. Stephens FB, Evans CE, Constantin-Teodosiu D, Greenhaff PL. Carbohydrate ingestion augments L-carnitine retention in humans. J Appl Physiol. 2007;102:1065–70.
34. Wall BT, Stephens FB, Constantin-Teodosiu D, Marimuthu K, Macdonald I, Greenhaff PL. Chronic oral ingestion of L-carnitine and carbohydrate increases muscle carnitine content and alters muscle fuel metabolism during exercise in humans. J Physiol. 2011;589:963–73.
35. Stephens FB, Roig M, Armstrong G, Greenhaff PL. Post-exercise ingestion of a unique, high molecular weight glucose polymer solution improves performance during a subsequent bout of cycling exercise. J Sports Sci. 2008;26:149–54.
36. Shannon C, Nixon A, Greenhaff P, Stephens F. Protein ingestion impairs insulin-stimulated net muscle carnitine uptake in healthy young men. FASEB J. 2014;28:LB812.
37. Pal S, Ellis V. The acute effects of four protein meals on insulin, glucose, appetite and energy intake in lean men. Br J Nutr. 2010;104:1241–8.
38. Morifuji M, Ishizaka M, Baba S, Fukuda K, Matsumoto H, Koga J, et al. Comparison of different sources and degrees of hydrolysis of dietary protein: effect on plasma amino acids, dipeptides, and insulin responses in human subjects. J Agric Food Chem. 2010;58:8788–97.
38. Koeth RA, Wang Z, Levison BS, Buffa JA, Org E, Sheehy BT, et al. Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. Nat Med. 2013;19:576–85.
39. Avison MJ, Rothman DL, Nadel E, Shulman RG. Detection of human muscle glycogen by natural abundance ^{13}C NMR. Proc Natl Acad Sci U S A. 1988;85:1634–6.
40. Raper JA, Love LK, Paterson DH, Peters SJ, Heigenhauser GJF, Kowalchuk JM. Effect of high-fat and high-carbohydrate diets on pulmonary O_2 uptake kinetics during the transition to moderate-intensity exercise. J Appl Physiol. 2014;117:1371–9.
41. Hansen M, Bangsbo J, Jensen J, Bibby BM, Madsen K. Effect of whey protein hydrolysate on performance and recovery of top-class orienteering runners. Int J Sport Nutr Exerc Metab. Metab. 2015;25:97–109.
42. Scott AT, O'Leary T, Walker S, Owen R. Improvement of 2000-m rowing performance with caffeinated carbohydrate-gel ingestion. Int J Sports Physiol Perf. 2015;10:464–8.
43. Helms ER, Zinn C, Rowlands DS, Naidooa R, Cronin J. High-protein low-fat short-term diet results in less stress and fatigue than moderate-protein moderate-fat diet during weight loss in male weightlifters, a pilot study. Int J Sport Nutr Exerc Metab. 2015;25:163–70.
44. Hill JC, San MI. Validation of musculoskeletal ultrasound to assess and quantify muscle glycogen content. a novel approach. Phys Sportsmed. 2014;42:45–52.
45. Jenkins DJA, Wolever TMS, Taylor RH, Barker H, Fielden H, Baldwin JM, et al. Glycemic index of foods: a physiological basis for carbohydrate exchange. Am J Clin Nutr. 1981;34:362–6.
46. Schenk S, Davidson CJ, Zderic TW, Byerley LO, Coyle EF. Different glycemic indexes of breakfast cereals are not due to glucose entry into blood but to glucose removal by tissue. Am J Clin Nutr. 2003; 78:742–8.
47. Jenkins DJA, Wolever TMS, Taylor RH, Barker HM, Fielden H, Gassull MA. Lack of effect of refining on the glycemic response to cereals. Diabetes Care. 1981;4:509–13.
48. Stevenson EJ, Thelwall PE, Thomas K, Smith F, Brand-Miller J, Trenell MI. Dietary glycemic index influences lipid oxidation but not muscle or liver glycogen oxidation during exercise. Am J Physiol Endocrinol Metab. 2009;296:E1140–7.
49. Mondazzi L, Arcelli E. Glycemic index in sport nutrition. J Am Coll Nutr. 2009;28Suppl:455S-63S.
50. Roberts MD, Lockwood C, Dalbo VJ, Volek J, Kerksick CM. Ingestion of a high-molecular-weight hydrothermally modified waxy maize starch alters metabolic responses to prolonged exercise in trained cyclists. Nutrition. 2011;27:659–65.
51. Harris RC, Soderlund K, Hultman E. Elevation of creatine in resting and exercised muscle of normal subjects by creatine supplementation. Clin Sci. 1992;83: 367–74.
52. Deldicque L, Decombaz J, Foncea HZ, Vuichoud J, Poortmans JR, Francaux M. Kinetics of creatine ingested as a food ingredient. Eur J Appl Physiol. 2008;102:133–43.
53. MacNeil L, Hill L, MacDonald D, Keefe L, Cormier JF, Burke DG, et al. Analysis of creatine, creatinine, creatine-d3 and creatinine-d3 in urine, plasma, and red blood cells by HPLC and GC-MS to follow the fate of ingested creatine-d3. J Chromatogr B. 2005; 827:210–5.
54. Jagim AR, Oliver JM, Sanchez A, Galvan E, Fluckey J, Riechman S, et al. A buffered form of creatine does not promote greater changes in muscle creatine content, body composition, or training adaptations than creatine monohydrate. J Int Soc Sports Nutr. 2012; 9:43.
55. Green AL, Hultman E, Macdonald IA, Sewell DA, Greenhaff PL. Carbohydrate ingestion augments skeletal muscle creatine accumulation during creatine supplementation in humans. Am J Physiol Endocrinol Metab. 1996;271:E821–6.
56. Green AL, Simpson EJ, Littlewood JJ, Macdonald IA, Greenhaff PL. Carbohydrate ingestion augments

creatine retention during creatine feeding in humans. Acta Physiol Scand. 1996;158:195–202.
57. Kerksick CM, Wilborn CD, Campbell WI, Harvey TM, Marcello BM, Roberts MD, et al. The effects of creatine monohydrate supplementation with and without D-pinitol on resistance training adaptations. J Strength Cond Res. 2009;23:2673–82.
58. Miller DW. Oral bioavailability of creatine supplements: Is there room for improvement? International Society of Sports Nutrition Annual Conference; 2009 June 14–15; New Orleans, Louisiana.
59. Rascol O, Ferreira J, Negre-Pages L, Perez-Lloret S, Lacomblez L, Galitzky M, et al. A proof-of-concept, randomized, placebo-controlled, multiple cross-overs (n-of-1) study of naftazone in Parkinson's disease. Fundam Clin Pharmacol. 2012;26:557–64.
60. Gill SR, Pop M, DeBoy RT, Eckburg PB, Turnbaugh PJ, Samuel BS, et al. Metagenomic analysis of the human distal gut microbiome. Science. 2006;312:1355–9.
61. The Human Microbiome Project Consortium. A framework for human microbiome research. Nature. 2012;486:215–21.
62. Turnbaugh PJ, Gordon JI. The core gut microbiome, energy balance and obesity. J Physiol. 2009;587:4153–8.
63. Greiner AK, Papineni RVL, Umar S. Chemoprevention in gastrointestinal physiology and disease. Natural products and microbiome. Am J Physiol Gastrointest Liver Physiol. 2014;307:G1–15.
64. Ridaura VK, Faith JJ, Rey FE, Cheng J, Duncan AE, Kau AL, et al. Gut microbiota from twins discordant for obesity modulate metabolism in mice. Science. 2013. doi:10.1126/science.1241214.
65. Wang Y, Tang H, Nicholson JK, Hylands PJ, Sampson J, Holmes E. A metabonomic strategy for the detection of the metabolic effects of chamomile (*Matricaria recutita* L.) ingestion. J Agric Food Chem. 2005;53:191–6.
66. Liu X, Blouin JM, Santacruz A, Lan A, Andriamihaja M, Wilkanowicz S, et al. High-protein diet modifies colonic microbiota and luminal environment but not colonocyte metabolism in the rat model: the increased luminal bulk connection. Am J Physiol Gastrointest Liver Physiol. 2014;307:G459–70.
67. Scott KP, Gratz SW, Sheridan PO, Flint HJ, Duncan SH. The influence of diet on the gut microbiota. Pharmacol Res. 2013;69:52–60.
68. Lan A, Andriamiha M, Blouin JM, Liu X, Descatoire V, Desclée de Maredsous C, et al. High-protein diet differently modifies intestinal goblet cell characteristics and mucosal cytokine expression in ileum and colon. J Nutr Biochem. 2015;26:91–8.
69. van Wijck K, Lenaerts K, Grootjans J, Wijnands KAP, Poeze M, van Loon LJC, et al. Physiology and pathophysiology of splanchnic hypoperfusion and intestinal injury during exercise: strategies for evaluation and prevention. Am J Physiol Gastrointest Liver Physiol. 2012;303:G155–68.
70. van Wijck K, Pennings B, van Bijnen AA, Senden JM, Buurman WA, Dejong CH, et al. Dietary protein digestion and absorption are impaired during acute postexercise recovery in young men. Am J Physiol Regul Integr Comp Physiol. 2013;304:R356–61.
71. van Wijck K, Wijnands KAP, Meesters DM, Boonen B, van Loon LJC, Buurman WA, et al. L-citrulline improves splanchnic perfusion and reduces gut injury during exercise. Med Sci Sports Exerc. 2014;46:2039–46.
72. World Economic Forum. Global Risks 2014, 9 Ed. Geneva; 2013 Dec 30. 60 p.
73. Weston S. Nestlé opens water-efficient Cero Agua dairy factory in Mexico. 22 Oct 2014 [cited 2014 Dec 10] http://www.foodbev.com/news/nestl-opens-water-efficient-cero-agua-da#.VI3kQqYYt5x
74. Popp A, Lotze-Campen H, Bodirsky B. Food consumption, diet shifts and associated non-CO2 greenhouse gases from agricultural production. Glob Environ Change. 2010;20:451–62.
75. Bellarby J, Tirado R, Leip A, Weiss F, Lesschen JP, Smith P. Livestock greenhouse gas emissions and mitigation potential in Europe. Glob Chang Biol. 2013;19:3–18.
76. Robinson SA, Erickson DJ. Not just about sunburn – the ozone hole's profound effect on climate has significant implications for Southern Hemisphere ecosystems. Glob Chang Biol. 2015;21:515–27.
77. Joy JM, Lowery RP, Wilson JM, Purpura M, De Souza EO, Wilson SMC, et al. The effects of 8 weeks of whey or rice protein supplementation on body composition and exercise performance. Nutr J. 2013;12:86.
78. Crowe MJ, Weatherson JN, Bowden BF. Effects of dietary leucine supplementation on exercise performance. Eur J Appl Physiol. 2006;97:664–72.
79. Ispoglou T, King RF, Polman RC, Zanker C. Daily L-leucine supplementation in novice trainees during a 12-week weight training program. Int J Sports Physiol Perform. 2011;6:38–50.
80. Areta JL, Burke LM, Ross ML, Camera DM, West DWD, Broad EM, et al. Timing and distribution of protein ingestion during prolonged recovery from resistance exercise alters myofibrillar protein synthesis. J Physiol. 2013;591:2319–31.
81. Witard OC, Jackman SR, Breen L, Smith K, Selby A, Tipton KD. Myofibrillar muscle protein synthesis rates subsequent to a meal in response to increasing doses of whey protein at rest and after resistance exercise. Am J Clin Nutr. 2014;99:86–95.
82. Moore DR, Churchward-Venne TA, Witard O, Breen L, Burd NA, Tipton KD, et al. Protein ingestion to stimulate myofibrillar protein synthesis requires greater relative protein intakes in healthy older versus younger men. J Gerontol A Biol Sci Med Sci. 2014;70:57–62.

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