Nutrition and Health
Series Editor: Adrianne Bendich

Connie Watkins Bales
Julie L. Locher
Edward Saltzman *Editors*

Handbook of Clinical Nutrition and Aging

Third Edition

Humana Press

Nutrition and Health

Adrianne Bendich, Ph.D., FASN, FACN, Series Editor

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Dr. Bales dedicates this book in honor of her brand new grandchildren, Ada Elizabeth and William Thomas Britton. Thank you for reminding us that tomorrow brings new life, fresh beginnings, and hope for a better world!

Dr. Locher dedicates this work to those in health care and community settings who are working together to comprehensively address nutrition risk and food insecurity among older adults.

Dr. Saltzman: To my mentors and those who have served as role models, whose contributions to my success have been incalculably great and for which I am more grateful than words can express.

Foreword

This new edition of the *Handbook of Clinical Nutrition and Aging*, edited by Connie Bales, Edward Saltzman, and Julie Locher, is a most timely comprehensive overview of relevant new findings for practitioners, investigators, and policy makers. The individual chapters share knowledge and expertise from authors who are preeminent leaders in the field.

As the twenty-first century unfolds, the world will confront many challenges in caring for aged adults that far exceed any ever experienced previously. The US population aged 65 years and older has increased by 21 % over the past two decades. In the coming years, it will grow even more rapidly, increasing more than twofold by 2060. Even more rapid change is projected for the oldest-old; those 85 years and older are expected to triple between 2012 and 2040. Such unprecedented increases in the numbers of adults reaching old age will produce major changes in population age distributions, not only in the Western world but around the globe, i.e., in developed as well as developing nations. These dramatic changes will have an indelible impact on health care and the practice of clinical nutrition.

To some extent, this is old news. These predictions have been on the radar for at least two decades, prompting efforts to consider new comprehensive systems of healthcare delivery for older persons. However, as we now engage the aging cohort of the "baby boomer" generation, the future has arrived, and we must face the realities of shifting demographics and limited resources. What it means to be an older person has also continued to evolve. Who imagined even 100 years ago that life expectancies would rise to the current degree? Who imagined that, for some, age 70 would functionally become the new age 60? Who imagined that so many older persons would have such active, rich, and fulfilling lives? Unfortunately a substantial number of older persons will not have these opportunities because they suffer aging-associated conditions like chronic disease, depression, dementia, poor oral health, sarcopenia, functional decline, and frailty. Malnutrition is associated with many of these conditions, both as a precipitating factor and as an adverse outcome that blunts the success of medical therapies and contributes to decline. Obesity has also become common among older persons and is strongly associated with disease burden and functional limitation. Sarcopenic obesity is especially common and may contribute to functional impairment. Paradoxically, many obese older persons consume poor quality diets and also suffer micronutrient deficiencies. Therefore, as highlighted in this book, practitioners will confront a complex spectrum of nutritional concerns among older persons, everything from malnutrition in the setting of classic starvation to malnutrition in the setting of disease or injury to malnutrition in the setting of obesity.

In most Western countries, including the United States, diet-related chronic diseases are the single largest cause of morbidity and mortality. Optimally implemented, preventive nutrition and medical nutrition therapies have the potential to be major determinants of the ultimate impact of aging on world populations. Sound nutrition offers opportunities to favorably alter health-related quality of life as well as healthcare resource use by older persons. With respect to related aging policies, we are

witnessing two evolving trends that bring nutritional concerns of older persons to the forefront. First, there is a growing movement to shift the emphasis of long-term care from institutional settings to home- and community-based settings. Central to this movement is the provision of nutrition services to older adults residing in the community who are at nutritional risk, especially those lacking resources (both financial and social), and those who experience chronic disease burden and functional decline that increase their likelihood of being hospitalized or placed in a skilled nursing facility. Second, there are increasing financial penalties to hospitals and healthcare providers when patients experience adverse outcomes like premature hospital readmission. Malnutrition is strongly associated with increased risk for such undesirable outcomes. Connecting medical and social services that address nutritional needs is vital in caring for older persons. An important new feature of this edition of this book is a focus on elders residing in the community and how best, both effectively and efficiently, to meet their nutritional needs.

Gordon L. Jensen, M.D., Ph.D.

Preface

It has been a decade since the first edition of this *Handbook* was created. The intervening time has indeed brought a mixture of blessings and concerns. Rapid scientific progress and advances in information transfer have fostered medical discoveries and dissemination of health-related information at an unprecedented rate. Consumers are more aware of the value of health-promoting behaviors than ever before, and older adults are paying close attention. For example, older persons are the greatest consumers of dietary supplements. Many employers have introduced wellness in the workplace initiatives, including to their retirees. Yet, the stark economic difficulties of the past few years have added unanticipated challenges for many individuals and families, often making it difficult to take advantage of these advances. The stress of limited time and resources and the confusion resulting from mixed messages in the media can be particularly challenging for older adults. Many are living on a fixed income and coping with a number of comorbidities as they make choices about health-related behaviors, including nutrition. As a result, they may not rank nutrition highly amongst the complex array of health-related recommendations they are offered, but we believe that they should!

In later life, as at any age, a poor diet and related factors like inactivity and obesity increase the risk of developing a long list of chronic conditions, such as cardiovascular disease, type 2 diabetes, metabolic syndrome, gallbladder disease, and cancer. Conversely, adherence to medical nutrition therapies for age-associated conditions such as renal disease and chronic heart failure can foster important improvements in health-related quality of life by preserving organ function and reducing problematic symptoms. With this in mind, we sought in this third edition of the *Handbook* to emphasize newer topics that have received limited attention heretofore, as well as mainstay topics for which assessment and therapies have continued to evolve and improve. For example, the increased recognition of physical function as a determinant of independence and well-being in later life is supported by three relevant chapters (Chaps. 6, 7, and 22). Two chapters (Chaps. 8 and 18) deal with aspects of diet and cognition, a current "hot topic" in geriatric nutrition. Chapters on food insecurity (Chap. 9), pressure ulcers (Chap. 14), feeding in late dementia (again, Chap. 18), and end of life issues (Chap. 19) highlight nutritional concerns in highly vulnerable populations. As in past editions, our "menu" of chapters on clinical conditions includes obesity, diabetes, heart failure, cancer, kidney disease, and osteoporosis. We are also pleased to include a new chapter on nutrition and anti-aging (Chap. 20) and the latest information on the ever-challenging topic of dietary supplements (Chap. 22), as well as a number of additional chapters relating to new knowledge about the role of nutrition in aging on a broader scope. The contents of these chapters reflect an optimistic outlook. Clearly, the authors contributing chapters to the *Handbook* support the idea that optimal nutrition benefits all older adults and they offer specific suggestions for accomplishing these benefits.

As with the first two editions, this book is a uniquely comprehensive and current resource on the topic of secondary disease prevention and medical nutrition therapy for older adults. We hope that it will be a valuable guide to clinical nutritionists/dietitians, physicians, nurses, and therapists in speech-language and occupational therapy, as well as many other health professionals, including social workers and case managers, who provide care for this high-risk population. We are indebted to many individuals who contributed as we put together this edition of the *Handbook*. In particular, we sincerely thank Diane Lamsback, Developmental Editor at Springer. With the consuming demands on the time of both editors and authors, her ongoing support was invaluable and truly helped to make this edition become a reality. CWB thanks Sarah B. Rose, MS, RD, who assisted with all the initial chapter reviews and supported the Duke Center for Aging work on the *Handbook*. CWB also thanks Amanda Quinn, who was with Springer until recently, for support and guidance as three editions of this *Handbook* have come together. We all as editors especially acknowledge the encouragement from our series editor, Dr. Adrianne Bendich, to explore the critical clinical issues in geriatric nutrition through this collaboration with the gifted and dedicated scientists who study them. It is these scientist-authors who ultimately made the book a successfully reality and we thank them all.

Durham, NC, USA — Connie Watkins Bales, Ph.D., R.D.
Birmingham, AL, USA — Julie L. Locher, Ph.D.
Boston, MA, USA — Edward Saltzman, M.D.

Series Editor Page

The great success of the Nutrition and Health Series is the result of the consistent overriding mission of providing health professionals with texts that are essential because each includes: (1) a synthesis of the state of the science, (2) timely, in-depth reviews by the leading researchers and clinicians in their respective fields, (3) extensive, up-to-date fully annotated reference lists, (4) a detailed index, (5) relevant tables and figures, (6) identification of paradigm shifts and the consequences, (7) virtually no overlap of information between chapters, but targeted, interchapter referrals, (8) suggestions of areas for future research, and (9) balanced, data-driven answers to patient as well as health professionals questions which are based upon the totality of evidence rather than the findings of any single study.

The series volumes are not the outcome of a symposium. Rather, each editor has the potential to examine a chosen area with a broad perspective, both in subject matter as well as in the choice of chapter authors. The international perspective, especially with regard to public health initiatives, is emphasized where appropriate. The editors, whose trainings are both research and practice oriented, have the opportunity to develop a primary objective for their book; define the scope and focus; and then invite the leading authorities from around the world to be part of their initiative. The authors are encouraged to provide an overview of the field, discuss their own research, and relate the research findings to potential human health consequences. Because each book is developed de novo, the chapters are coordinated so that the resulting volume imparts greater knowledge than the sum of the information contained in the individual chapters.

Handbook of Clinical Nutrition and Aging, Third Edition, edited by Connie W. Bales Ph.D., RD, Julie L. Locher Ph.D., MSPH and Edward Saltzman, M.D. is a very welcome addition to the Nutrition and Health Series and fully exemplifies the Series' goals. The first volume was published in 2004 and the Second Edition was published in 2009. Both volumes were given excellent evidence-based reviews by health professionals in both the geriatrics and clinical nutrition professional communities. Over the past 5 years, there have been major advances in the treatment of senior individuals, especially those with chronic diseases who require multiple medications, advanced treatments, and/or surgery. Likewise, research on the nutritional requirements of geriatric patients has expanded and reflects the changes in demographics, technical advances, and further emphasis on the interactions among a number of disease states that are at increased risk with aging. This Third Edition is therefore especially timely as almost 10 % of the US adult population is over 65 years of age and the number of seniors around the world is increasing. At the same time, major adverse health risks including obesity and diabetes continue to increase in this already at risk population.

The three editors of this volume, Connie W. Bales, Julie L. Locher, and Edward Saltzman, are internationally recognized leaders in the fields of clinical nutrition and geriatrics research, treatment and management. Each has extensive experience in academic medicine and collectively, they have over 500 peer-reviewed publications and numerous awards for their efforts to improve the care of the

geriatric population. The editors are excellent communicators and they have worked tirelessly to develop a book that is destined to continue as the benchmark in the field of nutrition and aging. Over the past 5 years, the editors have grown in their prominence in their fields and it is of benefit to the reader that these practice and research-oriented editors are committed to providing readers with the most up-to-date objective and balanced reviews as found in the last two excellent editions.

Dr. Connie Bales is a Professor in the Division of Geriatrics in the Department of Medicine and Senior Fellow in the Center for the Study of Aging and Human Development at Duke University Medical Center. She also serves as Associate Director for Education and Evaluation of the Geriatrics Research, Education, and Clinical Center at the Durham VA Medical Center. Dr. Bales received her doctorate in Nutritional Sciences at the University of Tennessee-Knoxville and held an appointment in the Graduate Nutrition Division at the University of Texas-Austin before joining the faculty at Duke. She maintains a clinical research laboratory at Duke's Center for Aging and is a well-recognized expert in the field of nutrition and aging. She has published broadly on such topics as obesity in later life, nutritional frailty, nutritional interventions for chronic diseases in aging, and calorie restriction as a modifier of the aging process. She is the recipient of numerous awards, including the Grace Goldsmith Award and Max K. Horwitt Distinguished Lectureship and has served on numerous grant review panels and editorial boards. She currently serves the American Society for Nutrition as Chair of the Medical Nutrition Council and is a past-president of the American College of Nutrition. Dr. Bales also serves as the Editor of the *Journal of Nutrition in Gerontology and Geriatrics*.

Dr. Julie L. Locher is a medical sociologist and health services researcher. She is Professor of Medicine, Public Health, and Medical Sociology at the University of Alabama at Birmingham (UAB). Her primary area of research focuses on social and environmental factors (including especially the roles of social support and community and healthcare practices and policies) that affect eating behaviors and nutrition-related health outcomes in different populations, especially older adults (particularly those who are frail and those who are transitioning from hospitals to home) and in cancer patients and survivors. She is the recipient of an Academic Career Leadership Award from the National Institute on Aging to build the UAB Program in Translational Nutrition and Aging.

Dr. Edward Saltzman is a physician specializing in clinical nutrition. He currently serves as Chair of the Department of Nutrition Sciences at the Friedman School of Nutrition Science and Policy at Tufts University and is a scientist in the Energy Metabolism Laboratory of the Jean Mayer USDA Human Nutrition Research Center at Tufts University. He also serves as Chief of the Division of Clinical Nutrition at Tufts Medical Center. Dr. Saltzman serves on the editorial board of the *American Journal of Clinical Nutrition* as well as other journals, and is a member of the board of the directors of the American Society for Nutrition.

This updated text, containing 23 chapters that integrate clinical practice and the underlying science, continues to include many unique features, such as highly relevant descriptions of case studies that help to illustrate the complexity of treating the aging patient. The volume is relevant for practicing as well as research-centered healthcare professionals as there are in-depth discussions of the basic assessment tools; demographics of the different diseases and disease conditions that affect the aging population preferentially, such as age-related macular degeneration and alterations in muscle metabolism that are often adversely affected by the aging process. There are also clear, concise recommendations about dietary intakes and use of drugs and supplements across the stages of aging. Thus, this volume provides a broad base of knowledge concerning the changes in anatomy, physiology, and pathology associated with growing older. This volume is appropriate for health professionals, students, and faculty who have an interest in the latest, up-to-date information on the consequences of loss of certain body functions, treatment of infectious, as well as the chronic diseases of aging and disease-related morbidity and mortality.

This volume serves a dual purpose of providing in-depth focus on the nutritional aspects of treating elderly individuals throughout the last 30 or more years of their lifespan who have lost some of their organ/tissue functions, as well as examining the current clinical modalities used in treating a number

of the chronic diseases of aging and the consequences of the treatments on nutritional status. The book is organized as a stand-alone resource text that provides the basics of nutritional assessment of the patient, intervention in healthy elderly and patients, and reflects upon the necessity of medical nutrition support as a keystone for disease management. The volume includes extensive, in-depth chapters covering the most important aspects of the complex interactions between diet, obesity, cardiovascular disease, diabetes, and loss of cognitive functions, development of sarcopenia, as examples, and the impact of loss of certain functions on nutritional status.

Handbook of Clinical Nutrition and Aging, Third Edition is organized into four relevant sections. The three introductory chapters in the first part, entitled "Overarching Issues for Nutritional Well-Being in Later Life" provide readers with the basics so that the more clinically related chapters can be easily understood. The first chapter describes the process of aging as a time in the life cycle where there are progressive physical, cognitive, and psychosocially related functional declines resulting in disproportionately high healthcare utilization especially in the final years of life. The chapter, that includes over 100 references, uses a multilevel approach to describe factors influencing the nutritional status and food intake of older adults, explores major concepts in the planning, implementation, and evaluation of nutrition interventions specific to older adults, provides examples of current and emerging nutrition interventions, and discusses future directions while taking into consideration the heterogeneity and varied needs of aging individuals. The next chapter reviews the importance of using systematic review processes, such as meta-analyses, to better understand the totality of the evidence concerning nutritional issues and the aging population. The basic steps in conducting such reviews are examined. Unique issues specific to nutrition-related topics include baseline exposure, nutrient status, nutrient bioavailability, nutrient bioequivalence, biological stores, multiple biological functions, undefined nature of nutrient intervention, and uncertainties in assessing dose-response relationships are discussed. The third chapter reviews and recommends nutrition assessment tools for screening elderly at risk for undernutrition including the Mini-Nutritional Assessment-Short Form and the Determine Checklist. These tools are recommended for evaluation of patients upon admission to the hospital and long-term care settings, upon first home care visit, enrollment in community-based programs and during annual primary care visits. The chapter describes the assessment exam which is a comprehensive exam focused on assessment of weight changes, body composition status, physical examination, comorbid conditions, functional status, medication history, dietary intake, and psychosocial and economic status. Additionally, adult disease-related malnutrition diagnoses applicable to older adults including starvation, chronic disease-related malnutrition, and acute disease-related malnutrition are described in detail.

The next six chapters (Chaps. 4–9) describe the fundamentals of nutrition with regard to geriatric syndromes. The next chapter, containing over 100 up-to-date references, reviews the major effects of aging on the eye. Both individual essential nutrients and foods containing these nutrients are examined with regard to primary and secondary reduction in risk of cataracts and age-related macular degeneration. Chapter 5 identifies and tabulates the critical requirement of the evaluation of the nutritional status of the geriatric patient who has suffered from adverse changes in the oral cavity. The chapter includes extensive discussions of edentulism, dental caries, periodontitis, oral cancer, and their effects on consumption of certain nutrients and dietary patterns. Chapters 6 and 7 examine the importance of voluntary, skeletal muscle function in the aging population and also the effects of obesity on muscle status. In aging, there may be the loss of muscle mass and/or muscle strength. Sarcopenia refers to the process of age-related skeletal muscle mass loss, and dynapenia refers to the process of age-related muscle strength loss. The chapter reviews the well-designed longitudinal studies that show little or no association between sarcopenia and the risk of impaired physical function, falls, and mortality. Conversely, dynapenia is consistently associated with these outcomes. Either or both of these losses of muscle function can be seen in the obese geriatric patient. Unfortunately, weight loss is associated with both muscle mass and muscle strength loss. The chapter includes a discussion of the benefits of resistance exercise as it is one of the most promising approaches for

preventing and treating both sarcopenia and dynapenia in obese and non-obese older adults. Muscle physiology is further explored in the next chapter, containing over 100 relevant references, that contrasts the effects of different types of exercise on the aging skeletal muscle. The authors conclude that endurance exercise should be recommended for the elderly as this type of exercise increases both mitochondrial and myofibrillar protein synthesis. Chapter 8 examines the potential for certain nutrients and dietary constituents to reduce the risk of cognitive decline and reviews the findings from published survey studies and intervention trials. Substances reviewed include chocolate, omega-3 fatty acids, B vitamins, vitamin D, and the Mediterranean diet. The chapter includes over 180 targeted references. The final chapter in this section, Chap. 9, discusses the consequences of food insecurity for the elderly population. The chapter reviews the public health responses to dealing with food insecurity among older adults in the United States. There is an extensive discussion of the need for a multipronged approach, including continued support for government programs, such as the nutrition services provided for by the Older Americans Act and the Supplemental Nutrition Assistance Program, and private sector programs, such as food banks.

The third section, entitled "Common Clinical Conditions" contains ten practice-oriented chapters covering topics from pressure ulcers to end of life nutritional decisions.

Chapters 10 and 11 review the effects of obesity, diabetes, and the metabolic syndrome and the potential to develop strategies that can improve activities of daily living while reducing the risk of loss of skeletal muscle functions as described in an earlier chapter. We learn that there is an age-related increase in the prevalence of all of the components of the metabolic syndrome. Relative to those who are <35 years of age, the odds of having metabolic syndrome for those who are over 65 years are almost six times greater in men and about five times greater in women. Increased abdominal fat is independently associated with metabolic syndrome in adults aged 70–79 years. The prevalence of type 2 diabetes mellitus is highest in older persons. The age-related increase in visceral fat is associated with the increased prevalence of diabetes mellitus and insulin resistance in the elderly. Chapter 11 emphasizes the consequences of diabetes in the elderly and the potential for beneficial interventions. The aim of diabetes intervention is to prevent or delay the development of long-term complications of high blood glucose and related metabolic abnormalities and improve the quality of life. The chapter includes over 100 references that are reviewed with regard to diabetes-related comorbidities including diabetic retinopathy, cardiovascular disease, peripheral vascular disease, and congestive heart failure that can limit activities of daily living, including transportation, shopping for food, and ability to read food labels and restaurant menus. The next two chapters follow logically and examine the effects of aging on the heart and the potential for preventive cardiology. The authors explain that preventive cardiology focuses on the prevention of future cardiovascular disease by reducing the burden of known cardiovascular risk factors such as hypertension, dyslipidemia, glucose intolerance, and obesity. Special concerns that affect implementation of cardiac prevention strategies in older at-risk adults include complicated comorbidities; functional limitations; alterations in taste, smell, and appetite, difficulties with medication use/effectiveness; and limited financial, social, and/or caregiver resources. Preventive cardiology nutrition recommendations stress increasing the intake of fruits, vegetables, whole grains, and omega-3 and omega-6 fatty acids while substituting non-hydrogenated unsaturated fats for saturated and *trans*-fats and minimizing the intake of beverages and foods with added sugar. The next chapter examines a major consequence of cardiac disease in the elderly and the potential nutritional interventions for secondary prevention of further adverse effects. We learn that heart failure is the leading cause of hospitalization in the elderly. The prognosis for established heart failure in those over age 65 is poor with 5-year survival rates of less than 50 % in both men and women. Unintentional weight loss in heart failure is likely due to both increased energy utilization and decreased availability of fat, protein, and carbohydrates despite normal caloric intake. Recommendations include moderate dietary sodium restriction and supplementation with potassium, calcium, and/or magnesium if adequate amounts cannot be obtained from the diet. The authors, who have reviewed the literature extensively and cite almost 150 references, note that the importance of

most vitamins and other micronutrients in the pathogenesis and treatment of chronic heart failure has not been well characterized.

Chapter 14 examines the relationship between nutritional status and the development and treatment of pressure ulcers that are frequently seen in elderly with limited mobility. There is a consistent epidemiological association between nutritional status and the incidence, progression, and severity of pressure sores. At present, however, there are inconsistent data from intervention trials with macro- and/or micronutrients that may be linked to underlying diseases that result in the synthesis of cachexia-inducing molecules.

Chapter 15 examines the conflicting data concerning the provision of nutrition support defined as the prescription and administration of enteral or parenteral nutrition to patients with incurable cancer at the last stages of their disease. The authors provide a sensitive analysis of this emotional as well as nutritionally related medical dilemma. Chronic kidney disease can be a serious adverse effect of diabetes and/or cardiovascular disease. Chapter 16 reviews the importance of nutritional support for the older patient with this disease that is often further complicated by other disease processes. There are discussions of both the development and progression of chronic kidney disease that is influenced by a number of dietary factors including salt, protein intake, and energy balance. High-protein intakes are detrimental to individuals with mild impairment of renal function. Specific dietary recommendations regarding protein level and intakes of sodium, phosphorus, potassium, and fluids are reviewed in detail. Osteoporosis is another chronic disease of aging that has a critical nutritional component that is reviewed in the next chapter (Chap. 17). The roles of calcium and vitamin D are discussed in detail and recommendations for supplementation levels are included. Bone physiology is stressed within the context of the balance between bone formation and bone loss that continues to favor bone loss throughout most of adult life. Chapter 18 provides practice-based recommendations for the nutrition management of dementia patients in long-term care facilities. The chapter concentrates on one of the major risk factors for experiencing nutritional problems in nursing homes which is cognitive impairment and/or severe dementia. Approximately 65 % of nursing home residents have documented moderate to severe dementia. The chapter provides a framework for reducing the risk of undernutrition due to mealtime difficulties. The final chapter in this section, Chap. 19, is related to the sensitive discussions in Chap. 15 concerning nutritional support in end-stage cancer patients. Chapter 19 examines the role of nutritional support at the end of life. The authors remind us that many of those emotionally attached to the terminal patient consider nutrition and fluid intake as an essential part of life and not a part of medical treatment. However, case law in the United States considers artificial nutrition (both enteral and parenteral) to be medical treatment and thus recognizes a patient's right to refuse artificial nutritional support. The chapter includes a discussion of feeding options as a key component of the overall goals of care for the patient, whether it is for curative treatment, rehabilitative treatment, or comfort-focused treatment.

The last section, that reviews contemporary diet-focused concerns, contains four insightful chapters. There has been a great deal of interest in the potential for calorie restriction to increase the lifespan. Chapter 20 looks at whether there are any antiaging effects of nutritional modification. The chapter reviews the data from earlier studies that examined the biochemical consequences of calorie restriction including reductions in oxidative biomarkers and insulin resistance. The chapter includes a detailed discussion of the ongoing intervention study, CALERIE, which is a randomized controlled trial that is testing the effects of prolonged calorie restriction in humans on biomarkers of aging and the rate of living theory hypothesis. Chapter 21 reviews the high-risk nutrients in the aging population. This comprehensive chapter that includes almost 150 references indicates that seniors have lower energy requirements and higher requirements for some nutrients. Population data indicate inadequate intakes of macronutrients including protein, n-3 fatty acids, and dietary fiber; vitamins B6, B12, D, E, and carotenoids; calcium, magnesium, and potassium. Individual supplements may not be as effective as obtaining the nutrients from whole foods. The exceptions are reviewed and include vitamin D and vitamin B12. Foods that are emphasized include fruit, vegetables, legumes, whole grains, nuts or

seeds, fish, lean meat, poultry, and low-fat fluid dairy products. The final two chapters in this comprehensive volume examine the role of physical activity and dietary supplements. The rationale for including physical activity in the management of age-related chronic diseases is provided in Chap. 22. There are discussions of cardiovascular disease, cancer, osteoporosis, obesity, diabetes, age-related loss of physical function and frailty, as well as the importance of exercise for improving mood and reducing the risk of depression. Public health guidelines for physical activity are reviewed and several are described. Specific programs that include aerobic exercise, resistance training, flexibility and balance exercises for older adults to decrease the risk of falls are reviewed based upon data from evidence-based programs. There is an emphasis on community-based programs that include both physical activity and nutrition programs. The last chapter in the volume provides an encyclopedic examination of the dietary supplements available in the United States and their use in seniors. The chapter, containing almost 250 references, includes detailed discussions of the demographics of supplement use, the regulatory structure, the claims made on supplements, and the evidence of both benefit and risk of using dietary supplements by seniors in the United States.

The above description of the volume's 23 chapters attests to the depth of information provided by the 49 well-recognized and respected chapter authors. Each chapter includes complete definitions of terms with the abbreviations fully defined for the reader and consistent use of terms between chapters. The volume includes over 75 detailed tables and informative figures, an extensive, detailed index, and more than 2,300 up-to-date references that provide the reader with excellent sources of worthwhile information.

In conclusion, *Handbook of Clinical Nutrition and Aging, Third Edition*, edited by Connie W. Bales Ph.D., RD, Julie L. Locher Ph.D., MSPH, and Edward Saltzman, M.D. provides health professionals in many areas of research and practice with the most up-to-date, well-referenced volume on the importance of maintaining the nutritional status of the elderly patient regardless of cause. The volume's chapters carefully document the critical value of medical nutrition evaluation, treatment support, and management for patients with many of the chronic diseases of aging that are extensively reviewed. This volume will serve the reader as the benchmark in this complex area of interrelationships between diet, nutritional, and non-nutritional supplements and the specific products for maintaining the nutritional status of the geriatric patient. Moreover, these physiological and pathological interactions are clearly delineated so that students as well as practitioners can better understand the complexities of these interactions. Unique chapters that examine the effects of the aging process on critical organ systems such as the eye, bone, brain, and heart are included along with resources for enhancing behaviors that can increase patient adherence to nutritional therapies. The editors are applauded for their efforts to develop the most authoritative resource in the field to date and this excellent text is a very welcome addition to the Nutrition and Health Series.

Adrianne Bendich, Ph.D., F.A.C.N., F.A.S.N.
Series Editor

About the Series Editor

Dr. Adrianne Bendich, Ph.D., F.A.S.N., F.A.C.N. has served as the "Nutrition and Health" Series Editor for over 15 years and has provided leadership and guidance to more than 120 volume editors who have developed the 60+ well respected and highly recommended volumes in the Series.

In addition to "*Handbook of Clinical Nutrition and Aging*, *Third Edition*" *edited by Connie W. Bales Ph.D.*, *RD*, *Julie L. Locher Ph.D.*, *MSPH*, *and Edward Saltzman, M.D.* major new editions in 2012–2014 include:

1. *Nutrition and Oral Medicine, Second Edition,* edited by Dr. Riva Touger-Decker, Dr. Connie C. Mobley, and Dr. Joel B. Epstein, 2014
2. *Fructose, High Fructose Corn Syrup, Sucrose and Health*, edited by Dr. James M. Rippe, 2014
3. *Nutrition in Kidney Disease, Second Edition*, edited by Dr. Laura D. Byham-Gray, Dr. Jerrilynn D. Burrowes, and Dr. Glenn M. Chertow, 2014
4. *Handbook of Food Fortification and Health, volume I* edited by Dr. Victor R. Preedy, Dr. Rajaventhan Srirajaskanthan, and Dr. Vinood B. Patel, 2013
5. *Handbook of Food Fortification and Health, volume II* edited by Dr. Victor R. Preedy, Dr. Rajaventhan Srirajaskanthan, and Dr. Vinood B. Patel, 2013
6. *Diet Quality: An Evidence-Based Approach*, *volume I* edited by Dr. Victor R. Preedy, Dr. Lan-Ahn Hunter, and Dr. Vinood B. Patel, 2013
7. *Diet Quality: An Evidence-Based Approach*, *volume II* edited by Dr. Victor R. Preedy, Dr. Lan-Ahn Hunter, and Dr. Vinood B. Patel, 2013

8. *The Handbook of Clinical Nutrition and Stroke*, edited by Mandy L. Corrigan, MPH, RD Arlene A. Escuro, MS, RD, and Donald F. Kirby, MD, FACP, FACN, FACG, 2013
9. *Nutrition in Infancy*, *volume I* edited by Dr. Ronald Ross Watson, Dr. George Grimble, Dr. Victor Preedy, and Dr. Sherma Zibadi, 2013
10. *Nutrition in Infancy*, *volume II* edited by Dr. Ronald Ross Watson, Dr. George Grimble, Dr. Victor Preedy, and Dr. Sherma Zibadi, 2013
11. *Carotenoids and Human Health*, edited by Dr. Sherry A. Tanumihardjo, 2013
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Contents

Part I Overarching Issues for Nutritional Well-Being in Later Life

1 Nutrition Interventions for Aging Populations 3
Jylana L. Sheats, Sandra J. Winter, and Abby C. King

2 Systematic Reviews in the Field of Nutrition 21
Alice H. Lichtenstein

3 Nutrition Assessment 35
Rose Ann DiMaria-Ghalili and Michi Yukawa

Part II Fundamentals of Nutrition and Geriatric Syndromes

4 Nutrition and the Aging Eye 57
Elizabeth J. Johnson

5 Nutrition and Oral Health: A Two-Way Relationship 81
Cristina Palacios and Kaumudi J. Joshipura

6 Loss of Muscle Mass and Muscle Strength in Obese and Nonobese Older Adults 99
Danielle R. Bouchard and Ian Janssen

7 Muscle Metabolism, Nutrition, and Functional Status in Older Adults 113
Douglas Paddon-Jones and Aaron P. Russell

8 Nutrition in the Prevention and Treatment of Cognitive Decline 125
Grace E. Giles, Kristen E. D'Anci, and Robin B. Kanarek

9 Food Insecurity and Hunger Among Older Adults 147
David R. Buys and Julie L. Locher

Part III Common Clinical Conditions

10 Obesity in Older Adults and Strategies for Weight Management 163
Dennis T. Villareal and Krupa Shah

11 Nutrition and Lifestyle Change in Older Adults with Diabetes Mellitus and Metabolic Syndrome 179
Barbara Stetson, Holly M. Knight, and Sri Prakash L. Mokshagundam

12 Preventive Cardiology: Counseling Older At-Risk Adults on Nutrition 203
William E. Kraus and Julie D. Pruitt

13 Chronic Heart Failure 215
Justin M. Vader, Christopher L. Holley, and Michael W. Rich

14 The Relationship of Nutrition and Pressure Ulcers 237
David R. Thomas

15 Nutrition Support in Solid Tumor Cancer Patients 253
Krishna A. Patel and Aminah Jatoi

16 Nutrition and Chronic Kidney Disease 261
Xiaorui Chen and Srinivasan Beddhu

17 Nutritional Concerns in Osteoporosis 273
Bess Dawson-Hughes

18 Dementia-Related Mealtime Difficulties: Assessment and Management in the Long-Term Care Setting 287
Melissa Batchelor-Aselage, Elaine J. Amella, Sarah Broome Rose, and Connie Watkins Bales

19 Nutrition at the End of Life 303
Michi Yukawa and Christine Seel Ritchie

Part IV Contemporary Diet-Focused Concerns

20 Anti-aging Effects of Nutritional Modification: The State of the Science on Calorie Restriction 315
L. Anne Gilmore, Eric Ravussin, and Leanne M. Redman

21 High-Risk Nutrients in the Aging Population 335
Katherine L. Tucker

22 Physical Activity and Exercise: Important Complements to Nutrition in Older Adults 355
Anne O. Brady, Alison Clune Berg, Mary Ann Johnson, and Ellen M. Evans

23 Dietary Supplements in Older Adults 375
Johanna T. Dwyer, Rebecca Costello, Joyce Merkel, and Paul M. Coates

Index 425

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Part I
Overarching Issues for Nutritional Well-Being in Later Life

Chapter 1
Nutrition Interventions for Aging Populations

Jylana L. Sheats, Sandra J. Winter, and Abby C. King

Key Points

- Optimal nutrition is essential for successful and healthy aging, as advancing age increased the risk of chronic disease and other health concerns.
- Aging populations are heterogeneous and require tailored, theory-based interventions to help ensure that their nutritional challenges are appropriately met.
- Recognition of issues specific to the population and using a variety of intervention delivery channels and strategies, will assist in the development of appropriate and clear intervention goals, measures, and outcomes.
- Nutrition-related behaviors are complex; thus, interventions need to be evaluated before, during, and after implementation.
- Special populations such as racial/ethnic minorities, persons with low socio-economic status, those with physical or cognitive impairments or limited access to food stores and food-related services, as well as persons who live in rural communities, may present unique nutrition challenges.
- Technology-based health promotion and intervention strategies may help reduce the burden of nutrition-related disease.

Keywords Older adults • Nutrition • Diet • Intervention • Health promotion • Health behavior change • Theory • Ecological model • Technology

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Introduction

Understanding Global Aging Trends, Successful Aging, and the Role of Nutrition

A major accomplishment of industrialized countries in the twentieth century has been vast improvements in human life expectancy [1]. In the United States it has been projected that the number of older adults, defined as individuals aged 65 years or older [2], will double from the current estimate of 40.2 million to 88.5 million [3]; and by 2030 the population of oldest-old Americans (i.e., aged 85 years or older) could grow to 19 million [3]. The "graying of America" is attributed to people living longer [1], the aging of the "baby boomer" cohort (those born between 1946 and 1964), and immigration [3]. It is also expected that there will be a demographic shift toward a more racially and ethnically diverse population of older Americans, with minorities (i.e., all races and ethnic groups other than non-Hispanic White) becoming the majority by 2042 [3]. As in the United States, it has been predicted that by 2036 the population of older adults in Canada will double [4]. Comparable trends are being experienced by other industrialized parts of the world, such as Europe [5], Australia [6], New Zealand, and Japan [1].

Aging can be characterized as a time in the life cycle where one experiences progressive physical, cognitive, and psychosocially related functional declines resulting in disproportionately high health-care utilization in the final years of life [7]. However, there are older adults who live healthy lives full of vitality [8]. According to the U.S. Administration on Aging [9], 41.6 % of noninstitutionalized older adults perceive their heath as "excellent" or "very good" relative to 64.5 % for individuals aged 18–64 years. Further, many adults aged 85 years or older are able to engage in Independent Activities of Daily Living (IADLs) [10], such as the ability to perform household tasks such as housework and laundry, shopping, preparing food, and handling finances. Positive health behaviors practiced early in life, such as routinely eating a healthful diet, are essential for healthy, successful aging [8]. While definitions vary, essential characteristics of successful aging have included factors such as having high levels of physical and cognitive functioning, the absence of significant chronic disease and disability, and the ability to socially engage with others [11].

The primary goal for the nation's older adults, as documented by Healthy People 2020, is to "improve health, function, and quality of life" [12]. Given the approaching "silver tsunami" [13], optimal nutrition is key and has the ability to improve health outcomes, quality of life, and well-being [14]. Individuals are products of their environment, and the factors that influence food intake, the etiology of health conditions, and the support of positive health behaviors often involve factors beyond the individual, so a holistic multilevel approach is suggested—especially in regard to addressing the nutritional health of older adults [15–17]. Thus, researchers increasingly use ecological models that focus on individual factors, as well as factors within a broader environmental context that may contribute to positive or negative health behavior and/or health outcomes [18]. Ecological perspectives posit that intrapersonal (individual characteristics), interpersonal processes, institutional, community, and public policy have the potential to impact behavior [18]. This chapter will use a multilevel approach to describe factors influencing the nutritional status and food intake of older adults; explore major concepts in the planning, implementation, and evaluation of nutrition interventions specific to older adults; provide examples of current and emerging nutrition interventions; and discuss future directions while taking into consideration their heterogeneity and varied needs.

Nutritional Status of Older Adults

As individuals age, they experience various life transitions and are at increased risk for having health problems [19, 20]. Nutrition status is typically a self-managed condition wherein small self-care and lifestyle improvements can yield significant benefits [14, 21]. Yet, a pilot study conducted by the U.S.

Administration on Aging [22] found that 48 % and 43 % of respondents had moderate or high nutritional risk, respectively. With advancing age individuals may have lower energy intake requirements and require more nutrient-dense foods (i.e., foods that are high in nutrients, but low in calories) [23]. Subsequently, they may have higher requirements for foods and/or supplements rich in antioxidant nutrients, calcium, fiber, folic acid, zinc, and vitamins A, B_{12}, C, D, and E [8, 24] to address age-related issues including, but not limited to, chronic disease, low bone density [8], poor vision [25], and cognitive impairment [26]. Studies have shown that older adults have problems meeting national recommendations for each food group—particularly, the grain group and dairy group, for example [27–30]. Further, of the six most frequently occurring health conditions reported among older adults (i.e., uncontrolled hypertension (34 %), diagnosed arthritis (50 %), all types of heart disease (32 %), any cancer (23 %), diabetes (19 %), and sinusitis (14 %)), four are nutrition-related chronic diseases. This is not surprising given that 80 % of older adults have at least one chronic disease diagnosis [9]; and 50 % have more than two [31]. The importance of a healthy, nutrient-dense diet of appropriate quantity and quality is essential for health maintenance as well as the prevention and delay of chronic disease and disability for all sectors of the population, but particularly for older adults [32].

Factors Influencing Food Intake Among Older Adults

Food intake among older adults can be influenced not only by individual, intrapersonal, and social level factors, but also by the neighborhood environment, healthcare service, and policy context in which they reside.

Interpersonal and Intrapersonal Factors

At an interpersonal, or individual level, food intake and appetite may be influenced by life-long eating behaviors, poor health, disability, and altered sensory functions (e.g., sight, taste, and smell). Among potentially influential factors are taking multiple medications, drug–nutrient interactions and/or side effects, poor oral health and functionality, hormone-related changes related to the control of satiety, difficulty in preparing foods because of arthritic joints, inadequate portion control, lack of information related to individual dietary needs, and having a restrictive diet or complex dietary needs due to current health status or other factors [8, 14, 33]. Other factors to consider are poverty or limited financial resources, transportation issues affecting access to food stores and meal/nutrition programs, and lack of food storage and preparation facilities [34–38]. Intrapersonal factors cited in the literature include self-efficacy, perceived barriers, intentions, and social support [38, 39].

Social Factors

Food intake among older adults is also affected by social factors such as loss of role functions caused by changes in employment status (e.g., retirement), an altered family structure (e.g., "empty nest"), loss of independent living, loneliness and social isolation due to the death or departure of family members and/or friends, caregivers, socio-cultural and religious/spiritual influences [8, 34–36].

Neighborhood Environment, Healthcare Services, and Policy-Related Factors

Older adults may live in neighborhoods where the availability of food stores offering healthy foods is scarce [34]; or where there is limited availability of nutrition support programs and services [40]. Many of the agencies offering nutritional support report being unable to meet increased demand, so prioritizing those most in need of services is required [40]. In addition, healthcare services are increasingly being provided in ambulatory rather than acute care settings. This shift in healthcare service delivery, in combination with early hospital discharge policies, can strain the ability of sick or recovering older adults to obtain and prepare healthy food [40, 41]. Circumstances such as this place older adults at higher nutritional risk and have been associated with an increased prevalence of depression and food-related anxiety [41]. Ensuring that a nutrition component is part of hospital discharge planning may ameliorate this burden. Finally, it has been noted that policies that promote community gardens, locally grown produce, and farmers markets may be useful in improving access to more healthful foods [40].

In summary, an examination of factors influencing the diets of older adults is an area that is complex and not well understood [42]. Regardless of age, improved dietary intake and habits have the ability to improve nutritional status [21]. Yet, diet-related behavior change can be difficult and may take a significant amount of time and effort [21]. In addition to the factors described here, age-related health concerns and changing nutritional requirements present unique challenges for older adults and require the development of tailored nutrition interventions [43].

Helping Older Adults Meet Nutritional Challenges Through Intervention

Nutrition Intervention Planning and Design

Nutrition interventions are typically designed to improve and where appropriate increase intake and variety of foods and/or nutrients (including oral supplementation), provide nutrition education or counseling, and/or increase access and availability of healthful foods for individuals and/or communities. Successful nutrition interventions have the potential to reduce the burden of disease and improve quality of life and well-being [42]. Addressing nutrition challenges experienced by older adults through the development and implementation of effective nutrition interventions is thus important. For older adults, however, staying current with changes taking place in the field of nutrition promotion and recommendations can be confusing. Therefore, identifying and implementing evidence-based best practices specifically targeted and developed for this population are essential [40, 37, 44]. Recognition of issues specific to the target population will assist in the development of appropriate and clear intervention goals, measures, and outcomes.

Frameworks to Guide the Development and Implementation of Nutrition Interventions

In an effort to assist interventionists, Bartholomew and colleagues [45] identified a framework for mapping interventions, proposing six fundamental steps:

1. Conducting a needs assessment.
2. Creating change objectives based on behavioral determinants and environmental factors.
3. Selecting theory-based intervention methods and practical strategies.
4. Translating methods and theories into an organized program.
5. Planning for adoption, implementation, and sustainability of the program.
6. Creating an evaluation plan.

In utilizing this approach, a thorough review of the literature and formative research with the target population should be conducted. For older adults (i.e., community-dwelling, homebound, institutionalized), interventionists should consider the heterogeneity of the population and factors influencing food choice/selection and intake and preparation, as well as perceived motivators and barriers, nutrition risks, needs, preferences, and contextual factors [46]. An evaluation of these factors for both the older adult and their caregivers (who may also be aged) is essential for successful interventions [47, 48]. Assessment methods may include dietary recalls and other nutrition assessment and screening tools such as interviews, surveys, and structured group discussions/focus groups and home visits [41, 47]. Other effective intervention design principles have been identified by Freudenberg and colleagues [49], who suggest that successful interventions: be tailored to the target audience and setting; involve participants in planning, implementation, and evaluation; link participant health concerns to broader life concerns and society as whole; use existing environmental resources; build on the strengths of participants and their communities; advocate for policy changes to support the achievement of health objectives; prepare and empower participants; support diffusion of innovation; and institutionalize and replicate effective intervention components. These principles cut across different populations, settings, and strategies [49].

The use of health behavior change theory to inform and guide interventions has numerous benefits and is recommended [50]. Such benefits include obtaining a better understanding of possible determinants of both risks and helpful strategies, and identifying methods to help promote changes in the determinants, behavior, and environmental conditions surrounding the dietary areas being targeted [45]. Several health behavior change theories and models have been used, or are recommended to guide nutrition interventions for older adults, such as the Health Belief Model [51], Trans-Theoretical Model [52], Social Cognitive Theory [48], Theory of Planned Behavior [53], social support models [54], and ecological models [48, 54]. These theories contain constructs deemed highly applicable to aging populations. For example, social ecological models are particularly useful for nutrition interventions in that eating is often influenced by micro and macro-level factors [48]. The effectiveness of behavior change theory depends on its application as part of an intervention [55, 56]. Thus, there has been an expressed need for more guidance in the application of theory in practice [45].

Delivery Channels and Intervention Components

The type of nutrition intervention delivery channels used and the specific components introduced into a population can vary. It is critical, however, that the intervention mechanisms are preferred by the intended audience [45, 47]. Examples of preferred nutrition delivery channels for older adult populations include engaging videos, carefully designed PowerPoint presentations (e.g., with large, simple text, bright colors, use of images with elderly individuals, and generational music) and the provision of supplemental handouts, and newsletters or pamphlets designed to complement the education components of an intervention [57].

Nutrition intervention components designed for older adults that have resulted in positive health outcomes have included theory-based behavior modification practices; older adults' active involvement in determining intervention goals and having targeted, clear, simple, yet impactful and

hard-to-ignore, practical and reinforced messages that are limited in number [15, 55]. Other effective means for promoting positive changes among older adults include integrating real-life scenarios into intervention content and processes; allowing for hands on, interactive learning to complement and promote an understanding of messages; fostering social support; providing access to relevant health-care professionals and resources; utilizing "geragogical" learning (i.e., guiding the learning of older adults in a way that is tailored to any special needs; for example, instructor-directed learning, supervised decision-making, person-centered activities); and applying relevant education and health behavior change theories [47, 55, 58–60]. Learning styles, abilities, and needs of older adults are often more varied compared to younger adults. To address this issue, the integration of multiple strategies can be used to enhance the quality and reach of nutrition interventions for older adults [21, 56, 57].

It is also important to focus on the robustness of intervention components to elicit behavior change and prevent Type II error (i.e., failing to find intervention effectiveness because the program is poorly designed or implemented) [45, 61]. Nutrition intervention design characteristics that increase the robustness of an intervention design highlighted by Kristal and Ollberding [62] include having a representative sample of potential participants; one or more measures of the evaluation outcome at the pre-intervention time point; one or more comparison groups (i.e., control group not receiving the intervention); randomized assignment to treatment (i.e. intervention group receiving the intervention); and one or more measures of the evaluation outcome at the post-intervention time point. While each component is important, all do not have to be present within an intervention, with the exception of the comparison group and post-intervention outcome measures [62].

Nutrition Interventions from an Ecological Perspective

In an assessment of behavioral health interventions Cutler [15] posits that individual behavior change cannot occur without environmental change (e.g., institutional, organizational, policy-focused interventions). Supporting this argument, Sahyoun and colleagues [55] advocate for the need to explore individual and environmental factors that can potentially impact older adults' nutritional health by utilizing ecological approaches. Here we provide examples of interpersonal, intrapersonal, institutional, community, policy, and multilevel nutrition interventions as well as insights.

Interpersonal and Intrapersonal Nutrition Interventions

Person-centered interventions (interpersonal, intrapersonal) require individuals to proactively make lifestyle changes. To address the needs of older adults requiring nutrient dense meals, a number of interventions have been successful using individual-level methods, such as conducting a series of personalized nutrition sessions by a trained food and nutrition practitioner [63]; the use of theory-based behavior change education materials in the form of manuals and newsletters, expert system assessment reports to personalize feedback, and telephone coaching [52, 56, 64]; and home visits, bi-weekly telephone contacts, and monthly newsletters that incorporate behavioral modification techniques; goal-setting [53]; and tailoring recommendations to participants' dietary patterns and lifestyle [65]. The usefulness of methods mentioned above in the design of nutrition interventions for older adults, such as tailoring to the individual learning needs of participants, having multiple in-person or phone-based contacts, and being theory-based, have been documented throughout the literature [38, 50, 65, 66]. Bernstein and colleagues [65] further note that in such interventions, compliance with protocols can be encouraged through participants' record keeping as well as continual monitoring and positive reinforcement from the research team. Future interventions should aim to increase the

dose of the treatment (i.e., intervention). Although longer-term interventions can be costly, it has been found that longitudinal health promotion activities can lengthen an older adults' number of healthy years [67]. In addition, investigations of older adults' perceived motivations and barriers to the use of programs and services should be examined, especially in view of the global economic downturn and the emergence of the "new poor" who may not be used to accessing nutrition support programs and services. To date, few randomized controlled intervention trials have included theoretically based behaviorally focused nutrition interventions targeted specifically at older adults. Randomized controlled trials with suitably representative sample populations and appropriate sample sizes are preferable to observational, cross-sectional, or quasi-experimental design because the randomization process reduces confounding from known or unknown factors; and allows researchers to posit causal associations. A major drawback of the sole use of a person-centered perspective is that the achievement of behavioral targets is ultimately controlled by the individual without recognition of external factors; changes in behavior are often short-term and not sustainable over time; and there are limited public health implications for larger segments of the population [53, 55]—further highlighting the need for an approach at multiple levels of influence.

Institutional and Community-Based Nutrition Interventions

Older adults transitioning from hospital to home have been found to lack in their consumption of fresh fruits, vegetables, and meat; and experience difficulty shopping for and preparing food [41]. Therefore, ensuring that a nutrition component is part of discharge planning is recommended. DiMaria-Ghalili and Amella [68] suggest that an assessment of the location in which meals are served is a key component to implementing environmental change. For example, the creation of a "home-like," environment as opposed to a traditional institution-like environment in long-term care hospital units has been found to optimize energy intake by older adults with cognitive impairments [69]. Other examples of changes that can take place in the food-service environments of institutionalized older adults are improved-lighting; the observation of rituals and practices prior to institutionalization (e.g., blessing food, washing hands before a meal); and the stimulation of senses via preparation of food in close proximity to the dining area [69]. In terms of a geographic, or locally-based community, Abusabha et al. [70] implemented an innovative, community-based study to increase access and the availability of produce. Their project was unique in that a *Veggie Mobile* (i.e., van) traveled to low-income senior housing sites to sell affordable fruits and vegetables.

Utilization of public health, or population-based, approaches to behavior change through the provision of information and environmental change (e.g., policy and use of media/mass communication) have proven successful [15, 56]. Further, collaborations with multidisciplinary institutional and organizational networks may help eliminate or reduce gaps in service, enhance the types of services available, reach more people, and increase awareness and the use of available community resources by older adults, their families, and caregivers [8].

Multilevel and Policy Nutrition Interventions

Person-centered interventions are more frequently conducted and assessed than environmental or policy interventions. In a review of health promotion interventions, Golden [71] found that of 62 nutrition interventions, 95 % focused on individual activities, 71 % on interpersonal activities, and only 3 % focused on the policy environment [71]. This review also showed that, compared to other health behavior change interventions, such as the promotion of physical activity and reductions in

smoking, nutrition interventions were significantly more likely to target three or more levels of intervention [71]. Cross-sectional studies have shown that, nutrition-related knowledge [72], self-efficacy, family support [73], and environmental factors are all associated with the eating behaviors of mid-life to older adults [74]. Therefore a variety of strategies implemented across multiple settings may be most promising to ensure successful nutrition interventions [55]. An example of multilevel intervention strategies successfully used by Johnson [75] to increase consumption of fruits and vegetables in an older adult population included: using serving size guides (individual level) and community volunteers (Meals-on-Wheels drivers) (interpersonal level); creating partnerships with community organizations and universities (community level); using existing infrastructures with similar missions (organizational level) as well as existing federal programs available throughout the United States (institutional level) [75]. Multilevel approaches such as this could potentially extend the reach of interventions into the population; set the stage for enhanced acceptance and diffusion of innovation by the target population and decision-makers alike; and have implications for policy [75]. To further increase the chance of success, a thorough understanding of older adults' social support systems and networks, or lack thereof, is essential in the development and implementation of multilevel nutrition interventions [55]. Within the policy realm, and relevant to both farmer's markets and the sale of reduced priced produce, a recent review of food subsidization programs in seven countries, including the United States, found that the subsidization of healthy foods (e.g., through supermarkets, restaurants, and farmers markets) can be effective in changing dietary behaviors [76]. The federal Senior Farmer's Market Nutrition Program (SFMNP) is an example of such a program. The SFMNP utilizes a coupon distribution system so that older adults can purchase locally grown, fresh fruits and vegetables [75], has the potential to help reduce food insecurity. Similar to person-centered interventions, robust assessments and evaluation methods beyond for example, cross-sectional and quasi-experimental designs, should be considered.

As a means to advance the science of multilevel intervention design, interventionists and nutrition practitioners may find it beneficial to consult with research scientists to assess proposed intervention methods. While consultation services may exceed the budgets of nonprofit and government programs, such efforts will help assess the efficacy, effectiveness, and validity of intervention findings [62]. Partnering with academic institutions and/or other organizations may help alleviate the burden of associated costs. To better inform policy, research studies should aim to identify predictive factors and interventions that can reduce food insecurity among older populations. Researchers should be encouraged to ensure that research budgets include appropriations to fund the translation and dissemination of research findings to the targeted populations. An increased effort to monitor and evaluate the impact and efficacy of food assistance programs is critical for the development of policy. Increased advocacy that involves multilevel collaborations focusing on reducing food insecurity, removing barriers to healthy eating, and improving the quality of older adults' diets will also inform program and service design as well as future nutrition policies.

Nutrition Intervention Evaluation and Assessment

There has been a call for the evaluation of well-designed intervention studies and methods to determine their effectiveness on nutrition outcomes [77]. Evaluating a wide range of nutrition intervention outcomes is particularly important because nutrition behavior is complex, individuals' self-report data are not always reliable, improving nutrition knowledge does not always lead to changes in behavior, and short-term programs do not necessarily result in long-term changes [78]. Thus, it is imperative that evaluations are conducted before, during, and after the implementation of interventions [45]. There are three types of evaluations: (1) formative evaluations, (2) process evaluations, and (3) outcome evaluations. Formative evaluation helps to ensure that the intervention is appropriate for both

the target audience and setting. Process evaluation helps to ensure that the intervention will be implemented as planned. Outcome evaluation helps to ensure that the desired objectives of the intervention have been met [62]. Formative evaluation methods used in nutrition interventions include interviews, focus groups, pilot testing, and, in some cases, participant-completed surveys [79, 80]. Process evaluation methods include post-intervention participant satisfaction questionnaires, evaluation of intervention fidelity (i.e., how well intervention personnel have followed intervention procedures and protocols), participation metrics (e.g., participant involvement in intervention activities and adherence to intervention components), and interviews of both participants and intervention personnel relating to intervention delivery and uptake [50]. Staff- and participant-maintained program activity notes, resource allocation documents, and video or audio recordings of the intervention processes can be reviewed to ensure the fidelity of interventions to protocols [81]. Outcome evaluations—the most frequently conducted type of intervention evaluation, can include a variety of outcomes, for example:

- Physiologic measures such as weight, waist circumference, body mass index, blood pressure, and serum cholesterol and glucose levels [82].
- Knowledge outcomes, including declarative knowledge (knowledge about facts and events) and procedural knowledge (knowing how to apply declarative knowledge) [83] for example, knowing that an adequate dietary intake of protein is important for older adults [84], and how to incorporate an adequate amount of protein into the diet.
- Psychological outcomes such as movement through motivational stages of behavior change, and changes in behavior-specific outcome expectations and self-efficacy [83].
- Behavior change outcomes such as reduction in daily percent energy consumption from fat, or increase in daily consumption of fruits and vegetables [55].

Interventions for all populations, including aging populations, must be carefully designed. Evidence- and theory-based strategies should be used in the planning, implementation, and evaluation phases of tailored nutrition interventions. Formative, process, and outcome evaluations should be conducted to tailor interventions and assess their quality of delivery and effectiveness. It has been suggested that complex interventions having multiple components consider utilizing a phased approach to intervention delivery as well as both quantitative and qualitative evaluation methods [85]. Further, if an ecological intervention approach is used that targets not only individual level characteristics but also social, environmental, and policy determinants, then an evaluation should be conducted for each level of intervention.

In summary, there is currently a need for more comprehensive evaluations of nutrition interventions that include: (1) formative, process, and outcome assessments, (2) a program or behavioral maintenance component to help individuals and communities sustain nutritional gains over the longer-term, and (3) a multilevel perspective to accommodate a social-ecological perspective.

Tailoring Interventions for Special Populations

As Americans increase in age, number, and diversity, nutritional interventions tailored to meet the needs of special populations will increasingly be required. Racial and ethnic minorities—the fastest growing population group in the nation—often have unique dietary patterns and differential disease risk profiles which require culturally tailored nutritional programs and policies [86, 87]. Nutrition screening and assessment tools, educational material, and interventions should be designed and validated for ethnic-specific diets [36], and interventions should be available in multiple languages and literacy levels [40].

Living in rural areas has been associated with higher rates of chronic disease, obesity, and poorer health [88]. A greater number of older adults live in rural areas than urban areas [89]. Social isolation, lower incomes, lack of transportation, increased distances to purchase food or utilize nutrition programs, low quality diets types of "country cooking" eating patterns that emphasize higher fat and sodium-based methods of food preparation; reduced availability of healthy foods and higher rates of physical inactivity may all be contributing factors to consider when tailoring interventions for this population [37, 88, 89]. Policies that support the operation of rural food stores and improvements in rural transportation networks are needed to address some of these issues [90].

Older adults with physical impairments, as well as those with difficulties traveling, have been shown to have reduced access to food sources and nutrition support programs, which increases risk of poor nutrition and health outcomes [91]. Older adults at risk for, or suffering from, chronic or degenerative conditions have also been shown to be at increased risk of poor nutrition [34, 35] and to benefit from tailored medical nutrition therapy (MNT) services [34, 92, 93] MNT is provided by a registered dietitian, focuses on disease management, and involves detailed and individualized nutrition diagnostic, therapeutic, and counseling services [94].

Individuals with fewer financial resources have been shown to be more likely to choose foods that are highly processed with increased calories and sugar content. These foods are generally less expensive [40]. Alarmingly, food insecurity issues have increased among older adults in the United States since 2007 [95]. Older adults are at higher risk for negative physical and mental health outcomes. In 2009, 15.6 million adults aged 50 years or older faced the threat of hunger (i.e., were marginally food insecure), 8.8 million faced the risk of hunger (i.e., were food insecure), and 3.5 million experienced hunger (i.e., were very low food secure) [95]. There are various government (e.g., Older American's Act Elderly Nutrition Program, Nutrition Services Incentive Program, Supplemental Nutrition Assistance Program, Senior Farmers' Market Program, and Child and Adult Care Food Program) and nongovernmental food assistance programs either targeted specifically to community-dwelling older adults or that allow their participation [32]. Unfortunately, a lack of awareness of these resources may result in less than optimal participation rates [40]. Efforts should be made to ensure that older adults and their caregivers are aware of such programs.

Implementing flexible programs can help broaden their reach to better accommodate subgroups within the older adult population. For example, it has been suggested that the traditional model of home-delivery programs be reevaluated. There is a need to target specific subgroups of recipients who may have differing nutrition needs, as, for example, food insufficient individuals who need more nutrient dense meals [96, 97]. Other examples include providing programs at various sites—including private households and institutional settings such as senior housing sites, assisted living and extended care facilities, and nursing homes [34], and using voucher programs that enable participants to obtain food from restaurants, grocery stores, homeless shelters, and hospital cafeterias [40].

In summary, while they are diverse in their purpose and strategies, nutrition interventions may be a potentially useful gateway through which special populations of older adults can have improved health and access to other needed social and health programs and services [34, 36].

Health-Promoting Information Technology: Emerging Interventions

Older adults have a range of barriers that may prohibit participation in community health promotion programs (e.g., poor health, physical mobility, transportation difficulties, and social factors) [98]. The development and design of technology-based health promotion has been described as a promising intervention strategy [99] and may be a viable option for meeting the demands of aging populations [100–105]. Older adults are increasingly using digital communication technology for a range of purposes. A recent nationwide survey conducted by the Pew Research Center's Internet and American

Life Project reports that 53 % of U.S. adults aged 65 years or older use the Internet or e-mail, 69 % have a mobile phone, and 33 % use social networking sites [106]. The use of technology-based health promotion using computers (traditional, touchscreen, kiosk), electronic-tablets, smartphones, Personal Digital Assistants (PDAs), and automated telephone systems provide opportunities to implement individually tailored, real time, convenient, cost-effective, and widely distributed evidence and theoretically based interventions. Nutritional interventions using PDAs [100, 107] the Internet [108, 109], and telephones [110] have been tested in older adult populations and have been successfully used to monitor changes in health, promote and support positive health behavior change, and provide personal feedback [111, 112]. Given that technology-based interventions do not require face-to-face interaction, interventionists may be able to reach more individuals compared to traditional intervention and health promotion strategies. Increasingly, innovative applications have been used to encourage health behavior change and adherence (e.g., for diet, physical activity, medication) though smartphones and wearable technologies, some of which utilize point-of-decision prompts [113, 114]. These innovative approaches warrant additional systematic evaluation to determine the effectiveness of such approaches [99, 115]. This is especially important for interventions designed for older adult populations [99, 116]. In designing electronic technologies for use by older adults, special considerations should be made to account for the sensory, motor skills, computer literacy, and cognitive abilities of older adults, for example, by creating simple user interfaces with large clear typefaces and easy navigation elements [117–119].

In summary, studies have been conducted to assess the use of technology-based and/or web-based interventions among older adults [99], but more research needs to be conducted to determine their efficacy, especially in view of the increasing use of the Internet and information technology by older populations.

Conclusion and Recommendations

With the global increase in persons aged 65 years or older, the translation and application of nutrition research findings into tailored interventions that are evidence-based and have a broad reach is of utmost importance to promote successful aging. Improvement in health outcomes will most often be experienced following improvements in diet and related behaviors, particularly after such behavior changes have been sustained for long periods of time [50]. The heterogeneity of older adult populations and the varied influential factors on diet and related behaviors may impact the length of time in which objective and subjective changes in health and well-being are observed. Over 20 years ago, researchers identified three categories of older adults based on their health status. Aging categories created by Rowe and Kahn [120] were “Successful Agers” (i.e., absence of chronic disease, minimal age-related physiological changes) and “Usual Agers” (i.e., the presence of chronic age-related medical conditions and disability), with “High-Risk Agers” (experiencing the heaviest burden of chronic disease and ability) subsequently described by Harris and Feldman [121]. Conceptualizing older adults in this way may help interventionists, and food, nutrition, and/or healthcare practitioners prioritize and tailor nutrition interventions accordingly. Other areas of prioritization and focus for future work should include:

- Meeting the needs of special populations such as the older-old (i.e., aged >75 years) [27], racial/ethnic minorities, people living in rural areas, and those experiencing economic hardships.
- Creating programs and services that address the needs of older adults along the continuum of weight status, i.e., those who are underweight and those who are obese or overweight.
- Explicitly targeting both nutritional and physical activity behaviors together in developing programs for aging adults, in light of the physiological and behavioral synergies accompanying the optimization of both of these key health behaviors [113].

- Creating urban and rural environments that support healthy behaviors through infrastructures that facilitate access to healthful food and physical activity opportunities;
- Promoting collaborative community partnerships (e.g., food banks, nonprofits, and faith-based institutions) specifically targeted toward older adults (with a dual advantage of meeting both nutritional and social engagement needs).
- Developing and using communication and technology-based interventions specifically targeted to the needs and preferences of older adults to promote positive health behaviors among older populations in an effort to reduce the burden of disease and help decrease the digital divide.

The increasing prevalence of obesity on a global scale, including among aging populations [122], emphasizes the need for evidence and theory-based nutrition interventions that adopt a life-course perspective—and take into account the social and environmental contexts in which people live. Such approaches have the potential to improve the health status and quality of life of many individuals in a cost-effective, yet efficient, manner. While much work remains to be done in this area, focusing scientific as well as public health energy and resources on the types of areas described above may yield important insights that can advance the field. Given current population trends in the aging field, the United States and other nations have much to gain from such investments, which can help older adults reach their full potential as individuals and as citizens, maximizing the potential of an aging population through shaping an active and vital old age [123].

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Chapter 2
Systematic Reviews in the Field of Nutrition

Alice H. Lichtenstein

Key Points

- Systematic reviews are valuable tools for staying abreast of evolving nutrition and aging-related topics, formulating dietary guidelines, establishing nutrient reference intakes, formulating clinical practice guidance, evaluating health claims, and setting research agendas.
- Basic steps of conducting a systematic review include identifying a review team, developing an analytic framework, formulating key questions, selecting inclusion/exclusion criteria, identifying search terms, searching the literature, selecting publications for inclusion, extracting and summarizing data, rating the methodological quality of the included studies, and if adequate data is available, conducting a meta-analysis.
- Unique issues specific to nutrition-related topics include baseline exposure, nutrient status, nutrient bioavailability, nutrient bioequivalence, biological stores, multiple biological functions, undefined nature of nutrient intervention, and uncertainties in assessing dose–response relationships
- Conclusions of systematic reviews or meta-analysis are helpful tools that can contribute to decisions but do not in themselves establish guidelines or research agendas.

Keywords Nutrition • Diet • Systematic review • Key questions • Analytic framework • Evidence tables • Meta-analysis • Bioavailability • Bioequivalence • Dietary supplements • Older adults

The amount of scientific literature published each year increases exponentially. Very few individuals have the time to keep abreast of the latest findings, and even fewer have the time to integrate the latest findings into prior work. For topics unaligned with one's primary area of expertise or research focus the task can become insurmountable. Under these circumstances, review articles can serve an important function.

There are two general types of reviews; narrative and systematic. Both summarize the literature on a specific topic. For the most part, narrative reviews do not use a consistent methodological approach to accomplish this task. Unclear are the criteria used to include or exclude studies, making it difficult to determine whether the review is a comprehensive and unbiased evaluation of the literature.

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A systematic review specifies inclusion/exclusion criteria and follows a relatively standard format designed to provide an impartial and complete assessment of all the literature available on the topic. This chapter will focus on the latter type, systematic review, and the unique considerations that should be addressed when performing a review of nutrition-related topics.

Background

Systematic review methodology was first developed in the field of medicine as an approach to formulate clinical practice guidelines [1–3]. The approach has been used to not only establish guidelines [4, 5] but also set research agendas [6] and formulate scientific consensus statements [7, 8]. More recently systematic review methodology has been applied to the field of nutrition [9–11]. In addition to helping professionals stay abreast of evolving topics, the reviews also serve as the basis for formulating dietary guidelines [12], establishing nutrient reference intakes [13], formulating clinical practice guidance [14], evaluating health claims [15], and setting research agendas [16].

Steps to Conducting Systematic Reviews

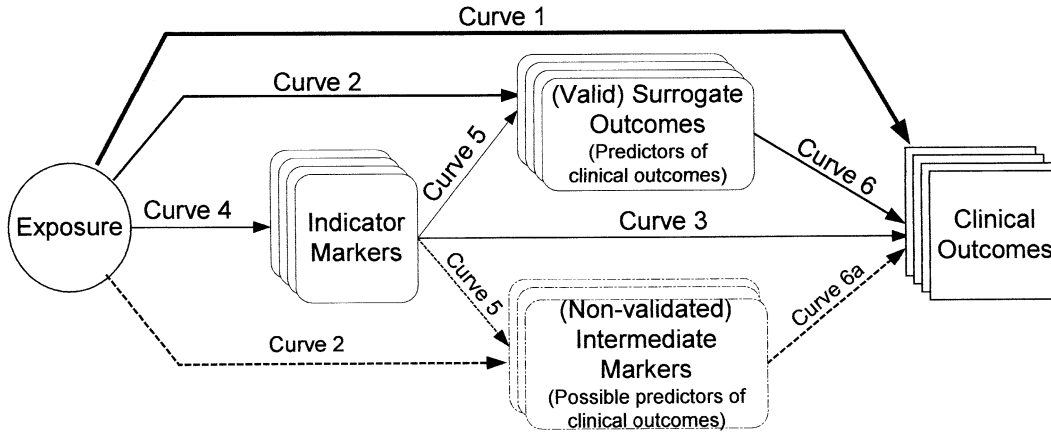
There are basic components that are integral to the systematic review process [17–19]. Critical is the ability to identify and synthesize all the available data in an unbiased manner to answer prespecified questions. A key component of conducting a systematic review is to thoroughly document all aspects of the process. This latter point is important not only to ensure validity and reproducibility but to also facilitate cost-effective periodic updates as new data emerge. Cochrane Collaboration [20] and the Agency for Healthcare Research and Quality [21] are two organizations that have developed guidelines for conducting systematic reviews.

Review Team

Prior to commencing work on a systematic review, it is important to identify the individuals who will be working on the project and their roles. The size of the team will depend on expertise of those involved, the range, number, and detailed nature of research questions to be addressed, and the scope of available literature. In addition to those individuals who will be responsible for conducting the actual systematic review, there may be others involved. These individuals are domain experts, commonly referred to as a technical expert panel. Particularly in the field of nutrition, it is important to include domain experts who represent multiple disciplines. Domain experts provide guidance in terms of refining the research questions and identifying search terms. They typically are not involved in the actual review process so as to ensure independence of those conducting the systematic review and to avoid potential bias or the appearance of bias according to prior publications or public statements. Once the systematic review is completed it is not uncommon for the technical expert panel to serve as reviewers.

Analytic Framework

An analytic framework provides a graphic representation of the organizational structure of a systematic review and includes the basic elements of the review: exposure(s), indicator marker(s), surrogate outcome(s), and clinical outcome(s) of interest. A generic analytic framework is depicted in Fig. 2.1 [11].



Curve 1. Association of exposure with clinical outcomes of interest
Curve 2. Association of exposure with surrogate outcomes or intermediate markers (with good or possible evidence for linkage with clinical outcomes)
Curve 3. Association of indicator markers to clinical outcomes
Curve 4. Association between exposure and indicator markers
Curve 5. Association of indicator markers to surrogate outcomes or intermediate markers (with good or possible evidence for linkage with clinical outcomes)
Curve 6. Association between surrogate outcomes and clinical outcomes ("good" evidence for linkage)
6a. Association between intermediate markers and clinical outcomes (uncertain linkage)

Fig. 2.1 Generic analytic framework of dietary reference intakes [22]. Reprinted with permission of the Agency for Healthcare Research and Quality from M. Chung, et al. Vitamin D and Calcium: A Systematic Review of Health Outcomes, p. 23

In general, solid lines indicate established paths between exposure, and indicator markers, surrogate markers, or clinical outcomes. The dashed lines indicate possible or yet to be validated relationships. Some component of each research question should be included in the analytical framework. The complexity of the analytic framework depends on the breadth of the topic and the number of questions to be addressed. For example, Fig. 2.2 depicts an analytical framework developed to address five key questions involving two nutrients, vitamin D and calcium [22]. This analytic framework was developed jointly by the methodologists and domain experts, prior to starting the systemic literature review.

Research (Key) Questions

The initial research questions, henceforth referred to as key questions, are drafted by either the sponsor or researchers. These questions are carefully reviewed, and frequently modified, by the research team to improve clarity or increase specificity. For example, a single question may be divided into multiple questions, each defined by specific criteria. The essential components of each key question are summarized by the acronym PICO. PICO is an abbreviation for population/patient (P), intervention/independent variable (I), comparator (C), and outcome (O). In some cases, PICO-D is used, with the D representing study design. Key questions must be carefully formulated to match the intent of the systemic review because they will define the literature search terms, inclusion criteria, and exclusion criteria. Prior to finalizing the key questions it is helpful to evaluate the available resources for the project and potential extent of the literature (horizon scan). This information may lead to a reassessment of the project scope and/or modifications in the PICO criteria.

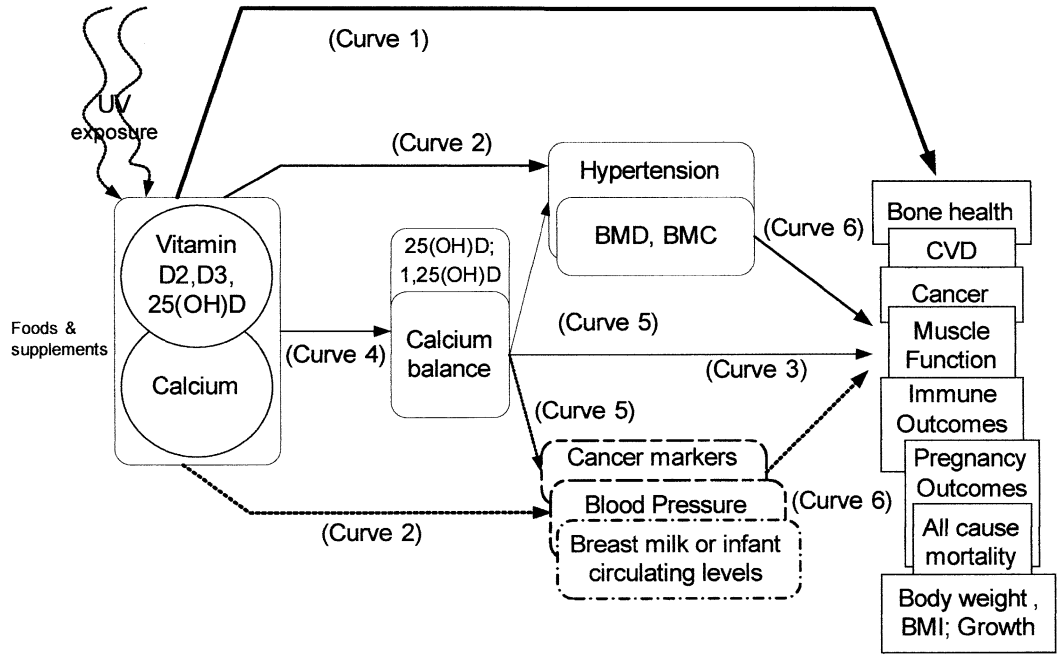


Fig. 2.2 Analytic framework for vitamin D and/or calcium estimated average requirement [22]. Reprinted with permission of the Agency for Healthcare Research and Quality from M. Chung, et al. Vitamin D and Calcium: A Systematic Review of Health Outcomes, p. 23

Inclusion/Exclusion Criteria

After the key questions are finalized, the next step in the systematic review process is to define the inclusion/exclusion criteria. These decisions should be made on the basis of the PICO components. The population will be defined by specific characteristics, e.g., age range, sex, health status. The intervention will be defined by the specific dietary component(s) (in the case of nutrition-related systematic reviews), dose, chemical form, and duration of intervention. For example, if the area of interest is omega-3 fatty acids, the intervention could be all omega-3 fatty acids, alpha-linolenic acid, eicosapentaenoic acid or docosahexaenoic acid, fish oil or fish, or some combination thereof. The dose could have minimum and maximum daily limits and the duration could be limited in terms of minimum/maximum length of time. To carry the omega-3 fatty acids example forward, the comparator(s) could be a placebo, such as another vegetable oil or, if the intervention is fish, an alternate food that has an equivalent amount of protein. The outcomes could be broad, e.g., all-cause mortality; narrow, e.g., coronary heart disease and stroke; or limited to indicator biomarkers, e.g., plasma triglyceride or C-reactive protein concentrations. For some topics if the analytical methodologies for the indicator biomarker have changed over time or the number of publications that appear to address the key questions is large, a cut-off publication date can be used as an inclusion criterion.

Search Terms

Search terms are identified on the basis of the key question components. Both the methodologists and domain experts should participate in identifying the search terms to ensure they are comprehensive enough to adequately capture all the available literature and specific enough to minimize identifying extraneous literature that does not address the key questions. Filtering out extraneous literature can be a time-consuming burden.

Literature Search

At this point the domain experts step back from the systematic review process and the remaining members of the research team should conduct the literature search. This division of labor is necessary to avoid potential bias or the appearance of bias during the review process. To ensure that all literature meeting the inclusion criteria is identified, multiple databases should be searched (e.g., Medline, CAB Abstracts, and Cochrane Library Central) and citations of recent publications should be reviewed to ensure the most relevant literature was identified by the search strategy. If more than a few relevant articles are identified using the latter approach the search terms should be reassessed by the research team. At all stages of the literature search it is critical to meticulously document the methodology.

Literature Selection

As a general rule, the majority of publications identified during the literature search will not meet the inclusion criteria. Screening is initially done on the basis of abstracts. Reasons for excluding publications are dictated by the inclusion/exclusion criteria. Typical reasons for exclusion include the type of article (e.g., editorials, reviews, case studies), study design (e.g., inadequate statistical analysis, lack of control group), and not meeting the inclusion criteria (relevant exposure or outcome measures, inadequate intervention period, study subject characteristics out of range). During the screening process it is important to generate a flow diagram that documents information for the total number of publications identified, and the number remaining during the preliminary screening process, with particular attention to documenting publications filtered out. The next step is to retrieve full texts of the remaining publications. As for the prior screening step, the reasons for screening out studies should be fully documented. One example of a flow diagram is shown in Fig. 2.3 [23].

Extract and Summarize Data

A system must be developed to accurately and comprehensively extract data from the included publications. This is assisted by the development of an evidence table template. The format can be unique to each systematic review. Critical components may include participant characteristics, study design, intervention, methods used to measure compliance, results, statistical significance, and outcomes. It is important to include all the information necessary to answer the key questions in a format that will facilitate comparisons among studies. Data extraction is time consuming and every effort should be made to avoid having to re-extract data due to an omission. Some systematic reviews include publications of studies with very different designs, such as clinical interventions and observation cohorts. In

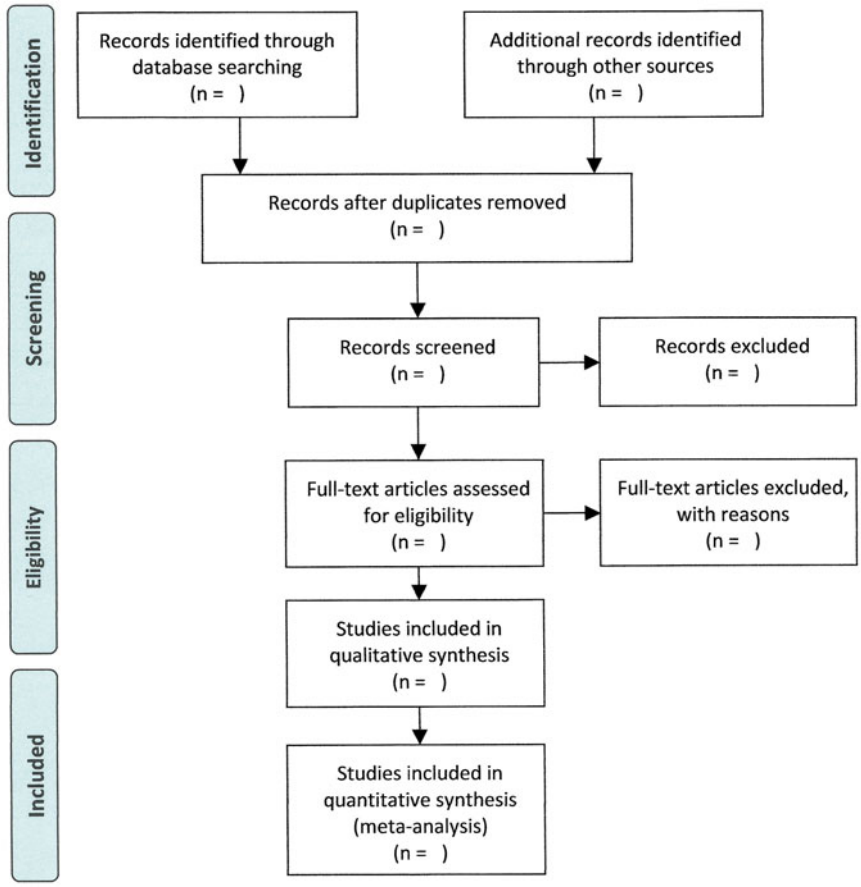


Fig. 2.3 Flow diagram (PRISMA) [23]

those cases separate evidence tables may be constructed to ensure the critical components of each type of study design is adequately captured. Evidence tables tend to be large in size and cumbersome to work with. Comparison among studies is facilitated by using the evidence tables to construct summary evidence tables that capture the specific elements necessary to synthesize the data.

Methodological Quality and Applicability of Studies

Some type of quality assessment is usually part of a systematic review. Table 2.1 proves a simple example with some common elements [17]. A number of quality assessment tools are available, for example, Cochrane Collaboration [20], the U.S. Preventive Services Task Force [21] and the Grading Recommendations Assessment, Development and Evaluation working group [24]. The choice of which to use depends on the topic and characteristics of the review.

Table 2.1 One approach to assessing methodological quality and applicability of studies[a]

Methodological quality
A Least bias; results are valid.
B Susceptible to some bias, but not sufficient to invalidate the results.
C Significant bias that may invalidate the results.
Applicability
I Sample is representative of the target population. It should be sufficiently large to cover both sexes, a wide age range, and other important features of the target population (e.g., diet).
II Sample is representative of a relevant subgroup of the target population, but not the entire population.
III Sample is representative of a narrow subgroup of subjects only, and is of limited applicability to other subgroups.
Overall effect
++ Clinically meaningful benefit demonstrated.
+ A clinically meaningful beneficial trend exists but is not conclusive.
0 Clinically meaningful effect not demonstrated or is unlikely.
– Harmful effect demonstrated or is likely.

[a]Adapted from [17]

Meta-analysis

Meta-analysis use statistical approaches to combine the data from multiple studies to derive a conclusion about the totality of the data. Frequently the result of a meta-analysis is to calculate an overall effect estimate. In some cases, a meta-regression can be performed to evaluate discrepancies among studies and to explore factors such as dose–response relationships. The major concern when performing and interpreting a meta-analysis is the appropriateness of combining studies that did not use identical experimental protocols. Decisions on whether it is appropriate to combine studies must be made on a case by case basis. Meta-analysis should not be confused with a pooled analysis. For a pooled analysis primary data from multiple individual studies are combined and analyzed. For a meta-analysis mean data derived from published studies are combined and analyzed.

Unique Issues Related to Nutrition-Related Systematic Reviews

Methodological approaches to performing systematic reviews were first developed to address questions in the field of medicine [25]. The literature on pharmaceutical interventions tends to be more straightforward than that related to nutrition. There are a number of unique factors that must be accounted for when performing systematic reviews of nutrition-related topics (Table 2.2). It is important to be aware of these prior to starting the review process so that accommodations, when necessary, can be made.

Baseline Exposure

There is a baseline exposure for all essential nutrients. This exposure can be the variable of interest, as for observational studies, or a starting point to be accounted for in interventional studies. For interventional studies this information is used as a starting point from which to increase or decrease intake. Inaccurate accounting for potential differences in baseline exposure among study subjects can alter the conclusions drawn from the data. Baseline exposure most commonly comes from foods and

Table 2.2 Unique issues related to nutrition-related systematic reviews

• Baseline exposure
• Nutrient status at baseline
• Nutrient bioavailability
• Nutrient bioequivalence
• Biological stores
• Multiple and interrelated biological functions
• Undefined nature of nutrient/food intervention
• Uncertainty in assessing dose–response relationships

beverages, nutrient and herbal supplements, endogenous synthesis (e.g., vitamin D, vitamin K), and/or environmental contamination (e.g., iron cooking pot). Limitations in accurately quantifying baseline nutrient exposure include factors such as the subjective nature of self-reported food and beverage intake, incomplete data bases with which to analyze the data, subject burden associated with collecting intake data, and inadequate methodology for quantifying in vivo synthesis. Currently, few biomarkers to characterize baseline nutrient exposure are available. Information on how the baseline food/nutrient intake is assessed should be included in the systematic review methodology section.

Nutrient Status

The nutrient status of an individual or population at baseline will impact on the ability to assess potential relationships between intake and outcomes within a cohort, and the response to altering the intake after an intervention. There is a wide range of approaches used to determine nutrient status, including, but not limited to concentrations in blood-borne cells, hard tissue concentrations (hair, nails), activity of enzymes for which the nutrient is a cofactor, saturation of carrier proteins, and nutrient or metabolite excretion. Homeostatic mechanisms, trafficking of nutrients to different tissues and storage capacity for the nutrient of interest precludes, with rare exceptions, the use of plasma concentrations as an indicator of nutrient status.

Nutrient Bioavailability

Not all forms of a nutrient are absorbed to the same degree of efficiency, otherwise referred to as bioavailability. Many factors determine nutrient bioavailability. These include, but are not limited to ionic state (e.g., ferric [Fe^{3+}]/ferrous [Fe^{2+}]); chemical form (e.g., folic acid/folate); nutrient–nutrient interactions (e.g., vitamin C and non-heme iron); nutrient–food interactions (e.g., dietary fat facilitates fat-soluble vitamin absorption, phytic acid/oxalic acid-containing foods impedes zinc absorption); nutrient–drug interactions (e.g., isoniazid and vitamin B_6, coumadin and vitamin K, folate and metformin); mineral salts (e.g., calcium carbonate, calcium citrate, calcium malate); single versus multiple daily doses (e.g., calcium, iron), and habitual intake (e.g., iron, vitamin C). Additional factors that may alter nutrient bioavailability include biological status (e.g., iron and pregnancy, vitamin B_{12} and achlorhydria), food processing (e.g., particle size and dietary fiber, lye-treatment [corn] and tryptophan, heat treatment and carotenoids), and for nutrient supplements completeness or rate of release (e.g., coatings, excipients, surfactants).

Nutrient Bioequivalence

Many nutrients occur in multiple forms that have different biological activity, commonly referred to as bioequivalence. The general approach used to address this issue is to calculate nutrient equivalents as was done when setting the recommended dietary allowances for vitamin A (preformed vitamin A and carotenoids), folate (folate and folic acid), vitamin K (phylloquinone and menaquinone), and niacin (niacin and tryptophan) [26–28]. The challenge of determining accurate conversion factors for the calculation of nutrient equivalents has recently been demonstrated for beta-carotene [27].

Nutrient Availability from Biological Stores

In humans, release of nutrients from storage depots can be unrelated to biological need. The release of vitamin A from hepatic stores is dependent on protein nutriture. The release or deposition in adipocytes of fat-soluble vitamins can be determined by changes in tissue mass rather than biological need for the nutrients.

Multiple and Interrelated Biological Functions of Nutrients

Most nutrients have multiple biological functions. The key questions define the nutrient-specific scope of the systematic review. This is often accomplished by narrowing the range of the work (e.g., vitamin D and bone health or breast cancer risk, vitamin A and infectious disease or xerophthalmia). Some biological functions of nutrients are dependent on the biological status of other nutrients (e.g., folate/vitamin B_{12}/vitamin B_6, vitamin D/calcium) and must be accounted for.

Undefined Nature of Nutrient Intervention

Food-based interventions, in contrast to supplement-based interventions, present unique challenges in accurately attributing a cause and effect to an individual nutrient or group of nutrients. For example, one approach to increasing very long-chain n-3 fatty acid (eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]) intake is to provide or instruct study participants to increase fish intake. However, there is considerable variability in the levels of EPA and DHA in different fish, within species of the same type of fish [29], season the fish was caught and animal husbandry practices for farm-raised fish. In addition, there are other compounds in fish, in addition to EPA and DHA, that could alter the biological outcomes assessed. Evaluating the effect of EPA and DHA using nutrient supplements is not without similar challenges due to the wide range of fatty acid profiles in available fish oil, potential changes in absolute levels during prolonged storage or heat exposure, and different chemical forms of the fatty acids (e.g., triglyceride, ethyl esters). Documentation of nutrient intake assessment is important to record.

Uncertainties in Assessing Dose–Response Relationships

It is difficult to accurately assess food, hence, nutrient intakes. In some cases systematic bias is unavoidable using currently available dietary instruments. This can be particularly important for systematic reviews designed to assess absolute rather than relative dose–response relationships. In general, food frequency questionnaires underestimate energy and protein intakes with greater biases than 24-h recall [30]. Potential biases for other nutrient intake estimates are not adequately documented but likely exist. Assay procedures for biomarkers of nutritional status can also significantly affect the mean and distribution of reported values and need to be factored into data interpretation [31, 32].

Strengths and Limitations of Systematic Review Approach for Nutrition Applications

Applying the systematic review approach to nutrition applications has both strengths and limitations (Table 2.3).

Strengths

Strengths of the systematic review process include representing an objective process while avoiding the appearance of bias, summarizing a comprehensive assessment of the available literature, defining the scope of the review as reflected in key questions, documenting the search strategy in a detailed manner, allowing for flexibility to customize searches by each topic without compromising rigorousness, generating a report that can be updated in a cost effective manner, identifying a transparent process of review, enhancing statistical power by simultaneously assessing multiple and frequently small studies, incorporating some ability to detect publication bias, providing an assessment of methodological quality, applicability and overall effect, and facilitating identification of research gaps.

Table 2.3 Strengths and limitations of the systematic review process

Strengths
• Represents an objective process and avoids the appearance of bias
• Summarizes a comprehensive assessment of the available literature
• Defines scope of the review as reflected in key questions
• Documents search strategy in a detailed manner
• Allows for flexibility to customize searches by each topic without compromising rigorousness
• Generates a report that can be updated in cost effective manner
• Identifies a transparent process of review
• Enhances statistical power by simultaneously assessing multiple and frequently small studies
• Incorporates some ability to detect publication bias
• Provides an assessment of methodological quality, applicability and overall effect
• Facilitates identification of research gaps
Limitations
• Confines imposed by key questions in terms of population, intervention, comparator and outcome measures
• Restrictions impact on the number of studies meeting the inclusion criteria
• Limitations imposed by the quality and scope of available data (e.g., poor study design, missing data, publication bias)

The detailed level of documentation is an integral part of the systematic review process. A beneficial byproduct of the systematic reviews is the ability to identify needed improvements in the quality and nature of data reporting. This is particularly valuable in the field of nutrition where the number of studies available to answer a key question is often limited.

Limitations

Limitations of the systematic review process include confines imposed by the key questions in terms of population, intervention, comparator and outcome measures, restrictions that impact on the number of studies meeting the inclusion criteria, and limitations imposed by the quality and scope of available data (e.g., poor study design, missing data, publication bias).

Confusion can be caused when multiple systematic reviews addressing what appear to be on the same topic come to different conclusions [9, 33, 34]. Such discrepancies can usually be attributed to differences in the key questions, study inclusion/exclusion criteria, evolution of available data, and changes in the analytical approaches used to generate the data or quality of the data. Meticulous documentation of the process can avoid confusion.

Contribution of Systematic Reviews to Nutritional Status of Older Adults

It is difficult to isolate an independent contribution of systematic reviews in defining the nutritional status specifically of older adults or understanding their unique nutritional challenges. However, the contribution of systematic reviews to the understanding of health outcomes, particularly in terms of chronic disease risk, has had a marked effect.

In 2013, it was reported that the prevalence of multi-morbidity, the concurrent existence of two or more chronic disorders, is increasing in the United States, paralleling the increased life-span and demographic shift in the population to the older aged groups [35]. The rates of multi-morbidity in individuals aged <65 years, 65–74 years, 75–84 years, and >85 years is 50 %, 62 %, 76 %, and 82 %, respectively. These data were corroborated using previously published systematic reviews [35]. It can be difficult to address the nutritional needs of individuals with multi-morbidities. To be most efficacious intervention approaches may need to be tailored to different age groups. However, a systematic review of nutrition and health literacy literature concluded that health literacy was a stronger predictor of health status than age, income, employment, education, and race [36]. This type of information is critical when designing intervention programs to improve health status of older adults.

Evaluating the nutritional status of older adults is an important component when assessing health status. A challenge is determining which nutritional screening tool is the best predictor of status for older adults and most likely to provide useful information to optimize health outcomes. A systematic review of the instruments available was used to address this issue [37]. In addition to providing valuable information on the relative strengths of each instrument for which data were available, research gaps that would benefit from being addressed were also identified. The most recent iteration of the Dietary Reference Intakes for calcium and vitamin D relied heavily on a systemic review of the evidence [13, 22]. The conclusions of the review resulted in changes in the vitamin D dietary reference intakes for most age groups, including individuals >70 years [22].

Multivitamins use is common in older adults [38, 39]. Strikingly, use is most prevalent among those with the most nutrient adequate diets [40, 41]. Conclusions of a systematic review indicate the most prominent motivator for nutrient supplement use among all U.S. adults is desire to improve overall health [42]. However, for older adults this is not the case, their motivations stem more from

specific health concerns and nutrient supplement use parallels engaging in more favorable health and lifestyle behaviors [42]. Recently, concern has been raised that multivitamin–multimineral supplement use in older adults is associated with increased mortality [43–45]. A systematic review was conducted to address this issue. The totality of the data indicated that there was no trend of multivitamin–multimineral supplement use with all-cause mortality, and there was a trend for reduced mortality from vascular and cancer causes [46]. In addition, no statistically significant evidence for heterogeneity or publication bias in the data was identified by the systematic review. Only an unbiased approach that considered all the data together could have adequately addressed this issue.

Conclusion

Systematic reviews are by their very nature an objective assessment of the available literature on a defined topic. The availability of systematic reviews that have addressed nutrition-related questions is extremely useful. The process is flexible, allowing for a wide range of topics to be addressed and facilitates periodic updates as new data emerge. However, it is important to note that by definition, systematic reviews are limited in scope as defined by the key question and restricted to what is frequently a less than complete dataset. The key questions answered are discrete units rather than interrelated entities. The conclusions of systematic reviews or meta-analysis do not in themselves establish guidelines or research agendas. They are an important tool that can contribute to decisions in these areas. A well-documented transparent process is critical for reviewing the data, and if inadequate data are available and expert opinion impacts on the final recommendations, there is a clear indication of when that occurred and within what context.

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Chapter 3
Nutrition Assessment

Rose Ann DiMaria-Ghalili and Michi Yukawa

Key Points

- Older adults are at risk for malnutrition (undernutrition) across the care continuum.
- Nutrition screening should be conducted upon admission to the hospital and long-term care settings, upon first home care visit, enrollment in community-based programs, and during annual primary care visits.
- Recommended nutrition screening tools are the Mini-Nutritional Assessment-Short Form and the Determine Checklist.
- Nutrition assessment should be performed for any older adult at nutrition risk.
- Nutrition assessment is a comprehensive exam focused on weight changes, body composition status, physical examination, comorbid conditions, functional status, medication history, dietary intake, and psychosocial and economic status.
- Adult disease-related malnutrition diagnosis applicable to older adults include: starvation, chronic disease-related malnutrition, and acute disease-related malnutrition.
- All health professionals (physicians, nurses, dietitians, pharmacists, dentists, speech pathologists, and physical therapists) should be knowledgeable about appropriate approaches for the nutrition screening and assessment of older adults.

Keywords Nutrition assessment • Nutrition screening • Malnutrition • Weight loss • Unintentional weight loss • MNA-SF • DETERMINE checklist

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Introduction

Nutrition plays an important role in the promotion and maintenance of optimal physical functioning and quality of life in older adults [1]. Nutritional status is the balance of nutrient intake, physiological demands, and metabolic rate. Malnutrition includes both undernutrition (protein and/or calorie deficiency) and overnutrition (obesity); in older adults malnutrition more commonly refers to undernutrition. Obesity (BMI $\geq$30 kg/m^2) is a key indicator of well-being in older adults, and 38 % of older Americans were obese in 2009–2010 [2]. While obesity is often easy to identify, unintentional weight loss and malnutrition are not. Malnutrition is a common geriatric syndrome [3] and 12–72 % of older adults are malnourished or at risk for malnutrition [4–9]. Malnutrition can impact quality of life [10, 11] and is associated with measurable adverse outcomes which include infections, pressure ulcers, falls, increased length of hospital stay, institutionalization, increased cost of care, and death [9, 12–19]. Identification of malnourished older adults through nutrition screening and assessment can lead to prompt interventions to promote or maintain nutritional health and improve health outcomes.

Nutrition Screening

Meeting the nutritional needs of the older adults includes screening for nutrition risk, performing a nutrition assessment, implementing nutrition interventions, monitoring responses to interventions, rescreening, and when appropriate diagnosing malnutrition (Table 3.1). Nutrition screening is the first step [20] and is defined as "a process to identify an individual who is malnourished or who is at risk for malnutrition to determine if a detailed nutrition assessment is indicated" [21]. Nutrition screening and rescreening can be performed by any health care professionals in any practice setting with valid and reliable tools for older adults [22]. Since nutrition screening can take place in a variety of care settings (primary care, ambulatory care, acute care, home care, community, and long-term care) the selection of the screening tool and timing of screening should be appropriate to the setting [22].

Nutrition Screening Regulations

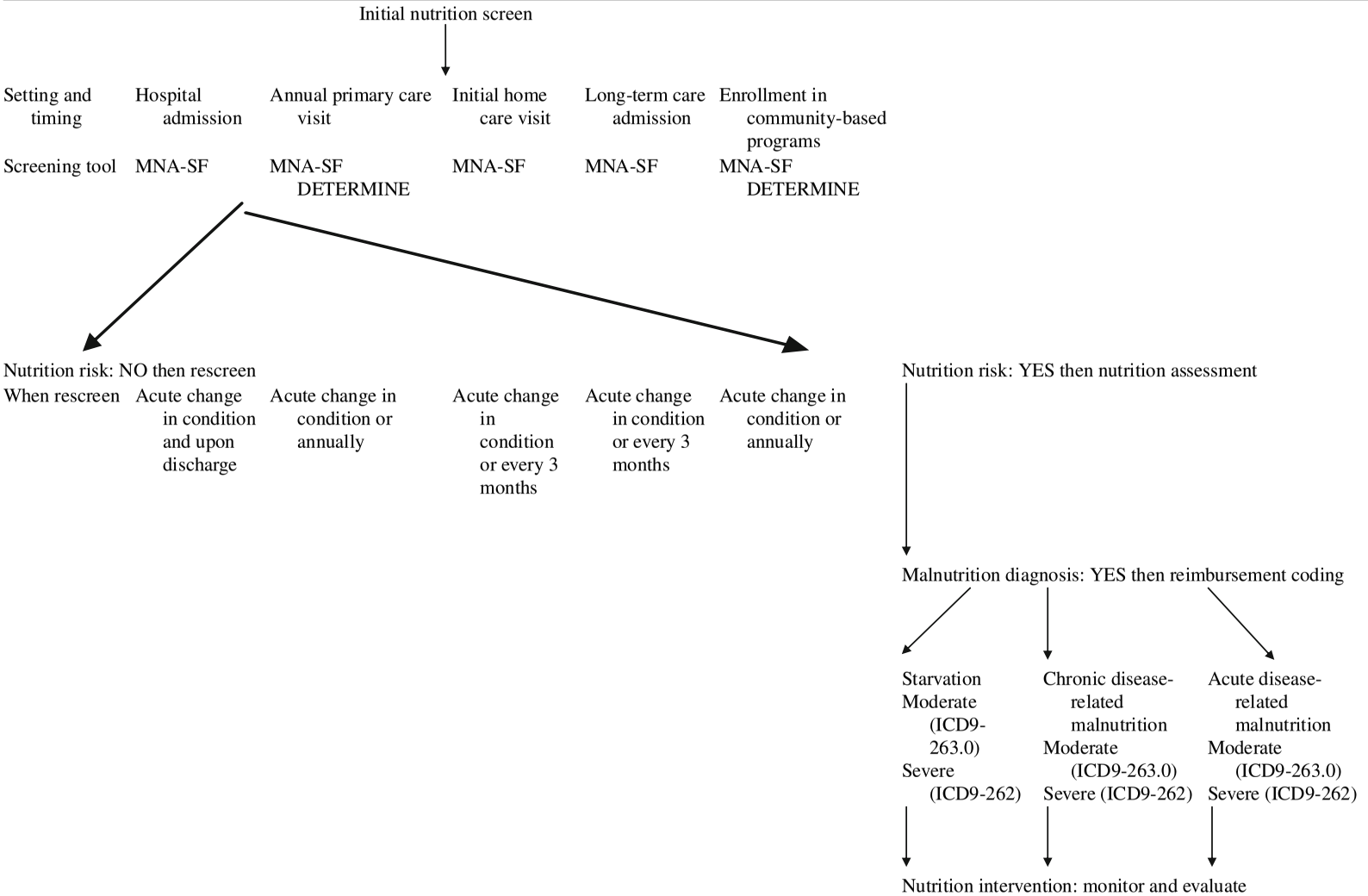
Hospital or Acute Care Settings

In the hospital setting the Joint Commission mandates that every patient admitted to the hospital or acute care setting have a nutrition screen performed within 24 h of admission [23]. The standard is not different for older patients and the elements to be included in the nutrition screen are not specified. Nutrition screening on admission identifies those patients at risk and who would benefit from in-depth nutrition assessment; it triggers follow-up by a dietitian at the beginning of hospital treatment. Nutrition status can deteriorate during the course of admission, and an older adult may be at increased risk for malnutrition at discharge than upon admission. Presently there is no regulatory requirement for continued rescreening of nutrition status during hospitalization, and most importantly, upon discharge.

Long-Term Care

Federal regulations require nutrition screening for new residents within 14 days of admission to the skilled care facility (nursing home). Nutritional status and unintentional weight loss in long-term care residents are monitored very closely. In fact, one of the quality measures mandated by the Centers for

Table 3.1 Nutrition screening and assessment in older adults across care settings



Medicare and Medicaid Services (CMS) is "significant weight loss" in residents of a long-term care facility. The MDS (Minimum Data Set) 3.0 tracks weights on nursing home residents, and CMS defines significant weight loss as weight loss of ≥5 % in 1 month or ≥10 % weight loss in the last two quarters in residents who were not on prescribed weight-loss regimen (www.CMS.gov/medicare/Quality-Initiative-Patient-Assessment-Instruments). The MDS nurse coordinator contacts the physician when a resident has lost significant weight.

Primary Care

According to the Joint Commission, ambulatory clinics, office practices, and primary care settings should have an organizational policy that details when nutritional screenings and assessments are performed [24]. The Joint Commission recommends "nutritional screening may be performed at the first visit" [24], and rescreening and assessment are needed only "when appropriate to the reason the patient is presenting for care" [24]. If a primary care practice is not accredited by the Joint Commission there is no specific regulation mandating monitoring of weight or nutrition screening. However, experts advocate for the monitoring of weight loss in geriatric patients [25–27].

Community

Significant weight loss in community-dwelling older adults is defined as ≥5 % weight loss in 1 year [26, 27]. The US Preventive Services Task Force does not provide a recommendation on monitoring weight changes or nutrition screening in older adults. However, the Academy of Nutrition and Dietetics' evidence-based nutrition practice guideline on unintended weight loss in older adults strongly recommends "older adults are screened for unintended weight loss regardless of setting" [28]. The Administration on Aging does require nutrition screening with the DETERMINE checklist [29, 30] for all community-dwelling older adults who receive home-delivered meals or take part in congregate meal programs through the Title III Older American Act Nutrition Programs [31].

Homecare

Nutrition screening is not included in the Outcomes and Assessment Information Set (OASIS) for Medicare home health agencies [32]. However, questions are asked regarding whether patient can perform certain activities for oneself, including feeding, preparing meals, and food shopping. The Joint Commission requires that a home care agency defines in writing which nutrition status information it collects in the patient's assessment and reassessment [33].

Types of Screening Tools

Nutrition screening tools identify those who have, or are at risk for, malnutrition [22]. In the United States, there is no standardized tool to screen for nutrition risk in older adults. Using different tools across practice settings and institutions limits the ability to benchmark nutrition risk or malnutrition and to determine the yearly prevalence of malnutrition. One literature review identified 21 different nutrition screening and assessment tools for use with older adults [34]. However, many of these tools are not fully developed and the validity, reliability, sensitivity, and specificity are not established [34]. The Mini-Nutritional Assessment Short-Form (MNA-SF), and the DETERMINE checklist are nutrition screening instruments recommended for use in older adults.

Mini-Nutrition Assessment-Short Form (MNA-SF)

The original or full MNA (www.mna-elderly.com) was developed in 1991 and consists of 18 items derived from four parameters of assessment: anthropometric, general, dietary, and subjective [35]. The full MNA has two components: a nutrition screen and a complete nutrition assessment. The full MNA is available in 24 languages and has been used in over 122 international studies in 30,000 older adults in different settings [35]. The reliability and validity of the full MNA is well established across care settings and the tool has a reported sensitivity of 96 % and specificity of 98 % [35]. The MNA-SF is a screening tool to identify older adults who are malnourished or at risk of malnutrition. The most recent version of the MNA-SF consists of six questions on food intake, weight loss, mobility, psychological stress or acute disease, presence of dementia or depression, and body mass index (BMI). When BMI is not available, then calf circumference is measured and used in place of BMI. The MNA-SF has a sensitivity of 89 %, specificity of 82 %, and a strong positive predictive value (Youden Index = 0.70) [36]. While the MNA-SF was developed from the full MNA, reliability of the MNA-SF is not yet available [37]. The MNA-SF takes about 5 min to complete and is a recommended evidence-based screening tool for use in older adults [20, 22, 38].

DETERMINE Checklist

The DETERMINE checklist was developed by the Nutrition Screening Initiative to assess nutrition risk in older adults. The tool was designed to be self-administered, though health professionals can administer the screen. The DETERMINE checklist consists of ten items that assesses eating and drinking habits, mouth problems, income, eating alone, medications, weight loss/gain, and ability to shop/cook/feed self [29, 30]. The tool has established validity [34], but it has a high positive screen rate [39]. While the DETERMINE checklist is recommended for use in older adults as an evidence-based nutrition risk screen [38], the tool is most appropriate for use in community-dwelling older adults [31] and in the primary care setting.

Developing Screening Programs

Nutrition risk screening can be easily incorporated into the routine care of older adults across practice settings. The DETERMINE checklist and the Self-MNA (www.mna-elderly.com) nutrition risk questionnaires can be completed by older adults in a physician waiting room and the results can be discussed during the office visit. Nutrition risk screening tools (MNA-SF) can be incorporated into the nursing admission assessment for older adults admitted to the hospital, extended care facility, long-term care, or home health. While nutrition screening programs identify those older adults at nutritional risk who need a more in-depth nutrition assessment and/or nutrition intervention, screening only provides a snapshot of nutrition risk at a precise point in time. While there are no evidence-based criteria for rescreening, any changes in the medical history, psychological status, social status, or functional status can impact the level of nutrition risk and warranting further rescreening. Hospitalized older adults may benefit from a nutrition screen upon discharge to identify nutrition concerns during the transition from hospital to home [40, 41]. Institutionalized older adults should be rescreened every 3 months, and normally nourished community-dwelling older adults should be rescreened annually [42] (Table 3.1).

Nutrition Assessment

Nutrition assessment is a "comprehensive approach to diagnosing nutrition problems that uses a combination of the following: medical, nutrition, and medication histories; physical examination; anthropometric measurements; and laboratory data" [21]. Psychosocial status, economic factors, and functional status are also important components of a comprehensive nutrition assessment for older adults.

Anthropometrics

Weight

Body weight is the mass of an individual and represents the sum of individual body compartments. Body weight is characterized at the atomic (oxygen, carbon, hydrogen, other), molecular (water, lipid, protein, other), cellular (cell mass, extracellular fluid, extracellular solids), tissue (skeletal muscle, adipose tissue, bone, blood, other), and whole body (head, neck, trunk, lower extremities, upper extremities) levels [43]. Change in one of these compartments can cause change in weight. On the molecular level, body weight is the sum of water (60 % of body weight in healthy individual is water) and dry body weight (minerals, protein, and lipid) [43]. Lean body mass and fat free mass are essentially the same—both include water, protein, and minerals, while lean body mass does not include the relatively small amount of essential lipids [43]. Body weight is dynamic as it represents the balance of energy intake and energy expended in the form of physical activity and metabolism.

Weight is a critical vital sign in older adults. Weight should be measured without shoes or heavy clothing. Bed scales and chair scales can be used for older adults who cannot stand erect. The percentage of weight loss should be calculated as follows: usual weight − current weight/usual weight × 100 %) [46]. If an individual cannot recall whether or not they have lost weight, ask about changes in clothing size, examination of the belt, or ask significant others [44]. Daily fluctuations in total body weight are minimal in healthy adults (i.e., less than ±0.5 kg) [45], while an increase in 1–2 kg/day indicates fluid retention [44] or fluid overload in individuals with heart failure [46]. Weight gain and/or weight loss over time reflect changes in body composition [47]; furthermore, body composition can change over time (i.e., increase or decrease in fat or lean mass) *without* a change in body weight [47, 48].

An acceleration of weight loss is not part of normal aging. Body weight changes throughout adulthood, generally increasing until age 60 [48], stabilizing until about age 70 [49] and then slowly decreasing after age 70–75 [50]. Studies in very healthy elderly subjects indicate that only very small decrements in weight (0.1–0.2 kg/year) appear to occur in association with normal aging [49]. Further research needs to be conducted to understand the normal weight trajectory in those 80 years of age and older.

Body weight may decrease 50–60 % of ideal weight during chronic semi-starvation [45]. Physiological function is significantly impaired when more than 20 % of body protein is lost [51]. Hill's early work demonstrated that a weight loss of >10 % of body weight is associated with physiological impairment [51] and protein loss is usually clinically significant when more than 15 % of body weight has been lost [51]; however, these studies were not performed exclusively in the elderly. While a weight loss of 4 % of usual body weight in 1 year was reported to be the most sensitive and specific cut-point to define clinically important weight loss [25, 52], a weight loss of 5 % of usual body weight over 6–12 months is the most widely accepted definition for clinically important weight loss in older adults [44].

Intentional Versus Unintentional Weight Loss

The intentionality of weight change should be considered when assessing weight loss. Voluntary weight loss is due to either intentional planned restrictions or modifications in dietary intake (i.e., dieting), increase in physical activity, or both. Involuntary or unintentional weight loss is a decrease in weight over a defined period of time without a desire or intention of the individual to reduce body weight. Unintentional weight loss is considered unexplained when a definitive cause of the weight loss cannot be made [53]. Unexplained, ongoing, weight loss in persons without a history of weight fluctuations (e.g., "yo yo" dieting) is cause for concern [44]. Unintentional weight loss can occur in isolation [50] or as component of geriatric syndromes such as malnutrition (undernutrition) [54] and frailty [55], as well as secondary to sarcopenia [56], cachexia [56], and inflammatory conditions [56]. Some patients may ignore or minimize their unintentional weight loss [44] and not report it to the physician [57]. Older adults who lose weight unintentionally may report being satisfied with weight loss after years of struggling to lose weight and indicate that they do not want to regain the weight they lost [57]. One study found cancer patients who lost up to 60 lb of their pre-cancer weight were pleased with the unintentional weight loss despite the impact on functional status [58]. Unintentional weight loss may go untreated if clinicians do not monitor weight changes in older adults over time. Unintentional weight loss in older adults is associated with increased morbidity and mortality, primarily due to the loss of muscle mass [48]. Clinicians should consider weight in older adults as an important vital sign.

Adverse Effects of Unintentional Weight Loss

Any weight loss in older adults is associated with a loss of lean mass [48, 59] and accelerates the development of sarcopenia [59], resulting in functional decline [60, 61]. Unintentional weight loss is associated with frailty [55], lower levels of self-reported physical health [62], hospital readmission [63, 64], and falls [65, 66]. Unintentional weight loss is a risk factor for malnutrition (i.e., undernutrition) [67] and increases the risk for death [52, 68–70]. If unintentional weight loss is from total starvation, death occurs when the maximal weight loss is approximately 30 % of initial body weight [45].

Height. Since older adults may lose height as part of normal aging [71], it is important to measure height (without shoes) at least on a yearly basis. Alternatives to standing height include demi-span measurement [71] or knee-height with a caliper when an older adult has difficulty standing erect [71, 72].

Body Mass Index. Body mass index is an indicator of body fatness. Compared to young adults of the same BMI, older adults have more body fat, and BMI may overestimate health risks with higher BMIs in the elderly [48]. BMI is the best metric to determine if weight for height is within normal limits since ideal body weight tables are not norm-based for older adults [73, 74]. However, the recommendations for normal BMI for older adults are conflicting (Table 3.2).

Body Composition

Important changes in body composition occur with normal aging. The decline in lean mass, mostly muscle, with and without intentional weight loss [48], starts in the third decade at a rate of 0.3 kg/year [50]. By the age of 70 there is an estimated loss of 40 % of lean mass since age 30 [75]. Loss of lean mass is attributed in part to physiological aging from physical inactivity, age-related declines in anabolic hormones, adverse effects of free radicals, increased cytokines, and effects of acute illness [50]. Both men and women lose lean body mass with aging [76], although women lose lean mass to a lesser

Table 3.2 BMI recommendations for older adults

Source	Normal BMI (kg/m^2) for older adults
Centers for Medicare and Medicaid Services [101]	≥23 and <30
Medline Plus [102]	25–27
National Heart, Lung, and Blood Institute [103][a]	18.5–24.9
Nutrition Screening Initiative [30]	22–27

[a]National Heart, Lung, and Blood Institute Guidelines do not differentiate BMI recommendations for young, middle-aged, and older adults

extent than men [76]. Individuals ≥75 years of age lose more lean mass over time (men: 0.4 kg/year; women: 0.2 kg/year) than those aged 65–74 years [76].

Lean mass is replaced by fat until around age 65–70 [50] and the distribution of fat changes with aging. Subcutaneous fat increases up to around age 60 [77] and lower circumferences in arms and legs are observed in older versus younger adults [77]. In those over 65 years of age there is an increase in waist diameters [77], higher waist to hip or waist to thigh ratios [76, 77], and an increase in abdominal adiposity [76, 77]. Changes in body composition with aging are also dependent on other age-related factors, such as acute and chronic illness, physical activity, medications, hormone, and nutrient intake [76]. Increased physical activity during aging may attenuate the loss of lean mass [76]. Most experts agree that weight loss should not be dismissed as part of normal aging [48, 50, 68], and that measurement of weight loss cannot distinguish between alterations in lean versus fat mass [68].

A variety of methods are available to measure body composition in older adults. Specialized measurements such as whole-body immersion, air-displacement plethysmography, neutron activation analysis, and dilution techniques are accurate and precise, but are available only in specialized research facilities [78]. Furthermore, frail older adults may not be able to withstand the testing procedures. Computed tomography, MRI scanning, and dual energy X-ray absorptiometry (DXA) are also used to assess body composition. Whole-body DXA is considered the gold standard in epidemiologic cohort studies on aging, is generally well tolerated, clinically applicable, and has minimal radiation exposure [78]. Bioelectrical impedance analysis (BIA) is relatively inexpensive, safe, portable, and easy to perform in the clinical setting [78]. Anthropometric measurements are the most inexpensive body composition measures and are easy to obtain in clinical practice. These measurements include skinfold thickness (estimate of subcutaneous body fat) as well as upper arm and calf circumference measurements (estimates muscle mass). While researchers continue to advance the field of body composition, these methods are not routinely integrated into clinical practice. Normal ranges need to be developed for the elderly. When suitable, body composition measurements should be performed over time to assess changes in fat and muscle mass by appropriately trained individuals.

Physical Exam

Physical signs of malnutrition should be noted during a physical exam: loss of subcutaneous fat (orbital, triceps over rib cage); muscle loss (wasting of the temples, clavicles, shoulders, interosseous muscles, scapula, and calf); and fluid accumulation (extremities, vulvar/scrotal edema, or ascites) [67]. Diminished immune response, cognitive dysfunction, osteopenia, and anemia have also been associated with protein malnutrition [79, 80]. Protein malnourished individuals may develop anasarca or lower extremity pitting edema due to loss of oncotic pressure to maintain intravascular volume, as well as dry, atrophic skin and dull hypopigmented fragile hair. Protein malnutrition may be physically indistinguishable from cachexia and sarcopenia. Starvation or chronic protein malnutrition can be reversed with refeeding, while cachexia and sarcopenia are not easily treated with increased calorie intake [56].

Table 3.3 Physical findings of micronutrient deficiencies [104]

	Physical findings
Fat-soluble vitamin deficiency	
A [105]	Night blindness, xerophthalmia, decrease immune function, dry skin, follicular hyperkeratosis, poor wound healing
E [106]	Spinocerebellar ataxia, areflexia or decreased deep tendon reflexes, peripheral neuropathy, myopathy, impairment of proprioception and vibratory sense, retinopathy, extraocular muscle paresis
D	Osteomalacia, osteoporosis, frequent falls, increased risk for vertebral and nonvertebral fractures
K	Increased risk for bleeding
Water-soluble vitamin deficiency	
B1 (thiamine)	Wernicke's encephalopathy (confusion, ataxia and nystagmus), Korsakoff's syndrome (retrograde amnesia, confabulation, inability to learn new things), beriberi, foot-drop or wrist-drop from nerve damages
B2 (riboflavin)	Corneal neovascularization, cheilosis, glossitis
B3 (niacin)	Diarrhea, cognitive impairment (delirium, memory loss, depression, mania and paranoia), dermatitis (bullae, vesicles, intertrigo, or chronic hypertrophy with hyperpigmentation)
B6 (pyridoxine)	Stomatitis, glossitis, angular cheilosis, sideroblastic anemia
B12	Peripheral neuropathy, depression, cognitive dysfunction, megaloblastic anemia
C [107]	Poor wound healing, reduced collagen cross-linking, hemarthrosis, perifollicular petechiae, hypertrophic gingivitis, gingival bleeding, ecchymoses, petechiae, nail bed splinter hemorrhages
Folate	Megaloblastic anemia
Minerals	
Copper [108]	Muscle weakness, ataxia, neuropathy, cognitive deficits, abnormally formed hair, depigmentation of the skin
Iodine [109]	Goiter, hypothyroidism
Iron	Microcytic, hypochromic anemia, lethargy
Manganese [84]	Scaly dermatitis, dyslipidemia
Selenium [100, 110]	Cardiomyopathy, skeletal muscle dysfunction, mood disorders, decreased immune function
Zinc [111, 112]	Poor wound healing, decreased immune function, impotence, hypogonadism, decreased taste, alopecia, acrodermatitis enteropathica

Older adults with protein calorie malnutrition may also experience micronutrient deficiencies. Physical findings associated with vitamin and trace mineral deficiencies are detailed in Table 3.3. While vitamin D is most notable for its impact on calcium and bone physiology, research on Vitamin D deficiency has been expanding due to its pleiotropic clinical effects. Vitamin D deficiencies have been linked to increased risk for arterial disease, heart failure, insulin resistance, poor glycemic control, and even cancer [81–83]. However, most notable physiological signs of vitamin D deficiency are osteomalacia, osteoporosis, and increased risk for fall, balance problems, and fractures. Although deficiency in manganese is very rare, one clinical study showed that it is associated with dyslipidemia and scaly dermatitis [84].

Visceral Proteins

While serum albumin, transferrin, and prealbumin are visceral protein measures, they lack sensitivity and specificity as indicators of nutrition status during inflammation [67, 72]. In order to determine if the depleted measures of albumin and prealbumin reflect malnutrition, it is recommended to obtain a C-reactive protein level [72]. If C-reactive protein is elevated and albumin and prealbumin are low then the changes in albumin and prealbumin are due to an underlying inflammation [72].

Dietary Intake

Dietary intake can be assessed with a modified diet history or 24-h food recall [72], though food recall may be inaccurate especially in older adults with cognitive impairment. If the older adult is in a health care setting, a 3-day calorie count [71] can help determine current intake from total calories as well as protein, fat, and carbohydrates. Older adults may have diminished dietary intake due to loss of appetite related to side effects of medications, depression, or anorexia of aging [27] (see also Chap. 18). Also chronic conditions that lead to an impairment in ADL or IADL may limit the ability to physically shop, cook, or feed self [71]. Dysphagia, difficulty swallowing, and poor oral health (cavities, gum disease, missing teeth) can limit dietary intake [71]. Poor oral health is a special concern in older adults since dental coverage is not provided under Medicare and many older adults may not have the money to visit the dentist (see also Chap. 5).

Functional Status

Physical performance is a component of a geriatric assessment. Unintentional weight loss and malnutrition can negatively impact muscle strength and muscle mass leading to frailty and physical disability. Hand-grip strength, an indicator of upper body muscle function, is used as an outcome variable in nutrition intervention studies as well as a marker of nutritional status [85]. Hand-grip strength measurements are noninvasive, portable, and can easily be measured at the bed side [86]. Ergonomic characteristics vary with each dynamometer, and the Jamar is considered as the "gold standard" [86]. The American Society for Parenteral and Enteral Nutrition and the Academy of Nutrition and Dietetics recommend reduced hand-grip strength as a clinical indicator of malnutrition [67]. However, there is a need to develop standardized measurement protocols as well as normative data to widely translate the use of hand-grip measurements to clinical practice [67, 85].

Medications

Side effects of medications can contribute to weight loss in geriatric patients [87, 88]. Common prescription and over-the-counter medications associated with unintentional weight loss are listed in Table 3.4. Some medications can cause dry mouth, and alter taste or smell, which can lead to decreased appetite. Other medications can slow gastric motility causing a sensation of persistent fullness leading to decreased food intake. Reviewing all medications, including over-the-counter medications, vitamins, and prescription medications in patients who are losing weight is recommended.

Psychosocial and Economic Factors

Poverty or limited income can impact shopping patterns; for example, financial limitations and/or lack of transportation may reduce availability of fresh fruits or vegetables and high quality protein foods [71]. Older adults with reduced income have also reported limiting the number of meals eaten each day for economic reasons [71]. Older adults who are primary caretakers of their grandchildren are more likely to have food insecurity [89]. Psychosocial factors can contribute to unintentional weight loss by either decreasing appetite, or reducing dietary intake. Older adults who live alone may be

Table 3.4 Nutrition-related side effects of medications [87, 88, 96, 113]

Nutritional alteration	Medications
Anorexic	Amantadine, amphetamine, benzodiazepines, digoxin, gold, levodopa, metformin, nicotine, opiates, SSRIs, theophylline
Altered taste or smell	ACE inhibitors, calcium channel blockers, spironolactone, iron, levodopa, pergolide, selegiline, opiates, gold, allopurinol
Dry mouth	Anticholinergic, diuretics, antihistamines
Nausea/vomiting	Antibiotics (atovaquone, ciprofloxacin clarithromycin, doxycycline, ethambutol, metronidazole, ofloxacin, pentamidine, rifabutin, tetracycline)
	Bisphosphonates, digoxin, levodopa, opiates, tricyclic antidepressants, SSRI
Slow gastric motility	Antibiotic (erythromycin)

SSRI selective serotonin reuptake inhibitors, *ACE* angiotensin converting enzyme

lonely and lose the desire to eat [71]. Grief due to loss of a spouse can impact desire to eat or enjoyment in eating [71]. If the wife was the primary caretaker of the home, older men who lose their spouse may not be accustomed to shopping for food, preparing meals, or cooking. Depression is a major contributor to decreased appetite in older adults [71].

Unintentional weight loss is a classic sign of Alzheimer's disease (AD) [90–92], occurring in 25–90 % of patients across the stages of the disease [52, 92, 93]. AD is considered a pro-inflammatory condition and elevations in cytokines can contribute to weight loss and wasting associated with AD [94]. While the exact mechanism is unclear, unintentional weight loss starts in the preclinical stage [90]. Neuropathological changes in the brain contributing to weight loss in AD include changes in feeding behavior and memory [90–92], disturbed appetite signaling [90], lower orexigenic factor concentrations [90], volitional swallowing disorders [91], and alterations in taste and smell [91]. Also, side effects of medications used to treat AD can impact appetite or ability to eat [90, 92]. Behavioral changes at each stage of the AD can profoundly impact dietary intake and contribute to unintentional weight loss.

Comorbid Conditions

A review of the medical history can identify comorbid conditions which are associated with unintentional weight loss and malnutrition. Medical conditions associated with unintentional weight loss are listed in Table 3.5. Involuntary weight loss can be categorized into three causes: malignant, nonmalignant, and idiopathic. The landmark studies on unintentional weight loss patients [95, 96] from the 1980s showed that 19–36.6 % of patients had a malignancy, 40.5 % had nonmalignant disease, and in 23.2–35 % no underlying causes could be found despite extensive work-up. The most common malignant diseases were gastrointestinal in origin (pancreatic, hepatic, esophageal, and colorectal) followed by genitourinary, hematologic, lung, breast, and brain [96]. For nonmalignant causes of weight loss, gastrointestinal disorders were frequently noted (26 %) and psychiatric disorders accounted for 10.3 % of involuntary weight loss [96]. Recent studies confirmed the previous findings that 38 % of patients with involuntary weight loss have underlying neoplasms; GI malignancies accounted for majority of the cases [87, 97, 98]. Twenty-three percent of patients had underlying psychiatric illness and nonmalignant GI causes were also more commonly seen in patients with unintentional weight loss. In approximately 11–25 % of cases, the cause of weight loss was not determined. For geriatric patients, underlying dementia could lead to unintentional weight loss, as previously noted.

Table 3.5 Comorbid conditions contributing to involuntary weight loss in older adults [87, 88, 96, 113]

Malignant causes	*Nonmalignant causes*
Gastrointestinal malignancy (esophageal, pancreatic, gastric cancer, colorectal, hepatic, biliary tract)	GI disorders (motility or swallow dysfunction, mesenteric ischemia, peptic ulcers, inflammatory bowel disease, chronic liver disease, chronic pancreatitis)
Lung	Congestive heart failure
Lymphoma/leukemia	Dementia
Prostate	COPD
Ovarian	Endocrine disorder (diabetes mellitus, hyperthyroidism, hyperparathyroidism)
Bladder	Stroke
Breast	End-stage renal failure
Brain	Infectious disease (tuberculosis, HIV)
	Alcoholism
	Connective tissue diseases (rheumatoid arthritis, polymalgia rheumatica)
	Oral or dental problems
Psychiatric causes	*Unknown causes*
Depression	
Anxiety disorder	

Diagnosing Malnutrition

The purpose of nutrition screening and assessment is to identify findings associated with malnutrition (undernutrition). Over the years, researchers and clinicians used a variety of clinical criteria to define malnutrition, as well as a variety of terminologies. Marasmus, kwashiorkor, and mixed-marasmus kwashiorkor were terms developed to classify macronutrient deficiencies in children during famine, and subsequently became used to characterize and diagnose disease-related malnutrition in adults. Leaders from the American Society for Parenteral and Enteral Nutrition (ASPEN) and the European Society for Parenteral and Enteral Nutrition (ESPEN) formed an International Consensus Guideline committee to propose an etiology-based diagnosis for adult starvation and disease-related malnutrition [99]. Inflammation has long been recognized as having a negative impact on nutrition status due to breakdown of skeletal muscle [99] and is now the cornerstone of the new adult malnutrition classification. ASPEN and the Academy of Nutrition and Dietetics (The Academy) published a consensus statement in 2012 on characteristics for the identification and documentation of adult malnutrition (undernutrition) [67], which is also applicable to older adults.

The three types of adult malnutrition are: starvation-related malnutrition or malnutrition in the context of social or environmental circumstances (i.e., pure chronic starvation, anorexia nervosa), chronic disease-related malnutrition (inflammation of a mild to moderate degree, for example, conditions such as organ failure, pancreatic cancer, rheumatoid arthritis, sarcopenic obesity), and acute disease-related malnutrition (acute inflammation with a marked inflammatory response, for example, major infection, burns, trauma, closed head injury) [67]. Each of the three types of malnutrition is further characterized as nonsevere/moderate and severe. Clinical characteristics include: decreased energy intake, weight loss, loss of body fat and muscle mass, fluid accumulation, and reduced grip strength [67]. A summary of the clinical characteristics to diagnosis malnutrition and associated ICD-9 codes is found in Table 3.6. ASPEN and The Academy recommend for the diagnosis of severe or nonsevere malnutrition (of either type, namely, starvation-related malnutrition, chronic disease-related malnutrition, or acute disease-related malnutrition) at least two of the six characteristics should be present [67]. These recommended clinical characteristics of adult malnutrition (see Table 3.6) will

Table 3.6 Clinical characteristics and associated reimbursement codes for adult malnutrition

Clinical characteristics[a]							ICD-9 Codes			
	Weight (amount weight loss/time)	Estimated energy intake required	Subcutaneous fat	Muscle mass	Edema	Hand grip strength	260	261	262	263.0
Starvation (malnutrition in the context of social or environmental circumstances)										
Moderate	5 %/1 month 7.5 %/3 months 10 %/6 months 20 %/1 year	<75 % for ≥3 months	↓	↓	+	NA	NA	NA	No	Yes
Severe	>5 %/1 month >7.5 %/3 months >10 %/6 months >20 %/1 year	≤50 % for ≥1 month	↓↓↓	↓↓↓	+++	Reduced	NA	NA	Yes	No
Chronic disease-related malnutrition										
Moderate	5 %/1 month 7.5 %/3 months 10 %/6 months 20 %/1 year	<75 % for ≥1 month	↓	↓	+	NA	NA	NA	No	Yes
Severe	>5 %/1 month >7.5 %/3 months >10 %/6 months >20 %/1 year	≤75 % for ≥1 month	↓↓↓	↓↓↓	++	Reduced	NA	NA	Yes	No
Acute disease-related malnutrition										
Moderate	1–2 %/1 week 5 %/1 month 7.5 %/3 months	<75 % for >7 days	↓	↓	+	NA	NA	NA	No	Yes
Severe	>2 %/1 week >5 %/1 month >7.5 %/3 months	≤50 % for ≥5 days	↓↓	↓↓	++	Reduced	NA	NA	Yes	No

Adapted from [67]

NA, not applicable; ↓, mild decrease; ↓↓, moderate decrease; ↓↓↓, severe decrease; +, present to a mild degree; ++, present to a moderate degree; +++, present to a severe degree

[a]A minimum of two of the six characteristics is recommended for the diagnosis of either severe or nonsevere malnutrition

continually be updated as new evidence becomes available [67]. It should be noted that acute phase proteins are no longer considered valid markers of nutrition status and instead are associated with the degree of inflammation [99].

Conclusion: Nutrition Screening and Assessment Across the Health Professions

Nutrition education and training in many health professions programs is inadequate, especially when it comes to geriatric nutrition. The Institute of Medicine noted, "Poor nutrition is prevalent among seniors, but most professionals are still not trained in the nutritional needs of older adults" [3]. Recently, the National Heart Lung and Blood Institute of the National Institutes of Health convened a "Working Group on Future Directions for Implementing Nutrition Across the Continuum of Medical and Health Professions Education and Training, and Research" (http://www.nhlbi.nih.gov/meetings/workshops/nutrition.htm).

The guiding principles summarized in the executive summary of this 2-day meeting are applicable to nutrition screening and nutrition assessment of older adults:

- Health professionals should implement recommended nutrition practices and promote current Dietary Guidelines for the prevention and treatment of disease with all patients.
- Health professionals should understand the fundamentals of the Nutrition Care Process, including assessing nutritional status and dietary intakes, diagnosing nutrition-related problems, and implementing, and monitoring and evaluating nutrition care plans. The roles and responsibilities of different health professionals—when to refer, how to interact, and how multidisciplinary teams work—need to be understood.
- The dietitian plays an important role on the health-care team and can help provide training for other health professionals as well as partner with physicians in the nutrition assessment, therapeutic recommendations, and joint follow-up of patients.
- Inter-professional nutrition education is critical to instill a team approach to teaching, training and learning and to patient care.
- Health professionals should know where to access nutrition education and advocacy resources and should use innovative approaches, including online resources and case-based approaches to enhance learning.
- Nutrition education in medical/professional schools should strive for a longitudinal integrated approach rather than single courses and involve a collaborative effort of multiple stakeholders.
- Research is needed to identify and validate strategies for providing nutrition education to health professional students and practicing clinicians.
- Health professionals should understand the role of evidence-based research in the development of diet and nutrition guidelines for public health and must be able to apply that knowledge toward better patient outcomes.

Nutrition screening and assessment is a responsibility of all health professionals (physicians, dietitians, nurses, pharmacists, physical therapists, occupational therapists, speech language pathologists) who provide care to older adults. Nutritional interventions should be implemented in a timely fashion when an older adult is malnourished. Under optimal circumstances, the older adult should be referred to a registered dietitian (RD) for an in-depth nutrition assessment and nutritional plan of care. However, work-force and policy issues, such as limited reimbursement for medical nutrition therapy provided by RDs in independent practice in primary care, home care, or community settings, can lead to long waits for consultation with an RD outside of the hospital setting. Therefore, all health professionals who provide care for older adults should develop competence in nutrition screening and assessment, and be knowledgeable of evidence-based diet and nutrition guidelines for older adults. Furthermore, there is an urgent need to increase efforts to advocate for expanded reimbursement for medical nutrition therapy for RDs who specialize in geriatrics.

Clinical recommendations include:

- Nutrition screening should be conducted upon admission to the hospital and long-term care settings, upon first home care visit, enrollment in community-based programs and during annual primary care visits.
- Recommended nutrition screening tools are the Mini-Nutritional Assessment-Short Form and the Determine Checklist.
- Nutrition assessment should be performed for any older adult at nutrition risk.
- A weight loss of 5 % of usual body weight over 6–12 months is the most widely accepted definition for clinically important weight loss in older adults.
- Nutrition assessment is a comprehensive exam focused on weight changes, body composition status, physical examination, comorbid conditions, functional status, medication history, dietary intake, and psychosocial and economic status.

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Part II
Fundamentals of Nutrition and Geriatric Syndromes

Chapter 4
Nutrition and the Aging Eye

Elizabeth J. Johnson

Key Points

- There is growing interest in the role that nutrition plays in modifying the development and/or progression of vision disorders in older persons, including age-related cataract and macular degeneration.
- Available evidence to date supports a possible protective role of several nutrients, including vitamins C and E, the carotenoids lutein and zeaxanthin, and the omega-3 fatty acids.
- Due to inconsistencies among the findings of currently available studies regarding doses and combinations of nutrients, it may be most practical to recommend specific natural diet choices rich in vitamins C and E, lutein and zeaxanthin, omega-3 fatty acids and zinc, which would also provide potential benefits from other components of these natural food sources.

Keywords Cataract • Macular degeneration • Eye disease • Retina

Introduction

Vision loss among the elderly is an important health problem. Approximately one person in three has some form of vision-reducing eye disease by the age of 65 [1]. Age-related cataract and age-related macular degeneration (AMD) are the major causes of visual impairment and blindness in the aging US population. Approximately 50 % of the 30–50 million cases of blindness worldwide result from unoperated cataracts [2, 3]. A clinically significant cataract is present in about 5 % of Caucasian Americans aged 52–64 years and rises to 46 % in those aged 75–85 years [4]. In the United States, cataract extraction accompanied by ocular lens implant is currently the most common surgical procedure done in Medicare beneficiaries [5]. Lens implantation is highly successful in restoring vision. However, the procedure is costly, accounting for 12 % of the Medicare budget and accounts for more than $3 billion in annual health expenditures [5, 6]. For these reasons, there is much interest in the prevention of cataract as an alternative to surgery.

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The prevalence of AMD also increases dramatically with age. Nearly 30 % of Americans over the age of 75 have early signs of AMD and 7 % have late stage disease, whereas the respective prevalence among people 43–54 years are 8 and 0.1 % [4]. Dry AMD is the most common form of AMD in its early or intermediate stages. It occurs in about 90 % of the people with the condition. Wet AMD is more severe than the early and intermediate stages of the dry form. Wet AMD occurs when abnormal blood vessels behind the retina start to grow under the macula. These new blood vessels can be fragile and leak blood and fluid. The blood and fluid cause the macula to swell and damage occurs rapidly. The damage may also cause scarring of the retina.

AMD is the leading cause of blindness among the elderly in industrialized countries. Because there are currently no effective treatment strategies for most patients with AMD, attention has focused on efforts to stop the progression of the disease or to prevent the damage leading to this condition [7].

Cataract and AMD share common modifiable risk factors, such as light exposure and smoking [7, 8]. Of particular interest is the possibility that nutritional counseling or intervention might reduce the incidence or retard the progression of these diseases. The components of the diet that may be important in the prevention of cataract and AMD are vitamins C and E, the carotenoids, lutein and zeaxanthin, the omega-3 polyunsaturated fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), and zinc.

Both vitamins C and E are found in the lens [9–11]. Omega-3 fatty acids, lutein, and zinc are highly concentrated in the eye [12–15]. Given that the lens and retina suffer oxidative damage, some of these nutrients are thought to be protective through their role as antioxidants. Vitamin E and carotenoids are lipid-soluble oxidant scavangers that protect biomembranes. Vitamin C is an important water-soluble antioxidant and also promotes the regeneration of vitamin E. Of the 20–30 carotenoids found in human blood and tissues [16], only lutein and zeaxanthin are found in the lens and retina [10, 17]. Lutein and zeaxanthin are concentrated in the macula or central region of the retina and are referred to as macular pigment. In addition to their role as antioxidants, lutein and zeaxanthin are believed to limit retinal oxidative damage by absorbing incoming blue light and/or quenching reactive oxygen species. Many putative risk-factors for AMD have been linked to a lack of macular pigment, including female gender, lens density, smoking, light iris color, obesity, and reduced visual sensitivity [7, 18]. Given that inflammation is also a component to the etiology of age-related eye disease [13, 19], the omega-3 fatty acids are thought to be protective. It has been suggested that atherosclerosis of the blood vessels that supply the retina contributes to the risk of AMD, analogous to the mechanism underlying coronary heart disease [20]. Long-chain omega-3 fatty acids may have a special role in the function of the retina in addition to their antithrombotic and hypolipidemic effects on the cardiovascular system. DHA is the omega-3 fatty acid of key interest. DHA is a major fatty acid found in the retina [21]. Rod outer segments of vertebrate retina have a high DHA content [21, 22]. Since photoreceptor outer segments are constantly being renewed, a constant supply of DHA may be required for proper retinal function and a marginal depletion may impair retinal function and influence the development of AMD.

Physiological Basis of Cataracts and AMD

The role of the lens is to transmit and focus light on the retina. Therefore, for optimal performance the lens must be transparent. The lens is an encapsulated organ without blood vessels or nerves (Fig. 4.1). The anterior hemisphere is covered by a single layer of epithelial cells containing subcellular organelles. At the lens equator the epithelial cells begin to elongate and differentiate to become fiber cells. Fully differentiated fiber cells have no organelles but are filled with proteins called crystallins, organized in a repeating lattice. The high density and repetitive spatial arrangement of crystallins produce a medium of nearly uniform refractive index with dimensions similar to light wavelengths [23].

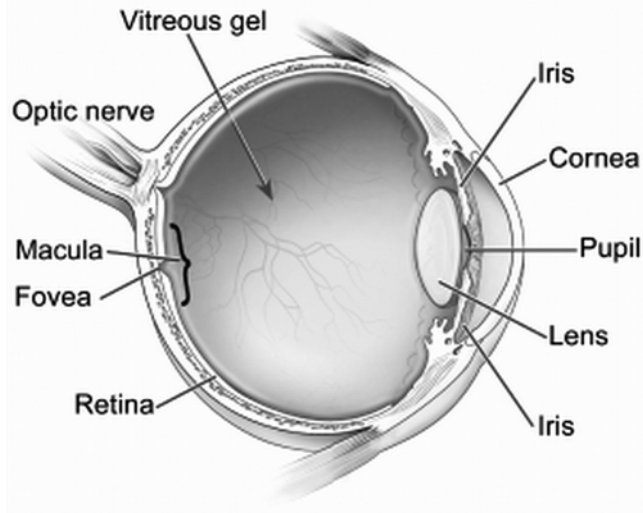

Fig. 4.1 The human eye showing typical organization and terminology. Courtesy of National Eye Institute, National Institute of Health

Cataracts result when certain events, e.g., light exposure, cause a loss of order and results in abrupt fluctuations in refractive index causing increased light scattering and loss in transparency in the lens. It is proposed that lens opacity results from damage to lens enzymes, proteins, and membranes by activated oxygen species, e.g., hydrogen peroxide, superoxide anion, and hydroxyl free radicals, which are the results of exposure to light and other types of radiation. There are three types of cataract, defined by their location in the lens. Nuclear cataract occurs in the center, or nucleus of the lens. Cortical cataract begins at the outer rim of the lens, which is referred to as the cortex, and progresses towards the center. Posterior subcapsular cataract (PSC) occurs in the central posterior cortex, just under the posterior capsule, the membrane that envelops the lens. Nuclear cataract is the most common type of cataract [1]. It interferes with a person's ability to see distant objects and is usually the result of advancing age. Cortical cataract is most commonly seen in patients who have diabetes. PSC can be present in younger individuals and progresses more rapidly resulting in glare and blurriness [24]. This type of cataract is usually seen in patients who use steroids, or who suffer from diabetes or extreme nearsightedness.

AMD is a disease affecting the central area of the retina (macula) (see Fig. 4.1) resulting in loss of central vision. In the early stages of the disease, lipid material (drusen) accumulates in deposits underneath the retinal pigment epithelium (RPE). This is believed to arise after failure of the RPE to perform its digestive function adequately and can be seen as pale yellow spots on the retina. The presence of a few small, hard drusen is normal with advancing age. However, the presence of indistinct, soft, larger, reticular, and more numerous drusen in the macula is a common early sign of AMD [25]. The pigment of the RPE may become disturbed with areas of hyperpigmentation and hypopigmentation. In the later stages of the disease, the RPE may atrophy completely. This loss can occur in small focal areas or can be widespread. In some cases, new blood vessels grow under the RPE and occasionally into the subretinal space (exudative or neovascular AMD). Hemorrhage can occur which often results in increased scarring of the retina. The early stages of AMD are in general asymptomatic. In the later stages there may be considerable distortion of vision and complete loss of visual function, particularly in the central area of vision [7]. Although the specific pathogenesis of AMD is still unknown, chemical and light-induced oxidative damage to the photoreceptors is thought to be important in the dysfunction of the RPE. The retina is particularly susceptible to oxidative stress because of its high consumption of oxygen, its high proportion of polyunsaturated fatty acids, and its exposure to visible light.

Currently, there is no treatment which can restore vision in AMD. Therefore, efforts have focused on its prevention or delay in progression.

Given the role of light damage in the etiology of cataracts and AMD, many antioxidant nutrients may prevent damage in the lens by reacting with free radicals produced in the process of light absorption as well as decrease oxidative stress in photoreceptors in the retina.

Epidemiological Studies on Dietary Intake and Blood Levels of Nutrients and Eye Disease

Studies with human subjects provide information on the strength of associations between nutritional factors and the frequency of a disease. Such studies can be a valuable means of identifying and evaluating risk factors. Although there are limitations to such studies, consistency of findings among studies lends credibility to the role that nutrition can play in age-related eye health.

Cataract

Vitamin C

Several studies have found a relationship between increased dietary vitamin C and decreased risk of cataract (Table 4.1). For example, it was observed that the prevalence of nuclear cataract was lower for men with total vitamin C intakes in the highest quintile category relative to the lowest intake quintile [26]. It has also been observed that the prevalence of cataract was about 75 % lower in persons with vitamin C intakes >490 mg/day than in those with intakes <125 mg/day [27]. Others have reported that vitamin C intake had no effect on cortical cataract, posterior subcapsular (PSC) and cataract extraction [26, 28–32].

Compared to diet, plasma concentrations of a nutrient are considered to be a better measure of nutrient status. There are many reports of an inverse relationship between plasma ascorbic acid concentrations and the prevalence of cataract [27, 33–36]. For example, the National Health and Nutrition Examination Survey II (NHANES II) correlated a 1 mg/dL increase in plasma ascorbate with a 26 % decreased risk of cataracts in older (62–70 years) Americans [33]. However, others have observed that plasma vitamin C concentrations were not associated with risk of nuclear or cortical cataract [30, 37]. Furthermore, the India-United States case control study of age-related cataracts found an increased prevalence of (PSC) and nuclear cataracts with increased plasma vitamin C concentrations [38]. In this study, however, when vitamin C status was combined with other indicators of antioxidant status (glutathione peroxidase, vitamin E, and glucose-6-phosphate dehydrogenase) the relationship became significantly protective (Table 4.2). This may reflect the synergistic actions of antioxidant systems.

Vitamin E

A protective effect of dietary vitamin E has been observed in several studies (Table 4.3). Persons in the highest quintile for vitamin E intake were reported to be 50 % less likely to undergo cataract extraction compared to those in the lowest quintile for vitamin E intake [31]. Mares-Perlman et al. [26] observed a lower prevalence of nuclear cataract in men in the highest quintile category of total vitamin E intake relative to those in the lowest vitamin E intake. Similarly, Leske et al. [39] reported that

Table 4.1 Summary of epidemiologic studies of dietary vitamin C[a] and cataract

Data analysis method	Result	Reference
Positive outcome		
Highest vs. lowest quintile (men, 104 vs. 33 mg/day)	Lower prevalence of cataract in highest quintile	Mares-Perlman et al. [26]
>490 mg/day vs. <125 mg/day	75 % lower prevalence of cataract with high intake	Jacques et al. [27]
Case-control	Lower dietary vit C in nuclear cataract	Leske et al. [39]
Highest vs. lowest quintile (767 vs. 101 mg/day)	45 % lower incidence of nuclear cataract	Tan et al. [32]
Null outcome		
Highest vs. lowest quintile (women, 171 vs. 34 mg/day)	No difference in prevalence of cataract between groups	Mares-Perlman et al. [26]
Highest vs. lowest quintile (705 vs. 70 mg/day) (women)	No difference in prevalence of cataract between groups	Hankinson et al. [29]
Highest vs. lowest quintile	No difference in prevalence of cataract extraction between groups	Tavani et al. [31]
Highest vs. lowest quartile (261.1 vs. 114.4 mg/day)	No difference in prevalence or nuclear or cortical cataract between groups	Vitale et al. [30]
Multiple logistic regression	No association of dietary vit C with nuclear or cortical cataract	Italian American Cataract Study Group [28]
Highest vs. lowest quintile (767 vs. 101 mg/day)	No difference in incidence of cortical and PSC cataract or cataract surgery	Tan et al. [32]

[a]RDA for adults: 60 mg/day

Table 4.2 Summary of epidemiologic studies of plasma vitamin C[a] and cataract

Data analysis method	Result	Reference
Positive outcome		
Multiple logistic regression	Serum vit C inversely associated with prevalence of cataract ($p=0.03$)	Simon et al. [33]
>90 vs. <40 µmol/L	Lower prevalence of cataract with high plasma levels	Jacques et al. [27]
Increase of 1 mg/mL plasma vitamin C	26 % decrease risk of cataracts	Valero et al. [34]
Case-control	Mean plasma vit C significantly lower in cataract patients than in controls (0.96 vs. 1.12 mg/dL, respectively)	Jalal et al. [36]
Highest vs. lowest tertile >15 vs. <6.3 µmol/L	Serum vit C inversely related risk of cataract	Dherani et al. [35]
Null outcome		
Highest vs. lowest quartile	Plasma vit C levels were not associated with risk of cortical or nuclear cataract	Vitale et al. [30]
Multivariate logistic regression	No relationship between plasma vit C and cataract	Ferrigno et al. [37]
Negative outcome		
	Higher prevalence of cataract with increased plasma vit C	Mohan et al. [38]

[a]Reference range: 23–125 µmol/L (Nutrition Evaluation Laboratory, Tufts University, 2001)

persons with vitamin E intakes in the highest quintile category had an approximately 40 % lower prevalence of cataract relative to persons with intakes in the lowest quintile category. Jacques and Chylack [27] found that although persons with vitamin E intake greater than 35.7 mg/day had a 55 % lower prevalence of cataract than did persons with intakes less than 8.4 mg/day, a significant difference was not found. Two other studies also reported no difference in cataract prevalence between persons with high and low vitamin E intake [26, 29]. In the first of these two studies, the null

Table 4.3 Summary of epidemiologic studies of dietary vitamin E[a] and cataract

Data analysis method	Result	Reference
Positive outcome		
Highest vs. lowest quintile	50 % lower cataract extraction in highest quintile	Tavani et al. [31]
Highest vs.	Lower prevalence of nuclear cataract	Mares-Perlman et al. [26]
Lowest quintile (men, 12.8 vs. 4.0 mg/day)	Cataract in highest quintile	
Highest vs. lowest quintile	40 % lower prevalence of cataract in highest quintile	Leske et al. [39]
Null outcome		
>35.7 mg/day vs. <8.4 mg/day	No difference between groups	Jacques et al. [27]
Highest vs. lowest quintile (women, 19.9 vs. 5 mg/day)	No difference between groups	Mares-Perlman et al. [26]
	No relationship between dietary vit E and cataract extraction in women	Hankinson et al. [29]

[a]RDA: 8 mg/day and 10 mg/day, women and men, respectively

relationship was in women only (in men, dietary vitamin E was protective). In the second study only women were studied.

Results from studies reporting relationships between plasma vitamin E and cataract have been mixed. In five of eight studies examining this issue, increased plasma vitamin E was observed to be protective against the risk of cataract [30, 40–43] (Table 4.4). However, one study observed that the prevalence of cataract was not related to plasma vitamin E concentrations [28] and one study observed that the prevalence of cortical cataract did not differ between those with high (>30 μmol/L) and low (<19 μmol/L) plasma vitamin E concentrations [30]. Mares-Perlman et al. reported a significantly increased prevalence of nuclear cataract among women and men in the highest serum vitamin E quintile relative to those in the lowest quintile. Several other studies have found increased levels of plasma alpha-tocopherol to be a risk factor for nuclear cataract [44], cortical [28, 37], and PSC cataracts [28]. These results are contrary to what would be expected. Because these are cross-sectional observational studies, there is the possibility that unadjusted confounding affected the findings.

Lutein and Zeaxanthin

The majority of the epidemiological data suggest that dietary lutein and zeaxanthin function in cataract prevention. The Melbourne Visual Impairment Study, an observational study of >3,000 over the age of 40 years, reported an inverse correlation between high lutein and zeaxanthin intake and the risk of nuclear cataracts [45].

Lower intake of lutein-rich foods, e.g., green leafy vegetables, was reported to be related to an increased rate of cataract extraction [29]. Similarly, it was observed that women in the highest quintile of lutein intake had a 27 % lower prevalence of nuclear cataract than those in the lowest lutein intake quintile [26]. In this study, this was not observed in men. In the Nurses' Health Study, those with the highest quintile of intake of lutein and zeaxanthin had a 22 % decreased risk of cataract surgery and nuclear cataract compared with those in the lowest quintile after adjusting for other risk factors [46]. The intake of other dietary carotenoids was not associated with nuclear cataract. Similar findings were observed in the US male Health Professional's prospective study, in which men in the highest fifth of lutein and zeaxanthin intake had a 19 % lower risk of cataract surgery relative to men in the lowest fifth. There was no relationship observed with the other carotenoids [47]. The Beaver Dam Eye Study found that the incidence of nuclear cataract in subjects in the highest quintile of lutein intake was half

Table 4.4 Summary of epidemiologic studies of plasma vitamin E[a] and cataract

Data analysis method	Result	Reference
Positive outcome		
Highest vs. lowest quartile	Decrease in cortical cataract progression in highest quintile	Rouhiainen et al. [42]
>30 µmol/L vs. <19 µmol/L	Less nuclear cataract in high plasma vit E group	Vitale et al. [30]
>20 µmol/L vs. <20 µmol/L	Higher plasma levels of vit E had one-half the amount of cataract surgery	Knekt et al. [40]
Highest vs. lowest quintile	Lower prevalence of nuclear cataract in highest quintile	Leske et al. [41]
Regression model	High plasma vit E related to decreased prevalence of nuclear cataract	Leske et al. [43]
Multivariate logistic regression	Plasma vit E significantly lower in patients with cataract than in controls (9.16 vs. 13.26 mg/mL, respectively)	Nourmohammadi et al. [113]
Null outcome		
>30 µmol/L vs. <19 µmol/L	No difference in cortical cataract progression	Vitale et al. [30]
Multivariate logistic regression	No relationship between plasma vit E and cataract	Italian-American Cataract Study Group [28]
Negative outcome		
Highest vs. lowest quintile men, 37.8 vs. 16.9 µmol/L women, 46.5 vs. 18.2 µmol/L	Increased prevalence of nuclear cataract in highest	Mares-Perlman [26]
Multivariate logistic regression	Higher plasma vit E associated with increase prevalence of cortical, PSC or any cataract	Ferrigno et al. [37]

[a]Reference range: 12.0–43.2 mol/L (Nutrition Evaluation Laboratory, Tufts University, 2001)

of that found in those in the lowest quintile [48]. Data from an observational study of 372 volunteers found that the risk of PSC cataract was lowest in those with the highest plasma concentrations of lutein [49]. There was no relationship between plasma lutein and zeaxanthin and cortical and PSC cataract. In a prospective observational study higher intakes of lutein and zeaxanthin from both food and supplements were significantly related to a 20 % decreased risk of cataract [50]. Delcourt et al. [51] observed a 75 % lower risk of nuclear cataracts among individuals with high plasma zeaxanthin, but not lutein, in a prospective study of 899 adults aged ≥60 years. A summary of studies evaluating the relationship between lutein and cataract is found in Table 4.5.

Omega-3 Fatty Acids

Cataract formation is associated with perturbations of lens membrane composition, structure, and function [52–54], as well as changes in fatty acid composition [55]. Studies in rats find that high intake of polyunsaturated fatty acids delays the cataract formation [56, 57]. High intakes of dietary omega-3 polyunsaturated fatty acids were shown to reduce the incidence of nuclear cataract in the Blue Mountains Eye Study cohort [58]. In a prospective study examining the relationship between dietary fat and cataract extraction in women ($n=71{,}083$, 16-years follow-up), women in the highest quintile of long-chain omega-3 fatty acids (0.21 % of energy) had a 12 % lower risk of cataract extraction compared to those in the lowest quintile (0.03 % of energy) (relative risk=0.88, 95 % CI: 0.79–0.98, p for trend=0.02) [59]. Both Arnarsson et al. [60] and Cumming et al. [61] report that there was no association between the intake of foods or oils containing omega-3 fatty acids and age-related cataract prevalence.

Table 4.5 Summary of epidemiologic studies of lutein/zeaxanthin status and cataract

Data analysis method	Result	Reference
Positive outcome		
Relationship with lutein/zeaxanthin intake	Inverse relationship with risk of nuclear cataract (nonsmoking women)	Vu et al. [45]
Consumption ≥5×/week vs. <1×/month spinach (women)	29 % decrease risk of cataract extraction	Hankinson et al. [29]
Highest vs. lowest quintile lutein/zeaxanthin intake (women)	27 % lower prevalence of nuclear cataract	Mares-Perlman et al. [26]
Highest vs. lowest quintile lutein/zeaxanthin intake (women)	22 % decrease risk of cataract extraction	Chasen-Taber et al. [46]
Highest vs. lowest quintile lutein/zeaxanthin intake (men)	19 % decrease risk of cataract extraction	Brown et al. [47]
Highest vs. lowest quintile lutein/zeaxanthin intake (women)	14 % decrease risk of incident cataract	Christen et al. [50]
Highest vs. lowest quintile lutein/zeaxanthin intake (1,245 vs. 298 μg/18 MJ)	Persons in the highest quintile were half as likely to have incident cataract as persons in the lowest quintile	Lyle et al. [48]
Logistic regression analysis of plasma carotenoids	Risk of posterior subcapsular cataract was lowest in those with higher concentrations of lutein	Gale et al. [49]
Relationship with serum carotenoids	75 % decreased risk of nuclear cataracts with increased serum zeaxanthin	Delcourt et al. [51]
Null outcome		
Risk estimated for tertiles 2 and 3 relative to tertile 1 using odds ratios	Serum lutein not associated with nuclear cataract	Lyle et al. [114]
Highest vs. lowest quintile lutein intake (men)	No difference in prevalence of nuclear cataract	Mares-Perlman et al. [26]

AMD

Vitamin C

Seddon et al. [62] observed that persons in the highest and lowest intake quintiles for vitamin C had the same prevalence of advanced AMD. No relationship between dietary intake of vitamin C and cataract risk was observed in the Age-Related Eye Disease Study [63]. However, in that study results examining relationships between plasma levels of vitamin C and AMD suggests that increased plasma vitamin C may decrease the risk of AMD. West et al. [64] reported that individuals with plasma vitamin C concentrations >80 μmol/L had a 45 % lower prevalence of AMD compared with individuals who had concentrations <60 μmol/L. Others have reported that individuals with serum vitamin C concentrations ≥91 μmol/L had a 30 % lower prevalence of neovascular AMD compared with those who had concentrations <40 μmol/L [65] (Table 4.6).

Vitamin E

A protective effect of increased diet and plasma vitamin E against AMD has been found in some [62, 64, 65], but not in others [44, 66] (Table 4.7).

Table 4.6 Summary of epidemiologic studies of dietary and plasma vitamin C[a] with AMD

Data analysis method	Result	Reference
Dietary vitamin C		
Highest vs. lowest quintile for vit C intake (1,039 vs. 65 mg/day)	No difference in prevalence of advanced AMD between groups	Seddon et al. [62]
Vit C intake energy adjusted, classified by quintiles. Relationship between diet and AMD assessed with logistic regression analyses.	Vit C intake not associated with AMD	AREDS [63]
Plasma vitamin C		
>80 μmol/L vs. <60 μmol/L	45 % lower prevalence of AMD in high plasma vit C group	West et al. [64]
>91 μmol/L vs. <40 μmol/L	Lower prevalence of neovascular AMD in high plasma vit C group	EDCCSG [65]

[a]RDA for adults: 60 mg/day. Reference range 23–125 μmol/L (Nutrition Evaluation Laboratory, Tufts University, 2001)

Table 4.7 Summary of epidemiologic studies of dietary and plasma vitamin E[a] with AMD

Data analysis method	Result	Reference
Dietary vitamin E		
Highest vs. lowest quintile for vit E intake (405 vs. 3.4 mg/day)	No difference in prevalence of advanced AMD between groups	Seddon et al. [62]
Plasma vitamin E		
>30 μmol/L vs. <19 μmol/L	Lower prevalence of AMD with high plasma vit E	West et al. [64]
>43 μmol/L vs. <25 μmol/L	Lower prevalence of AMD with high plasma vit E	EDCCSG [65]
>23 μmol/L vs. <23 μmol/L	No difference between groups in prevalence of AMD	Mares-Perlman J et al. [44]
Patients with AMD vs. age-, sex-matched controls	No difference in plasma concentration of vit E between groups	Sanders et al. [66]

[a]RDA: 8 mg/day and 10 mg/day, women and men, respectively. Reference range: 12.0–43.2 μmol/L (Nutrition Evaluation Laboratory, Tufts University)

Lutein and Zeaxanthin

Findings from several case control studies suggest that high intakes of carotenoids, particularly lutein and zeaxanthin, are related to lower risk of advanced neovascular AMD [62, 65, 67]. A relationship between carotenoid status and age-related eye disease risk was evaluated in the Carotenoids in Age-Related Eye Disease Study (CAREDS), a cross sectional study of 1,678 women (54–86 years) [68]. In CAREDS, high dietary lutein and zeaxanthin were related to a decreased risk of intermediate AMD in women <75 years, but not in women ≥75 years [68]. Similarly, the Blue Mountain Eye Study found that high intake of lutein/zeaxanthin was related to a reduced risk of incident neovascular AMD and indistinct soft or reticular drusen over 5 and 10 years [69]. In the Age-Related Eye Diseases (AREDS) study, lutein/zeaxanthin intake was associated with a decreased risk of prevalent neovascular AMD and large or extensive intermediate drusen when comparing the highest and lowest quintiles of intakes [63]. However, a nested case control study from the Beaver Dam Eye Study found no difference in serum levels of lutein/zeaxanthin between early AMD and age-, sex-, and smoking-matched controls [44].

Evidence that high macular pigment concentrations may lower the risk of AMD comes from analysis of retinas from donors with AMD and controls for lutein and zeaxanthin [70]. Concentrations of lutein and zeaxanthin in retinal tissue were less, on average, for the AMD donors than for the controls.

Table 4.8 Summary of studies of lutein/zeaxanthin status and AMD

Study design	Result	Reference
Positive outcome		
Case-control	Dietary lutein/zeaxanthin was significantly associated with a decreased risk for AMD	Seddon et al. [62]
Case-control	Risk of neovascular AMD decreased by half in the >20th to 80th percentile of lutein/zeaxanthin intake group compared to the low percentile group (≤20th percentile)	EDCCSG [65]
Case-control	Prevalence of AMD in subjects with low lutein intake was twice as high as that in subject with high intake	Snellen et al. [67]
Cross-sectional	Prevalence of intermediate AMD was not different between high and low lutein/zeaxanthin intake groups. Lower odds ratio in women <75 years at risk for diet changes compared to women >75 years	Moeller et al. [68]
Prospective	Subjects in the top tertile for dietary lutein/zeaxanthin were significantly less likely to develop neovascular AMD and indistinct soft drusen	Tan et al. [69]
Case-control	High lutein/zeaxanthin intake associated with lower odds of neovascular AMD, geographic atrophy and large or extensive intermediate drusen	AREDS [63]
Case-control	Higher quartile of retinal lutein/zeaxanthin associated with 82 % decreased risk of AMD compared to lowest quartile	Bone et al. [70]
Healthy eyes at risk for AMD healthy eye not at risk	Healthy eyes at risk had significantly less macular pigment	Beatty et al. [72]
Case-control	32 % lower macular pigment in AMD patients than in controls	Bernstein et al. [73]
Prospective	Higher macular pigment significantly related to decreased risk of late AMD	Schweitzer et al. [74]
Null outcome		
Case-control	No association between serum lutein/zeaxanthin and AMD risk	Mares-Perlman et al. [44]
Cross-sectional	Risk for AMD among women in the highest and lowest quintile for macular pigment not different	LaRowe et al. [75]

Macular pigment can be measured noninvasively in vivo [71]. In subjects (21–81 year) with healthy eyes and in healthy eyes of subjects at high-risk of AMD due to advanced disease in the fellow eye, at-risk eyes had significantly less macular pigment than eyes not at risk [72]. In another study, macular pigment in the eyes of AMD patients were 32 % lower in than that in healthy eyes [73]. In a prospective study in patients with early and late AMD, their children, and normal controls, it was found that macular pigment density was reduced in late AMD [74]. In contrast, in CAREDS, macular pigment density was not related to AMD [75]. Inconsistencies among studies may be due to the cross-sectional study design, suggesting that prospective studies are needed to determine if there is a relationship between AMD risk and macular pigment density. A summary of studies evaluating the relationship between lutein/zeaxanthin status and AMD risk is found in Table 4.8.

Omega-3 Fatty Acids

A meta-analysis, including nine prospective studies and three randomized clinical trials, reported that a high dietary intake of omega-3 fatty acids was associated with a 38 % reduction in the risk of late AMD [76]. Fish intake at least twice a week was associated with a 24 % reduced risk for early AMD and 33 % reduced risk for late AMD (pooled OR, 0.67; 95 % CI, 0.53–0.85). In a prospective

follow-up study of the Nurses' Health Study and the Health Professionals Follow-up Study, odds of AMD decreased with increased DHA intake. Consumption of >4 servings of fish per week was associated with a 35 % lower risk of AMD compared with ≤3 servings per month in pooled multivariate analysis [77]. Of the individual fish types examined, a significant inverse association was found only with tuna intake.

The Dietary Ancillary Study of the Eye Disease Case–Control Study [65] reported results for participants with neovascular AMD and control subjects without AMD [78]. In demographically adjusted analyses, increasing intake of linoleic acid (an unsaturated n-6 fatty acid) was significantly associated with higher prevalence of AMD (p for trend = 0.004). This association remained in multivariate analyses (p for trend = 0.02). However, intake of omega-3 fatty acids was not associated with AMD after controlling for confounding variables. When the study population was stratified by linoleic acid intake (≤5.5 or ≥5.6 g/day), the risk for AMD significantly decreased with high intake of omega-3 fatty acids only among those with low linoleic acid intake (p for trend = 0.05; p for continuous variable = 0.03). A prospective cohort study reported similar findings. In this study, 261 persons aged 60 years or older at baseline with an average follow-up of 4.6 years were evaluated for progression to late AMD. Higher fish intake was associated with a 64 % lower risk of progression to advanced AMD among subjects with lower linoleic acid intake [79]. Others have also observed a benefit of a high omega-3 fatty acid intake with low intake of linoleic acid [80]. These findings indicate an interaction or competition between omega-3 and omega-6 fatty acids such that both the levels of omega-3 fatty acids and its ratio to the n-6 acids may be important when considering the risk/benefit to AMD.

The Blue Mountain Eye Study was a population-based survey of vision, in which patients (≥49 years) were evaluated for AMD at baseline, 5 and 10 years after initial enrollment and energy-adjusted nutrient intakes were assessed for relationships with AMD risk [81]. In the 2,915 subjects, more frequent consumption of fish was related to a decreased risk of late AMD after adjusting for age, sex, and smoking. The protective effect of fish intake was observed at a relatively low consumption (1–3 times per month compared with intake <1 time per month (OR = 0.23, 95 % CI: 0.08–0.63 after adjusting for age, sex, and smoking). Although the OR was approximately 0.5 at higher intakes, this was not significant. There was little evidence of a decreased risk for early AMD with increased fish intake. A prospective cohort study from the AREDS trial found that increased intakes of omega-3 fatty acids reduced the risk by 30 % of developing central geographic atrophy and neovascular AMD [82].

In the Beaver Dam Eye Study, a retrospective population-based study, a relationship between fish intake, neovascular AMD, or geographic atrophy was not found. A null finding may be due to the observation that fish intakes were very low [83] and not varied enough to measure a difference in risk for AMD. In the NHANES III study, consuming fish more than once a week compared with once a month or less was not associated with either early or late AMD [84]. A summary of the studies that have evaluated the relationship between omega-3 fatty acids and AMD can be found in Table 4.9.

AREDS 2 clinical trial evaluated the benefit of 1 g eicosapentaenoic acid + DHA (2:1) on the progression to late AMD [85]. Addition of DHA + EPA to the AREDS formulation in primary analyses did not further reduce risk of progression to advanced AMD.

Zinc

In a study by Newsome et al. [85], zinc supplementation given to elderly people with early stages of AMD resulted in better maintenance of visual acuity than in those receiving placebo; scientific evidence that zinc intake is associated with the development or progression of AMD is limited. A recent study found zinc levels in the RPE and choroid to be reduced significantly by 24 % in AMD eyes compared to normal eyes, lending support to the possible importance of zinc in AMD [87].

Table 4.9 Multivariable odds ratios for neovascular AMD and late ARM and omega-3 fatty acid intake

Study	Sample design	Exposure (high vs. low)	Outcome	Cases	OR	95 % CI	Reference
NHS/HPFU	Prospective	LCPUFA	NV AMD	9	0.4	0.2–1.2	[77]
EDCCS	Case-control	LCPUFA	NV AMD	349	0.6	0.3–1.4	[78]
BDES	Population-based	Fish	Late ARM	30	0.8	0.2–1.5	[83]
NHANES	National Survey	Fish	Late ARM	9	0.4	0.2–1.2	[84]
BMES	Population-based	Fish	Late ARM	46	0.5	0.2–1.2	[81]
Seddon et al.	Prospective	Fish	Late AMD	261	0.4	0.1–0.95	[79]

Adapted from [13]

Abbreviations: *BDES* Beaver Dam Eye Study, *BMES* Blue Mountains Eye Study, *NHS/HPFU* Nurses' Health Study/Health Professionals Follow-Up, *NHANES* National Health and Nutrition Survey, *EDCCS* Eye Disease Case-control Study, *AREDS* Age-related Eye Disease Study, *Late ARM* biographic atrophy or neovascular age-related macular degeneration, *NV AMD* neovascular age-related macular degeneration

In the Blue Mountain Eye Study, the relative risk comparing the top decile of zinc intake (≥15.8 mg/day) with the remaining population was 0.56 (95 % CI, 0.32–0.97) for all forms of AMD and 0.54 (95 % CI, 0.30–0.97) for early AMD. However, in two large prospective studies (Nurses' Health Study and the Health Professionals Follow-up Study) involving men and women ($n=72{,}489$) with no diagnosis of AMD at baseline, zinc intake, either in food or in supplements, was not associated with a reduced risk of AMD [88]. Furthermore, no association was observed between zinc intake and prevalence of AMD-related drusen in the cohort of the Nurses' Health Study who also participated in the Nutrition and Vision project [89]. A protective effect of zinc is in contrast to the findings of high concentrations in sub RPE deposits, with levels being particularly high in eyes with AMD [14].

In summary, the studies examining dietary intakes of certain nutrients and eye disease relationships are not entirely consistent. Methodology differences among studies may, in part, explain the inconsistencies. Also, there are limitations to such studies that examine relationships between a nutrient and disease because calculations from dietary recall may not always accurately estimate nutrient intakes due to limitations of the database or recall abilities of the subjects. Furthermore, a single blood value for a nutrient may not always be an accurate indicator of long-term status. In addition, the high degree of correlation in intake among the various dietary micronutrients makes it difficult to determine which specific nutrient or nutrients are related to the observed relationships. Despite these drawbacks, a possible protective role of certain nutrients cannot be dismissed given the number of studies that found a protective effect and the comparatively fewer studies that found a negative effect. In some cases, it may be difficult to measure an outcome if nutrient intake levels are at those found in diet alone. That is, dietary and plasma levels may not be sufficiently high to see an effect. In this regard, review of studies that have examined the relationship between supplemental nutrient intake with cataract and AMD risk may be useful.

The Effect of Nutrient Supplements on Eye Disease Risk

Supplemental vitamins C and E have been long available to the general public. Currently, there are a variety of supplement products available in health food stores that contain lutein in amounts of 6–25 mg/capsule. At this point lutein can be found in a few multi-vitamin products. Centrum was the first multivitamin supplement with lutein and contains 250 μg per capsule. Alcon Laboratories and Bausch & Lomb have made available multivitamin supplements formulated for eye care. These products contain lutein in higher amounts.

Table 4.10 Summary of epidemiologic studies of supplemental vitamin C[a] and cataract

Data analysis method	Result	Reference
Positive outcome		
Usage ≥10 year vs. usage <10 year	Decrease in cataract in long-term users of vit C supplements	Jacques et al. [90]
Usage ≥10 year vs. usage <10 year	Decrease in cataract surgery with increased usage of vit C supplement	Hankinson et al. [29]
>300 mg/day vs. nonusers of vitamin C supplements	Lower prevalence of cataract in vit C supplement users	Robertson et al. [91]
Null outcome		
Usage ≥10 year vs. nonusers	No difference between groups	Chasen-Taber et al. [92]
Logistic regression analysis	No relationship between serum vit C and cortical and nuclear cataract	Vitale et al. [30]
Regression models	No relationship between vit C intake and cataract extraction	Tavani et al. [31]
Highest vs. lowest quintile for intake (705 vs. 70 mg/day)	No relationship between vit C intake and cataract extraction	Hankinson et al. [29]
Case-control	No relationship between vit C intake and cataract	Italian-American Cataract Study [28]
Negative outcome		
Usage 5–9 years vs. 1–4 years	Increase risk of cortical cataract	Gritz et al. [93]
1,000 mg/day vit C vs. multivitamin use	Increase risk of cataract	Rautianen et al. [94]

[a]RDA for adults: 60 mg/day

Cataract

Jacques et al. [90] observed a >75 % lower prevalence of early opacities in women who used vitamin C supplement for ≥10 years (Table 4.10). None of the 26 women who used vitamin C supplements for ≥10 years had more advanced nuclear cataract. Hankinson et al. [29] observed that women who reported use of vitamin C supplement for ≥10 years had a 45 % reduction in rate of cataract surgery. The study of Robertson et al. [91] observed that the prevalence of cataract in persons who consumed vitamin C supplement of >300 mg/day was approximately one-third the prevalence in persons who did not consume vitamin C supplements. However, Chasen-Tabar et al. [92] prospectively examined the association between vitamin supplement intake and the incidence of cataract extraction during 12 years of follow-up in a cohort of 73,956 female nurses. After adjusting for cataract risk factors, including cigarette smoking, body mass index, and diabetes mellitus, there was no difference in the incidence of cataract between users of vitamin C supplements for 10 years or more and nonusers. There was an increased risk of cortical cataract in older women (≥60 years) who consumed vitamin C supplements for 5–9 years compared to the those taking vitamin C for 1–4 years, ≥10 years and those who never used vitamin C supplements [93]. Similarly, in a population-based, prospective study involving 24,593 women (≥65 years), a significantly higher risk of cataract was observed in those consuming ~1,000 mg vitamin C supplements but not among those consuming a multivitamin, which contain much lower levels of vitamin C [94]. However, such relationship was not always observed [28–31].

Nadalin et al. [95] cross-sectionally examined the association between prior supplementation with vitamin E and early cataract changes in volunteers (Table 4.11). Of 1,111 participants 26 % reported prior supplementation with vitamin E. Only 8.8 % of these participants took supplementation greater than the recommended daily intake (10 mg/day). A statistically significant association was found between prior supplementation and the absence of cortical opacity, after adjusting for age. However, the levels of nuclear opacity were not statistically different between those who reported intake and those with no prior vitamin E supplementation. Leske et al. [43] examined the association of

Table 4.11 Summary of epidemiologic studies of supplemental vitamin E[a] and cataract

Data analysis method	Result	Reference
Positive outcome		
Vit E supplement users vs. nonusers	Decrease in cortical cataract in users of vit E supplements	Nadalin et al. [95]
Vit E supplements users vs. nonusers	Decrease in nuclear cataract in users	Leske et al. [41]
Vit E supplements users vs. nonusers	Decrease in cataract in users	Robertson et al. [91]
Null outcome		
Vit E supplement users vs. nonusers	No difference in nuclear cataract	Nadalin et al. [95]
Vit E supplement users vs. nonusers	No difference in prevalence of cataract between users and nonusers	Hankinson et al. [29]

[a]RDA: 810 mg/day and 10 mg/day, women and men, respectively

antioxidant nutrients and risk of nuclear opacification in a longitudinal study. The risk of nuclear opacification at follow-up was decreased in regular users of multivitamin supplements, vitamin E supplements, and in persons with higher plasma levels of vitamin E. The investigators concluded that in regular users of multivitamin supplements, the risk of nuclear opacification was reduced by one-third. They also reported that in regular users of vitamin E supplement and persons with higher plasma levels of vitamin E, the risk was reduced by approximately half. These results are confirmed by Robertson et al. [91] who reported that the prevalence of cataract was 56 % lower in persons who consumed vitamin E supplement than in persons not consuming supplements. One study observed no relation between risk of cataract and vitamin E supplements [29, 95].

To date, there are few data from intervention trials of vitamins and cataract risk. There has been only one randomized, double-masked, placebo controlled trial evaluating a vitamin E intervention and cataract prevention. Pharmacological doses of vitamin E (500 IU) for 4 years was reported to reduce the incidence or progression of nuclear, cortical, or PSC cataracts in subjects aged 55–80 years [96]. This may provide the best evidence for a role for vitamin E in cataract prevention.

It was reported that a high dose combination of antioxidants (vitamins C and E, beta-carotene, and zinc) had no significant effect on the development or progression of cataract [97]. The LINXIAN trial [98] examined the role of antioxidants in prevention of cataract, and effect is not clear. The intervention was a combination dose of 14 vitamins and 12 minerals. Therefore, a specific role of any one nutrient could not be accurately evaluated. The multivitamin component demonstrated that nutrition can modify the risk of nuclear cataract, but specific nutrients were not evaluated. Also, the population examined had suboptimal nutritional intakes at the study start and the effect may have been due to a correction of certain nutrient deficiencies.

The Roche European-American Anticataract Trial (REACT) was carried out to examine if a mixture of oral antioxidant micronutrients (beta-carotene, 18 mg/day; vitamin C, 750 mg/day; vitamin E, 600 mg/day) would modify the progression of age-related cataract [99]. This was a multi-center prospective double-masked randomized placebo-controlled 3-year trial in 445 patients with early age-related cataract. REACT demonstrated a statistically significant positive treatment effect after 2 years for US patients and for both subgroups (US, UK) after 3 years, but no effect for the UK patients alone. The conclusion from this study was that daily supplementation with these nutrients for 3 years produced a small deceleration in progression of age-related cataract.

AMD

A recent study reported that high levels of antioxidants and zinc significantly reduce the risk of AMD and its associated vision loss [97]. In the AREDS study it was found that people at high risk for developing advanced stages of AMD (people with intermediate AMD or advanced AMD in one eye but not the

Table 4.12 Summary of epidemiologic studies of supplement use and AMD

Data analysis method	Result	Reference
Positive outcome		
Vitamins C, E, β-carotene zinc, copper (AREDS formulation)	25 % decrease in risk for late AMD, in patients with intermediate or advanced AMD in one eye	Age-Related Eye Disease Study [97]
Zinc vs. placebo	Better visual acuity with zinc supplementation in patients with early AMD	Newsome et al. [86]
Zinc (50 mg/day, 6 months) vs. placebo	Improved macular function in dry AMD	Newsome et al. [106]
Vitamins C, E, β-carotene zinc, copper (AREDs formulation plus lutein (10 mg/day)) and zeaxanthin (2 mg/day)	Those with low dietary intake of lutein/zeaxanthin at the start of the study, but took AREDS formulation with lutein + zeaxanthin during, were ~25 % less likely to develop advanced AMD compared with those with similar dietary intake who did not take lutein and zeaxanthin	Age-Related Eye Disease Study [85]
Null outcome		
Vitamin C supplement users (>2 years) vs. nonusers	No difference between groups in AMD prevalence	EDCCSG [65]
Vitamin E supplement users (>2 years) vs. nonusers	No difference between groups in AMD prevalence	Seddon et al. [101]
Vitamin E (600 IU/day, 10 year) vs. placebo (women)	No effect on risk of AMD	Christen et al. [102]
Vitamin E (500 IU, 4 years) vs. placebo	No effect on risk of AMD	Taylor et al. [103]
Vitamin E (50 mg/day 5–8 years) vs. placebo	No effect on risk of AMD	Teikari et al. [104]

other eye) lowered their risk by about 25 % when treated with a high-dose combination of vitamins C and E, beta-carotene, and zinc. In the same high risk group the nutrients reduced the risk of vision loss caused by advance AMD by about 19 % [97] (Table 4.12). For those subjects who had either no AMD or early AMD, the nutrients did not provide a measured benefit. Because single nutrients were not evaluated, specific effects could not be determined. AREDS 2 aimed to refine the findings of AREDS by including the xanthophylls lutein and zeathanxin as well as omega-3 fatty acids into the test formulation [100]. In secondary analysis, lutein and zeaxanthin supplements on top of the AREDS supplement lowered the progression to advanced AMD in persons with low dietary lutein and zeaxanthin [85].

It has been reported that the prevalence of AMD in persons who consumed vitamin C supplement for >2 years was similar to those who never took vitamin C supplements [65] (see Table 4.12). In a study conducted by Seddon et al. [101] the prevalence of AMD was also similar between those who took vitamin E supplement for >2 years and those who never took vitamin E supplements. The results of three double-masked, placebo-controlled primary prevention studies involving high doses of vitamin E and AMD found that there was no association of treatment group with any sign of AMD [102–104]. The Alpha-Tocopherol, Beta-Carotene trial evaluated the effect of nutritional antioxidants on AMD. Overall there were 728 people randomized to any antioxidant (alpha-tocopherol and/or β-carotene) and 213 to placebo. The results of this study found that there was no association of treatment group with any sign of maculopathy. There were 216 cases of the disease in the antioxidant groups and 53 in the placebo group. The majority of these cases were early age-related maculopathy. There was no association with the treatment group and development of early stages of the disease. The findings are similar when each of the antioxidant groups—alpha-tocopherol, beta-carotene, alpha-tocopherol + beta-carotene—are compared with placebo. Although this was a large, high quality study there were few cases of late AMD (14 cases in total) which means that the study had limited power to address the question as to whether supplementation prevents late AMD. Furthermore, the 5–8-year intervention with alpha-tocopherol and/or beta-carotene may not have been a long enough intervention

period to assess a difference in the prevalence of late AMD. This study was conducted in Finnish male smokers and caution must be taken when extrapolating the findings to other geographical areas, to people in other age-groups, to women, and to nonsmokers. However, the incidence of AMD, particularly neovascular disease, is likely to be higher in smokers [105], which means that they provide a good population to demonstrate any potential protective effects of antioxidant supplementation.

As mentioned above, The AREDS 2 trial found that lutein and zeaxanthin supplements lowered the progression to advanced AMD in persons with low dietary lutein and zeaxanthin.

Zinc supplementation (100 mg zinc sulfate for 12–24 months) given to elderly people with early stages of AMD resulted in better maintenance of visual acuity than in those receiving placebo [86]. A more recent randomized, placebo-controlled study showed supplementation with 50 mg/day for 6 months of zinc monocysteine significantly improved macular function in persons with dry AMD [106]. However, patients with wet AMD in one eye had no positive effect on the other eye diagnosed with drusen after 200 mg/day zinc supplementation for 2 years [107].

In summary, of the studies that have examined nutrient supplement use vs. the risk of eye disease, it is difficult to determine if supplements provide any added protection against eye disease. The number of studies reporting a positive outcome, i.e., a decreased risk, was about the same as the number of null outcomes. Further, in a recent meta-analysis it was concluded that there is insufficient evidence to support the role of dietary antioxidants including the use of dietary antioxidant supplements for the primary prevention of AMD [108]. However, AREDS 1 and 2 strongly support the beneficial effects of supplementation with a combination of antioxidants on delaying the progression from intermediate to late AMD.

Clinical Recommendations/Treatment Guidelines

The inconsistencies among studies in terms of the amount of nutrient required for protection against eye disease makes it difficult to make specific recommendations for dietary intakes of these antioxidants. Therefore, it may be more practical to recommend specific food choices rich in vitamins C and E, lutein and zeaxanthin, omega-3 fatty acids and zinc, thereby benefiting from possible effects of the components in food that may also be important. This necessitates an awareness of dietary sources of nutritional antioxidants for both the patient and clinician. Good sources of vitamin C include citrus fruit, berries, tomatoes, and broccoli (Table 4.13). Good sources of vitamin E are vegetable oils, wheat germ, whole grain cereals, nuts, and legumes (Table 4.14). The two foods that were found to have the highest amount of lutein and zeaxanthin are kale and spinach (Table 4.15). Other major sources include broccoli, peas, and brussels sprouts. Fish oils are the primary source of omega-3 fatty acids (Table 4.16)

A healthy diet including a variety of fresh fruit and vegetables, legumes, fish, and nuts, will have many benefits, will not do any harm, and will be a good source of the antioxidant vitamins and minerals implicated (but not proven) in the etiology of cataract and age-related macular degeneration. There is no evidence that nutrient-dense diets high in these foods, which provide known and unknown antioxidant components, are harmful. In fact, intake of fruits and vegetables is associated with reduced risk of death due to cancer, cardiovascular disease, and all causes [109]. Thus, recommendations such as consuming a more nutrient-dense diet, i.e., lower in sweets and fats, and increasing levels of fruit and vegetable intake do not appear to be harmful and may have other benefits despite their unproven efficacy in preventing or slowing disease. Until the efficacy and safety of taking supplements containing nutrients can be determined, current dietary recommendations [110] are advised.

In addition to antioxidant vitamins, patients ask about a wide variety of unproven and often untested nutritional supplements. These include bilberries, shark cartilage, and Ginko biloba extract. Unfortunately, little is known about the effect of these products on cataract or AMD: no clinical trials

Table 4.13 Vitamin C content of foods[a]

Food	Amount	Milligrams
Orange juice	1 cup	12
Green peppers	1/2 cup	96
Grapefruit juice	1 cup	94
Papaya	1/2 med	94
Brussels sprouts	4 sprouts	73
Broccoli, raw	1/2 cup	70
Orange	1 medium	70
Cantaloupe	1/4 melon	70
Turnip greens, cooked	1/2 cup	50
Cauliflower	1/2 cup	45
Strawberries	1/2 cup	42
Grapefruit	1/2 medium	41
Tomato juice	1 cup	39
Potato, boiled with peel	2 1/2″ diam.	19
Cabbage, raw, chopped	1/2 cup	15
Blackberries	1/2 cup	15
Spinach, raw, chopped	1/2 cup	14
Blueberries	1/2 cup	9

Table created with data from [115]
[a]Edible portion

Table 4.14 Vitamin E content of foods[a]

Food	Amount	Milligrams (alpha-tocopherol equivalents)
Wheat germ oil	1 tb	26.2
Sunflower seeds	1/4 cup	16.0
Almonds	1/4 cup	14.0
Safflower oil	1 tb	4.7
Peanuts	1/4 cup	4.2
Corn oil	1 tb	2.9
Peanut butter	2 tb	4.0
Soybean oil	1 tb	2.0
Pecan, halves	1/4 cup	2.0

Table created with data from [115]
[a]Edible portion

Table 4.15 Lutein/zeaxanthin content of foods[a]

Food	Amount	Milligrams
Kale, cooked	1/2 cup	8.7
Spinach, raw	1/2 cup	6.6
Spinach, cooked	1/2 cup	6.3
Broccoli, cooked	1/2 cup	2.0
Corn, sweet, cooked	1/2 cup	1.5
Peas, green, cooked	1/2 cup	1.1
Brussels sprouts, cooked	1/2 cup	0.9
Lettuce, raw	1/2 cup	0.7

Table created with data from [116]
[a]Edible portion

Table 4.16 EPA + DHA content in fish

Fish	EPA + DHA, g/3-oz (85 g) serving (edible portion)
Trout	
Farmed	0.15
Wild	0.20
Crab, Alaskan King	0.35
Flounder/sole	0.42
Haddock	0.20
Halibut	0.40–1.00
Herring	
Atlantic	1.71
Pacific	1.81
Mackerel	0.34–1.57
Salmon	
Atlantic, farmed	1.09–1.83
Atlantic, wild	0.90–1.56
Chinook	1.48
Sockeye	0.68
Sardines	0.98–1.70
Shrimp, mixed species	0.27
Tuna	
Fresh	0.24–1.28
White, canned in water, drained	0.73

Created with data from [117]

have been conducted. Patients with eye disease who are offered these often expensive and sometimes risky treatments are given little information as to their benefit or risk. Patients should be advised to avoid unproven treatments.

Conclusion

The hypothesis that antioxidant nutrients may protect against the cataract and AMD is a plausable one given the role of oxidative damage in the etiology of these diseases. It is not known at what stage the protective effect may be important. The question that needs to be addressed is whether people who begin to consume antioxidant vitamins in their 60s and 70s alter their risk of age-related macular degeneration. Although data regarding the use of nutrient supplements suggest protection in cataract, the data are less convincing for AMD. The research to date has not sufficiently evaluated the effectiveness vs. safety of nutrient supplements. But advocating the use of nutrient supplementation must be done with a cautionary note given that there have been trials which have suggested that supplementation with beta-carotene may have an adverse effect on the incidence of lung cancer in smokers and workers exposed to asbestos [111, 112]. Clearly further trials are warranted to address the usefulness of nutrient supplementation in eye disease prevention.

It is likely that cataract and AMD develops over many years and the etiology of these diseases is due to many factors. There are likely to be differences in the potential protective effect of antioxidant supplementation depending on the stage of the disease. Future research needs to take into account the stage at which oxidative damage, and therefore antioxidant supplementation, may be important.

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Chapter 5
Nutrition and Oral Health: A Two-Way Relationship

Cristina Palacios and Kaumudi J. Joshipura

Key Points

- Tooth loss reduces the ability to consume a more varied diet and increases systemic disease risk.
- The consumption of fermentable carbohydrates, along with increased use of xerogenic medications, places older adults at high risk for dental caries.
- Recent studies suggest an important role for calcium, vitamin D, and possibly vitamin C in reducing periodontitis risk.
- Diets high in fruits and vegetables have consistently been shown to reduce oral cancer risk.
- Tooth loss is associated with increased tendency among older adults to consume poorer quality diets, which in turn could increase cardiovascular risk.

Keywords Edentulism • Dental caries • Periodontitis • Oral cancer • Nutrients • Dietary patterns • Foods

Introduction: Oral Health Status in Older Adults

Oral health contributes greatly to quality of life in older adults. Poor oral health can hinder a person's ability to sustain a satisfying diet, participate in interpersonal relationships, and maintain a positive self-image [1–3]. Oral health problems may lead to chronic pain, discomfort, and alterations in diet that may adversely impact systemic disease.

Dental caries and chronic periodontitis are by far the most common oral diseases in the elderly [4]. These two diseases are the major causes of tooth loss and thus the major cause of dental morbidity. Caries, periodontal disease, and tooth loss still continue to be significant public health problems in the United States. Other oral diseases or conditions are relatively rare, of lesser importance from a public

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health perspective, and less related to nutrition, even though they may predominantly affect the elderly (e.g., denture stomatitis and other soft-tissue lesions). We will therefore focus on dental caries, chronic periodontitis, and tooth loss as the most common oral health problems in the elderly. In addition, we will also discuss oral cancer, which although rare, is often fatal and thus of high public health importance.

Common Oral Conditions in Older Adults

Dental Caries

Among dentate adults aged 60 years or older, 93 % had caries experience, which was higher among whites (93.3 %) compared to blacks (84.6 %) and Mexican Americans in 1999–2002 (83.5 %) [4]. In addition, 18.6 % had untreated tooth decay and there was a mean of 9.1 decayed and filled permanent teeth. A more recent statistic shows that almost 20 % of dentate adults 65 years of age or older had at least one tooth with untreated tooth decay in 2005–2008 [5]. On average, these seniors had about 18 decayed, missing, or filled teeth.

Root Caries

Root caries is also an important problem in older adults. Data from the National Health and Nutritional Examination Survey (NHANES) 1988–1994 and 1999–2002 shows that the prevalence of root caries is 31.6 % among those aged >60 years [4]. Overall, the prevalence of untreated root caries decreased in this age group (from 20 to 12.8 %). In addition, approximately 22 % of those aged >60 years had one or more filled roots (restored), which is higher compared to those aged 40–59 years (8.0 %) and those aged 20–39 years (1.7 %).

Periodontal Disease

Data from NHANES 2009–2010 show that the prevalence of periodontitis was 47 % in adults aged 30 years and older; and in those aged 65 years and older, 64 % had either moderate or severe periodontitis [6]. Furthermore, this report also shows that periodontitis was highest among men, Mexican Americans, current smokers and among those with less than a high school education and below 100 % of Federal Poverty Levels.

Tooth Loss

In 2009–2010, 15 % of adults aged 65–74 and 23 % of seniors aged 65 and over were edentulous (i.e., had lost all their natural teeth) [5]. The good news is that data from several representative health surveys in the United States clearly demonstrate a steady decline in the prevalence of edentulism, caries, and periodontitis over the past several decades beginning in the 1960s. However, not all segments of the population have benefited equally from this trend and tremendous heterogeneity and disparities exist between socioeconomic and racial/ethnic groups. For example, more non-Hispanic black adults aged 65 and over were edentulous (32 %) compared with non-Hispanic white adults (22 %), whereas only 16 % of Mexican-American adults had complete tooth loss [5]. Also, data from the National Health Interview Surveys from 1999 to 2008 shows that there was a significant reduction in edentulism rates between these years, with the highest rate among Native Americans (24 %), followed by African Americans (19 %), Caucasians (17 %), Asians (14 %), and Hispanics (14 %) [7].

Also, the prevalence of complete edentulism was more than twice as high for those living at or below 100 % of the federal poverty level (34 %), compared to those above this level (13 %) among adults aged 65–74 years but not among those aged 75 and over.

In summary, dental caries and periodontitis remain highly prevalent in the elderly. Although in most industrialized countries the prevalence of caries has declined over the past decades, dental caries and periodontitis and the associated tooth loss continue to be major public health problems.

Oral Cancer

The most serious and potentially fatal oral condition among older adults is oral cancer. By far the most common form of malignant oral cancer is squamous cell carcinoma. Squamous cell carcinoma of the oral cavity (including the gums, tongue and floor of mouth and other oral cavity), the oropharynx, hypopharynx, and larynx is frequently called "head and neck squamous cell carcinoma" or "head and neck cancer."

More than 7,800 people, mostly older Americans, die from oral and pharyngeal cancers each year [8]. In 2007, there were 34,360 newly diagnosed cases of oral and pharyngeal cancers (24,180 in males, 10,180 in females) and 7,550 oral and pharyngeal cancer deaths (5,180 males, 2,370 females) in the United States [8]. This increased in 2012 to 40,250 newly diagnosed cases of oral (28,540 in males, 11,710 in females) and 7,850 oral and pharyngeal cancer deaths (5,440 in males and 2,410 in females) [9]. In 2009, the oral cancer incidence increased from 10.5 cases per 100,000 individuals in 2000–2004 to 10.9 cases, with increasing rates in men (16.1/100,000) and in women (6.2/100,000) [10]. However, this report also showed that mortality from oral and pharyngeal cancer decreased to 2.4/100,000 individuals compared to 2000–2004 (males: 3.7/100,000; females: 1.3/100,000). Oral and pharyngeal cancer incidence and mortality are the highest among persons 65 years and older. In 2005–2009, the age-standardized incidence rate for this age group was 39.7/100,000 (males: 59.6/100,000, females: 24.9/100,000) and the mortality rate was 11.8/100,000 (males: 17.7/100,000, females: 7.4/100,000).

There are major racial/ethnic disparities in oral cancer incidence and particularly in oral cancer mortality and survival. For example, mortality rates per 100,000 were 5.7 and 1.4 for Black males and females, compared to 3.6 and 1.4 for White males and females, respectively [10]. The 5-year survival rate for oral and pharyngeal cancer diagnosis slightly improved from 60.4 % in 1999–2001 to 64.6 % in 2002–2008. This improvement was observed in Whites (55 % in 1975–1977 to 66.5 % in 2002–2008), as in African Americans (36.1 % in 1975–1977 to 45.2 % in 2002–2008). Although the oral cavity and pharynx are easily accessible for inspection, only 33 % of oral and pharyngeal cancers are diagnosed in a localized stage (35 % among Whites, 21 % among Blacks). The 5-year relative survival rate is highly dependent on stage of diagnosis. More than 80 % of patients with localized disease survive 5 years, compared to 57.3 and 34.9 % with regional and distant metastases, respectively. However, even if diagnosed at the same stage, Blacks have lower 5-year relative survival rates than Whites.

Impact of Nutritional Status on Oral Health

Plaque and Calculus Formation

Bacteria in the mouth, or oral flora, form a complex community or biofilm that adheres to teeth and is called plaque. These bacteria ferment sugars and carbohydrates and generate acid, which can in turn dissolve minerals in tooth enamel and dentin and lead to dental caries. Furthermore, bacterial products and components elicit an inflammatory immune response in the gingival epithelium and underlying

connective tissues (gingivitis) that may lead to periodontitis in susceptible individuals. Although the presence of plaque itself is not sufficient to cause either caries or periodontitis, the current understanding of the pathogenesis views bacterial plaque as a necessary cause for both diseases. Hence, oral hygiene measures that aim to remove or reduce bacterial plaque are a key strategy for the prevention of both caries and periodontitis.

Plaque can be present in subjects who do not consume carbohydrates, but is more prolific and produces more acid in individuals who eat sucrose-rich food. Frequency of carbohydrate consumption, physical characteristics of food (e.g., softness and stickiness), and timing of food intake all contribute to plaque formation and composition [11]. Plaque on tooth surfaces mineralizes to form calculus or tartar, which is often covered by unmineralized biofilm [12]. Hence, dietary factors are important determinants of plaque quantity and quality and are therefore important in the pathogenesis of dental disease, in particular dental caries (see below).

Dental Caries

Dental caries are characterized by the demineralization of dental hard tissues (enamel and dentin) by acids produced by plaque bacteria. Many factors that influence the quantity and timing of bacterial acid production ultimately determine the risk of caries. Here, diet plays an important role in caries occurrence and progression. Foods containing fermentable carbohydrates result in acid production by cariogenic plaque bacteria. The production of organic acids by sugar metabolizing bacteria then leads to significant decreases in plaque pH. If plaque pH falls below 5.5 for an appreciable period of time, demineralization of dental enamel occurs. As the plaque pH varies according to the availability of fermentable carbohydrates to plaque bacteria, de-mineralization and remineralization processes occur in a dynamic process. Factors other than diet that affect this dynamic process include, for example, the fluoride concentration. If de-mineralization is not compensated by remineralization, a breakdown of the enamel surface and formation of a cavity that can extend through the dentin (the part of the tooth located under the enamel) to the pulp tissue will result.

Because of the complexity of the demineralization/remineralization processes, the effects of fermentable sugars and other carbohydrates are not just determined by their amount. Most importantly, the frequency of sugar intake (e.g., eating sweets with main meals or as snacks at multiple occasions between meals) has been clearly shown to be a major determinant of caries risk [13]. Consumption of soft drinks containing sugar is also related to increased caries prevalence and incidence [14].

Furthermore, the effect of dietary intake of sugars or other carbohydrates is modified by other factors, primarily fluoride intake and oral hygiene. Fluorides (e.g., in toothpastes) have become highly abundant over the past decades and dietary factors may be less important in subjects with good oral hygiene and regular fluoride exposure [15]. Artificial sweeteners such as aspartame and saccharin and sugar alcohols such as sorbitol, mannitol, and xylitol were shown to be non-cariogenic in clinical trials [16]. Chewing sugar-free gum with added xylitol or sorbitol has been shown in clinical trials to be effective in reducing caries [17], although this caries-preventive effect of chewing gums with sugar alcohol could be related to stimulation of the salivary flow. Indeed, saliva also contains components that can directly attack cariogenic bacteria and contains calcium and phosphates that help remineralize tooth enamel.

Studies have also found the consumption of dairy products is non-cariogenic. A high yogurt intake was significantly associated with a lower prevalence of dental caries consumption compared with low yogurt consumption in Japanese children [18]. In addition, cheese consumption was inversely associated with caries experience in children from Spain [19]. A longitudinal study in 600 Japanese aged 70 years or more also found that intake of milk and other dairy products was protective of root caries [20].

Chronic Periodontitis

Bacterial plaque is considered a necessary cause of periodontitis, as bacterial components and products elicit an inflammatory response in the periodontal host tissues. In susceptible individuals, this inflammatory response leads to the resorption of periodontal ligament and alveolar bone. Susceptibility to periodontitis is determined by environmental and genetic host factors. For example, smoking and diabetes are established as major risk factors for periodontitis and tooth loss [21, 22]. Genetic risk factors that increase periodontitis susceptibility have been proposed, although to date data on specific genetic factors remain equivocal [23, 24], except for vitamin D receptor (VDR) polymorphism (discussed later in the chapter).

Diet and nutrients could affect periodontitis risk by influencing plaque quality and quantity, but may also, and perhaps more importantly, affect the inflammatory response and thus affect periodontitis susceptibility. It is important to note that research in the nutritional determinants of periodontitis risk is scant and most of the currently available data are from cross-sectional surveys, particularly from the NHANES III. In NHANES III, inverse associations between the intake of calcium [25, 26] and dairy products [26]—which is highly correlated with calcium intakes in the United States—and periodontitis prevalence have been reported. In addition, a study in more than 900 Japanese found that an increased intake of lactic acid foods (yogurt and lactic acid drinks or fermented milk, also known as kefir) was associated significantly with lower periodontal disease [27]. An intake of 55 g or more of lactic acid significantly lower the prevalence of deep probing depth and severe clinical attachment loss compared to those not eating these foods, after adjusting for confounding variables. More recently, a study in older Danish adults showed that intakes of dairy foods, milk, and fermented foods were significantly associated with a reduction of periodontitis risk ($p<0.05$), but cheese and other dairy foods intakes were not associated after adjusting for confounding variables [28]. Krall et al. have reported a beneficial effect of calcium and vitamin D supplementation on tooth retention [29] in a small cross-sectional study. Vitamin D status is associated with bone mineral density [30] and a recent meta-analysis showed that vitamin D supplementation is effective in preventing bone loss and fractures, particularly in doses greater than 800 IU/day and combined with calcium supplementation [31]. Because osteoporosis has been proposed as a risk factor for periodontitis, we studied the association between vitamin D status and periodontitis and found lower periodontitis prevalence among subjects older than 50 years of age with higher serum 25(OH)D levels [32]. In a recent publication among 42,730 participants of the Health Professionals Follow-Up Study, the highest quintile of the predicted 25(OH)D score (which is derived from variables known to influence 25(OH)D levels) was associated with a 20 % lower incidence of tooth loss (risk = 0.80, 95 % CI: 0.76–0.85) and 20 % lower incidence of periodontitis (risk = 0.80; 95 % CI: 0.71–0.90) compared to the lowest quintile [33]. In addition to its established effect on calcium metabolism and bone, vitamin D also has immuno-modulatory functions by which it may reduce periodontitis susceptibility. This hypothesis is consistent with the finding of a strong inverse association between vitamin D status and gingivitis (a precursor of periodontitis not affected by osteoporosis) prevalence [34]. If vitamin D status is truly a risk factor for periodontitis, these findings could have significant public health implications as hypovitaminosis D is highly prevalent in the United States and elsewhere [35], particularly in individuals who are overweight/obese have lower milk intake and/or have less sun protection [36].

Interestingly, VDR polymorphisms are among the genetic factors implicated as putative risk factors for periodontitis. A meta-analysis exploring the association between VDR polymorphisms (Taq-I, Bsm-I, Apa-I, and Fok-I) and periodontitis found that in Asians, chronic periodontitis cases had a significantly lower frequency of bb genotype of BsmI but higher frequency of AA genotype of ApaI with no associations with the other variants or with the aggressive form of the disease [37]. A more recent meta-analysis found that Taq-I variants could be protective of chronic periodontitis, while Fok-I locus could be a risk factor of aggressive periodontitis in Asians, but not in whites [38].

However, intervention studies will be necessary to evaluate if vitamin D supplementation is effective for periodontitis prevention. Up to date, there are no clinical trials examining this. A small cross-sectional study in 51 subjects receiving periodontal maintenance therapy found that those taking calcium (≥1,000 mg/day) and vitamin D (≥400 IU/day) supplements had a better periodontal health compared to those not taking supplements [39]. A 1-year follow-up showed that those still taking the supplements had a modest positive effect on periodontal health compared to those not taking the supplements [40].

Given our increasing understanding of the role of immune function and inflammatory response in periodontitis, it is likely that immune-modulating nutrients, such as some antioxidants and omega 3 fatty acids could alter the inflammatory process in periodontitis. Deficiencies of ascorbate have been associated with severity of gingivitis [41]. Furthermore, NHANES III data demonstrate an inverse association between vitamin C intakes and periodontitis prevalence in the United States [42]. Serum levels of vitamin C have been shown to be strongly associated with periodontitis prevalence, which was also confirmed among never smokers [43]. A retrospective cohort study in community-dwelling older Japanese found that a higher intake of dietary antioxidants (vitamin C, E, and β-carotene) was inversely associated with the number of teeth with periodontal disease progression, controlling for other variables [44]. The carotenoids beta-cryptoxanthin and beta-carotene [45], and omega 3 fatty acids [46], particularly docosahexaenoic acid [47], could also alter the inflammatory process in periodontitis. Interestingly, Merchant et al. reported an inverse association between whole-grain intake and risk of self-reported periodontitis incidence in a large cohort of male U.S. health professionals [48]. Men in the highest quintile of whole-grain intake were 23 % less likely to develop periodontitis.

Associations between obesity and periodontitis have been noted in several cross-sectional studies [49, 50] and in a longitudinal study [51]. More recently, a meta-analysis found a 35 % greater risk of periodontal disease in obese individuals, with some evidence of a stronger association found among younger adults, women, and nonsmokers [52]. The Risk of periodontal disease was found to be significantly greater in men with high BMI (≥30 kg/m^2) when compared to men with BMI in the normal weight range (18.5–24.9 kg/m^2; HR = 1.30; 95 % CI: 1.17–1.45) [53]. Increased WC and WHR were highly associated with a greater risk of periodontal disease (HR for extreme quintiles: WC = 1.27, 95 % CI: 1.11–1.46; WHR = 1.34, 95 % CI: 1.17–1.54). In addition, a higher mean body mass index (BMI) was found among periodontal patients and a greater mean clinical attachment loss was found among obese individuals. Given that adipose tissue serve as a reservoir for inflammatory cytokines, it is possible that increasing body fat increases the likelihood of an active host inflammatory response in periodontitis. This was recently evidenced in a study in 893 men followed for 40 years, whereas those overweight at baseline with the highest rapid weight gain follow-up (>0.19 kg/year) had significantly more probing pocket depth (PPD) events than those in the lowest tertile of weight gain (≤−0.05 kg/year) [54]. In addition, this study found that an increase in waist circumference (WC) in overweight men led to more PPD events than those with little change in WC. Furthermore, BMI and WC-to-height ratio were significantly associated with periodontal disease progression regardless of periodontal disease indicator.

Oral Cancer

Oral cancer is generally preceded by precancerous lesions, which include oral epithelial dysplasia, erythroplakia, leukoplakia, lichen planus, and submucous fibrosis (rare in Western countries). The major risk factors for oral cancer are tobacco and alcohol use. In Asian countries chewing tobacco, beetle nut, and beetle quid are major risk factors. Chewing tobacco use is also increasing in the United States. The relation between nutrition and oral cancer, and the impact of oral cancer on the patient's ability to eat and swallow are discussed below.

Fruits and Vegetables

Fruits and vegetables are rich in many nutrients, including fiber, vitamin C, vitamin E, folate, carotenoids, phenolics, isoflavonoids, isothiocyanates, and indoles, among others. The consumption of these foods has been shown in many studies to be protective of chronic disease, including cancer. A consistent finding across numerous studies is that a diet high in fruits and vegetables is protective against oral pre-cancer [55–57] and cancer [58, 59]. A review of six cohort studies and about 40 case–control studies found a relative risk for high vegetable and fruit consumption of 0.65 (95 % CI: 0.53–0.80) and 0.78 (95 % CI: 0.64–0.95) from three cohort studies on upper aerodigestive tract cancers and 0.52 (95 % CI: 0.45–0.61) and 0.55 (95 % CI: 0.47–0.65) from 18 case–control studies of oral and pharyngeal cancer, respectively [60]. In addition, a generous consumption of fruits is associated with a 20–80 % reduced risk of oral cancer even when smoking and alcohol intake and other factors including total caloric intake are taken into account. Furthermore, a high fruit and vegetable diversity has also been shown to be protective of oral cancer.

However, not all studies show a protective effect of fruits and vegetables in reducing cancer risk [61]. The inconsistencies may be explained by variation in specific vegetables and fruits consumed, as there are differences in the ability between these foods to suppress carcinogenesis. Allium vegetables (such as onions and garlic), carrots, green and leafy vegetables, cruciferous vegetables, and tomatoes, have been shown to be fairly consistently oral cancer protective [60, 62]. In particular, cruciferous vegetables, such as broccoli, cabbage, cauliflower, kale, and mustard, which are rich in carotenoids, vitamin C, folate, soluble fiber, and glucosinolate, also have potent anti-carcinogenic activity. A large Japanese study and the Iowa Women's Health Study also found that a high consumption of green and yellow vegetables decrease oral cavity and pharynx cancer risks [63, 64]. Tomato also shows a strong and consistent inverse association for oral cancer in 12 of 15 studies [65] and in one study on leukoplakia [57]. Citrus fruits have also been shown to have beneficial effect on oral and pharyngeal cancer risk [60].

Also, there is more evidence of an anti-carcinogenic effect of raw vegetables compared to cooked vegetables [66, 67], particularly raw and green/leafy vegetables. Raw tomatoes were more associated with reduce risk of oral cancer than cooked tomatoes [65]. This difference between raw and cooked vegetables could be related to changes that occur during cooking, such as loss of some nutrients, destruction of digestive enzymes, and changes in the structure and digestibility of the food [66]. Studies that have evaluated subgroups have generally found higher beneficial effects of fruits and vegetables and their constituent micronutrients among smokers and drinkers than among abstainers [68].

Anti-oxidants and Other Micronutrients

Several nutrients found in vegetables and fruits show an inverse association with oral cancer. These include vitamin A, vitamin B_{12}, vitamin C, tocopherol (vitamin E), retinoids, carotenoids, lycopene, beta-carotene, folate, glutathione, thiamin, vitamin B_6, niacin, lutein, and flavonoids have been inversely associated with oral cancer [58] and pre-cancer [57, 69, 70] in one or more studies.

Vitamin C, in particular, has been shown to reduce the risk of oral premalignant lesions, but only from dietary sources, not from supplements in an analysis of the Health Professionals Follow-up Study in 42,340 men [71]. However, a recent pooled analysis of 12 case–control studies of head and neck cancer (7,002 cases and 8,383 controls) did find a decreased risk with the ever use of vitamin C, particularly if used for 10 or more years [72].

Retinoids and beta-carotene in controlled therapeutic doses show protective effects, with fewer new primary tumors in persons with previous oral cancers and reversals or reduction in size of premalignant lesions [73]. High doses of 13-cisretinoic acid (50–100 mg/m^2 body surface area/day for a year) have been effective in the treatment of oral leukoplakia [74]. This therapy has resulted in

complete resolution in 27–57 % of patients and a partial response in 45–90 % of patients. Trials using beta-carotene supplements (60 mg/day for 6 months) have shown reduced risk of oral cancers and remission of pre-cancers with an improvement of at least one grade dysplasia in 39 % and no change in 61 % [75]. Cohort and case–control studies also suggest reduced risk of oral cancer among people who consumed different carotenoids [76], including beta-cryptoxanthin and alpha-carotene [71].

Lycopene, a red-colored carotenoid mainly found in tomatoes but also in other fruits and vegetables, has been shown in epidemiologic studies to have anti-carcinogenic effects for preventing oral cancer and in preliminary human clinical trials to have potential therapeutic effects in precancerous lesions [77]. Folate intake has been found to be also associated with oral cancer risk, but a significant interaction is found with alcohol intake. A cohort of 87,621 women in the Nurses' Health Study found that low alcohol intake reduced the risk of oral cancer compared to nondrinkers and to those with high alcohol intake (RR = 0.59; 95 % CI: 0.39–0.87) [78]. However, among those with high alcohol (≥30 g/day) and low folate (<350 μg/day) intakes, cancer risk increased (risk = 3.36; 95 % CI: 1.57–7.20) compared with nondrinkers with low folate intake. This was not observed among those with high alcohol intake and high-folate (≥350 μg/day). This could be explained to interactions between alcohol and folate intakes with aldehyde dehydrogenase 2 genotype [79]. Glutathione—an antioxidant found in fruits and vegetables—was protective only if it was derived from fruit and raw vegetables [80].

Other Food and Nutrients

A protective effect of fiber and whole grains was observed for both oral submucous fibrosis and leukoplakia [57] and for oral cancer [58], particularly in women [81, 82]. There is a suggestion that meat, desserts, maize, and saturated fats and/or butter may be risk factors while olive oil may be protective [58]. Nitrate, nitrite, and nitrate reductase activity in saliva [83] and high intake of nitrite containing meats [84] have been linked with increased risk. Iron is suggested to be protective against oral cancer [70] and leukoplakia [85]. Ever use of calcium supplement also has been shown to reduce the risk of oral cancer [72].

Dietary Patterns

Studies have also investigated the association of dietary patterns with oral cancer risk, as opposed to individual foods or nutrients. A case–control study in Indonesia found that a dietary pattern characterized by cooked and raw vegetable, fast foods, fermented foods, seafood, canned food, snacks high in fat and sugar increased two times risk of oral cancer (OR = 2.17; 95 % CI: 1.02–4.50) [86]. Although vegetable intake has been shown to reduce the risk in other studies, this case control study did not observe this when combined with other nonhealthy patterns. However, a dietary pattern characterized by dairy products, meat, and fruit reduced the risk (OR = 0.50; 95 % CI: 0.24–1.00), even though total meat consumption is related to an increase risk of oral cancer, particularly red meat [87]. Another case–control study in Brazil found that a pattern characterized by vegetables and raw vegetables, fruit, dairy products, potato, and fish reduced the risk of oral cancer (OR = 0.44; 95% CI: 0.25–0.75) as well as a pattern characterized by rice and pasta and pulses (OR = 0.53; 95% CI: 0.30–0.93), while a pattern characterized by bread, butter, cheese, pork, sandwich meat, egg, and sweets and dessert appeared to increase the risk (OR = 1.25; 95% CI: 0.73–2.15) [88]. An Italian case–control study in 804 with oral cancer and 2,080 controls found that a vitamin and fiber-rich dietary pattern was inversely associated with oral cancer (OR = 0.47; 95 % CI: 0.34–0.65) [59]. A recent pooled analysis of five case–control studies also found that a pattern characterized as rich in antioxidant vitamins and fiber decreased oral cancer risk (OR = 0.64; 95 % CI 0.45–0.90), whereas the fat-rich pattern or the animal products and cereals pattern did not show a significant association [89]. Another case–control study in Malaysia

found that a pattern characterized by intake of beverages and starches or a pattern rich in dairy, fermented/salted, and meat/by-products significantly increased oral cancer risk [90].

In summary, most studies show that a consumption of fruits, vegetables, other fiber-rich foods, and fish are associated with a reduced cancer risk while saturated fat, processed and refined foods, and fast foods are associated with an increased risk.

Impact of Oral Health on Nutrition

This section focuses on the impact of tooth loss and dentition status, oral cancer, and xerostomia on nutrition. Other aspects of oral health such as oral pain, periodontal disease, and altered taste could also have some impact on nutritional status [91] but will not be reviewed here.

Impact of Tooth Loss on Nutritional Status

A number of studies have demonstrated an association between tooth loss and dietary intake. Many studies show that edentulous individuals (people with no teeth) are more likely to eat an unhealthy diet (e.g., ingesting too few nutrient-dense foods and too much calorie-rich, high-fat foods) compared to people with natural teeth. Joshipura et al. [92] observed that edentulous male health professionals consumed fewer vegetables, less fiber and carotene, more cholesterol, saturated fat, and calories than participants with 25 or more teeth after adjusting for age, smoking, exercise, and profession. In a representative sample from a state in Nigeria among 500 randomly selected Nigerians, aged 50 and above, people with 20 or fewer teeth were more likely to indicate that they avoided certain food items because of their teeth/mouth conditions. Multivariable logistic regression analysis, controlling for age, gender, income, and education showed that the number of remaining teeth was significantly associated with the selection of vegetables/fruits and other hard food items [93]. In other studies of healthy older adults, edentulous individuals have been noted to consume fewer fruits and vegetables, lower amounts of fiber, and higher amounts of fat [94, 95]. Edentulous individuals are more likely to have lower intakes of micronutrients, such as calcium, iron, pantothenic acid, vitamins C, and E, than their dentate counterparts [95–97]. In summary, most of the studies relating tooth loss and nutrition suggest that people with fewer teeth are more likely to have compromised nutritional intake. Possible changes in fruit, vegetable, and micronutrient intake after tooth loss may explain part of the associations between tooth loss and cardiovascular and other systemic disease [98]. Therefore patients with tooth loss warrant aggressive counseling regarding methods to maintain dietary quality, such as blending or shredding fresh fruits and vegetables to preserve adequate intake [99].

Although eating with dentures may be preferable to eating with no teeth, most studies suggest that the diet of denture wearers differs from the diet of people who retained their natural teeth. In a study of veterans [100], individuals with full dentures consumed fewer calories, thiamin, iron, folate, vitamin A, and carotene than individuals with a number of natural teeth remaining. Also, those wearing dentures consume more refined carbohydrates, sugar, and dietary cholesterol than their dentate counterparts [101, 102]. The above studies could be interpreted such that the presence of dentures contributes to poorer intake across multiple nutrients compared to dentate subjects. Poor denture fit may contribute to some of these differences. However, all of these studies report cross-sectional associations, and tooth loss resulting from caries and/or periodontitis may well be the outcome of poor nutrition rather than its determinant. Alternatively, both pathways may have a role and explain the cross-sectional association between tooth loss and diet.

Surprisingly, longitudinal studies investigating whether tooth loss leads to dietary changes (secondary to an assumed functional impairment) are scarce. A longitudinal study of 8 years among 31,813 male U.S. health professionals found that men who lost five or more teeth had significant detrimental changes in dietary intakes of dietary fiber, whole fruit, dietary cholesterol, and polyunsaturated fat compared to men who did not lose teeth [103]. Similarly, results from the Nurses' Health Study showed detrimental dietary changes over a 2-year period subsequent to incident tooth loss, with a tendency for women who lost teeth to avoid hard foods such as raw carrot, fresh apple, or pear [104]. However, these differences were relatively small in absolute terms. The significance of these findings with respect to chronic disease risk is uncertain, although small effects on several nutrients could add up to impact disease risk.

Impact of Tooth Loss on Body Weight Status

The relationship between dental status, weight, and BMI varies with the population studied. In nursing home residents, compromised oral functional status was associated with lower BMI (less than 21 kg/m^2) after controlling for functional dependence and age [105]. Another study in community-dwelling older adults found a similar association between masticatory ability and lower body weight, after controlling for age and sex [106]. However, another study found that healthy older edentulous adults actually had higher BMIs, compared to dentate subjects [107]. Similarly, a study in Brazilian older adults found that edentulous persons wearing only upper dentures and those wearing 0–1 prosthesis were more likely to be obese [108]. A recently published longitudinal study of 16,416 Swedish older adults found a significant association between edentulism and obesity, particularly in women [109]. The differences in findings in these studies may be due to the different characteristics of the populations evaluated, with sicker older adults more likely to lose weight in response to altered dentition, and healthier older adults more likely to maintain adequate intake but alter intake to softer foods that are more calorie dense. However, as noted above, cross-sectional studies are insufficient to make causal inferences and obesity may itself be a risk factor for tooth loss secondary to caries or periodontitis. One longitudinal study in community dwelling older adults found that over a 1-year period of follow-up, approximately one-third of the sample had lost 4 % or more of their previous total body weight, 6 % of men and 11 % of women lost 10 % or more of their previous body weight [50]. Edentulism remained an independent risk factor for significant weight loss (OR 1.6 for 4 % weight loss and 2.0 for 10 % weight loss) after controlling for gender, income, advanced age, and baseline weight.

Impact of Dentate Status on Blood Nutrient Status

The largest study to date to evaluate blood nutrient status in relation to dentate status is the British National Diet and Nutrition Survey [96]. In their cross-sectional study of 490 free-living and institutionalized older adults, the authors reported that edentulism subjects had significantly lower mean plasma levels of retinol, ascorbate, and tocopherol than dentate subjects, after controlling for age, sex, social class, and region of residence. Among dentate subjects, mean plasma vitamin C levels were positively associated with increased numbers of occlusal pairs of teeth. Another study of adults in Sweden [107] reported lower serum high-density lipoprotein levels among edentulous individuals compared to those who were dentate. These results are consistent with the studies relating dietary intake to dentition status.

Once again, most studies mentioned are cross-sectional and have to be interpreted with caution; it is not clear if nutrition impacts tooth loss through its impact on caries and periodontal disease or if tooth loss impacts nutritional intake or both. Another important issue that needs to be considered when evaluating the evidence relating to tooth loss and diet is the possibility for residual confounding, in particular by socioeconomic status and health-conscious behaviors. Although caries and/or periodontitis are the main causes of tooth loss, a decision to extract a tooth is influenced by many other factors working at the patient, provider (dentist), and community level (access to care), and confounding by socioeconomic factors is a particular concern in this context [110]. In summary, individuals with compromised dentition tend to have poorer dietary quality. Whether or not this association is causal, i.e., whether or not tooth loss leads to important unfavorable changes in a person's diet, is uncertain [91]. Additional longitudinal studies are necessary to answer this important question. Prevention of dental caries and periodontal disease, and preventing tooth loss, is likely important for maintaining chewing ability and facilitating consumption of a healthy diet.

Impact of Tooth Replacement Strategies on the Nutritional Status of Partially-Dentate Elders

Indirect evidence that functional impairment associated with tooth loss may be a determinant of dietary changes also comes from studies comparing different modalities of replacements for missing teeth. In a study of denture wearers in Quebec, those that wore dentures providing poor masticatory performance consumed significantly less fruits and vegetables than those with dentures that provided good masticatory performance [111]. Likewise in Swedish older adults, poorly fitting upper dentures were associated with decreased intake of vitamin C [112]. Among older Australians, women who reported poorly fitting dentures consumed greater amounts of sweets and dessert items [113].

Studies have also examined dietary differences among edentulous subjects with and without dentures. Perhaps not surprisingly, edentulous subjects without dentures usually consume more mashed food. Whether the placement of dentures in an edentulous patient makes a substantial improvement in the patient's intake remains unclear. In the only available randomized controlled trial (RCT) among patients with partial tooth loss, no differences were found in dietary intakes between patients who received either no dentures, fixed partial dentures, or removable partial dentures [114]. Sebring et al. [115] studied the effect of conventional maxillary and implant-supported or conventional mandibular dentures on patients who were edentulous with no prostheses. In both groups, calorie intake decreased; percentage of calories from fat also decreased significantly over the subsequent 3 years. Lindquist [116] evaluated the impact of prosthetic rehabilitation, using optimized complete dentures and then tissue-integrated mandibular fixed prostheses on 64 dissatisfied complete denture wearers. There was no change in diet after optimizing complete dentures, but there was a persistent increase in fresh fruit consumption with the prostheses. Prosthetic relining in addition to dietary counseling in the edentulous found an improvement in chewing ability and fiber intake from fruits and vegetables [117]. However, because there was no group that did not receive dietary counseling, it was not possible to separate the effect of relining from the counseling. More recently, a RCT to evaluate a conventional treatment using removable partial dentures versus functionally orientated treatment based on the shortened dental arch did not find differences in the nutritional assessment tests performed between groups [118]. A RCT comparing dietary intake in subjects with implant-retained overdentures and conventionally relined denture found that among those dissatisfied with current complete mandibular dentures, no significant differences regarding nutrient intake of food choices were found between the two treatments. In summary, dietary quality may improve with the placement of dental prostheses, but the changes are not substantial. Dietary counseling at the same time prostheses are fitted may assist patients in behavioral change and in optimizing the impact of their new chewing capabilities.

Table 5.1 Problem management in oral cancer patients

Problem	Management
Xerostomia, which could lead to other problems such as caries	Sugar-free mints and gums, artificial saliva, increased intake of water, or induce salivation medically by pilocarpine hydrochloride
Increased caries susceptibility	Instruction on oral hygiene and avoidance of food high in sugar, dental referral, daily fluoride gel
Trismus makes chewing difficult	Recommend appropriate jaw exercises
Dysphagia	Assess swallowing ability and risk of aspiration, monitor feeding capabilities, modify food consistency as indicated, use alternative route of nutritional support if necessary
Risk of aspiration	Use airway protection techniques and use of feeding devices as indicated
Malnutrition	Obtain a dietary consultation. Consider a multivitamin/mineral supplement and/or enteral or parenteral routes for patients who cannot meet their nutritional needs by mouth

Impact of Oral Cancer on Nutrition

Oral cancer (OC) has a major impact on eating and swallowing. The location or progression of the tumor itself and the side effects of treatment hamper feeding and swallowing. Side effects of radiation, primarily a result of damage to the salivary glands and reduction in saliva production, include xerostomia, dental caries, oral mucositis, and bacterial and fungal infections. Side effects of chemotherapy include mucositis, fungal infections, xerostomia, throat and mouth pain, taste changes, food aversions, nausea, and diarrhea. Other complications include aspiration, osteoradionecrosis, and trismus [119]. Side effects of surgery vary according to location and extent of surgery. The oral phase of swallowing is affected by surgical resection. Means to counter common problems faced by OC patients are listed in Table 5.1. These interventions can improve nutritional intake and overall quality of life.

Impact of Xerostomia on Nutrition

Xerostomia is associated with increased risk of dental caries, periodontal disease, speaking problems, swallowing problems, reduced chewing ability that contributes to malnutrition, and taste disturbances. With xerostomia, individuals may have inadequate lubrication and moisture in the mouth to chew food and create an adequate food bolus for swallowing. In addition, xerostomia may contribute to altered taste perception and to food sticking to the tongue or hard palate. Three studies of xerostomia have found that diet/nutrition and the quality of saliva were affected by exposure to Sjögren's syndrome (an immunologic disorder in which the body's immune system mistakenly attacks its own moisture producing glands) and xerogenic medications. In patients with Sjögren's syndrome, those with xerostomia have significantly lower caloric and micronutrient intakes [120]. Also, individuals with xerostomia were more likely to avoid crunchy vegetables (e.g., carrots), dry foods (e.g., bread), and sticky foods (e.g., peanut butter) [121] and have significantly lower intakes of energy, protein, fiber, vitamin A, C, and B_6, thiamin, riboflavin, calcium, and iron [122]. These studies suggest that xerostomia impairs optimal nutrient intake; however, these studies are hampered by their small size and cross-sectional design. These studies also noted that BMI was significantly lower in those with xerostomia compared to controls, as well as possibly lower triceps, skin fold thickness, and arm circumference.

Conclusion

Oral conditions that affect and are affected by nutrition, including dental caries, periodontal disease, xerostomia, and oral cancer, are more common in older adults. The causal role of dietary behaviors in the pathogenesis of dental caries throughout the life has been unequivocally demonstrated. Avoidance of in-between meal snacks, especially those high in refined carbohydrates, use of sugar-free candy or gum, and consumption of carbohydrates with meals and water, can reduce caries incidence. On the other hand, a higher meal frequency has metabolic benefits such as improving control of diabetes [123]. Hence, in order to reduce caries risk without increasing metabolic risk, it may be best to avoid refined carbohydrates, have more frequent meals and to brush after meals and snacks. Effects of nutritional factors on periodontitis risk and oral cancer risk on the one hand, and dietary effects of tooth loss on the other hand are highly plausible; however, evidence from well-designed longitudinal or intervention studies is limited.

Nutritional modulation of immune function, as, for example, through the use of antioxidants, may reduce progression of periodontal disease, but intervention studies are limited. Many epidemiologic studies have demonstrated the protective effect of fruits and vegetables and antioxidants on oral cancer risk. Studies suggest tooth loss impacts dietary quality and nutrient intake in a manner that may increase risk for several systemic diseases. Further, impaired dentition may contribute to weight change, depending on age and other population characteristics. Prevention of oral conditions and maintaining a healthy dentition is important for maintaining healthy nutrition status. Attention to dietary quality is particularly important among individuals with chewing disability from tooth loss or edentulism. Patients with oral cancer experience numerous complications that increase their risk for poor dietary intake. Close attention should be given to prevention of caries in patients with xerostomia, modification of food consistency in patients with dysphagia, and alternative feeding routes if nutritional needs cannot be met orally.

Recommendations

1. To help in maintaining a healthy diet, oral health and public health professionals should focus on preventing and managing caries and periodontal disease, as well as in retaining teeth, by improving self-care, professional care, and modifying preventable risk factors.
2. Clinicians should advise their dentate patients to restrict between-meal snacks that are high in sugar and to prefer low-sugar snacks such as low-sugar dairy products, fresh fruits, and nuts. Also, to eat carbohydrates with meals, and limit sugar and other foods that are cariogenic.
3. Consumption of a diet rich in a diversity of fruits and vegetables appears to reduce the risk for the development of oral cancer.
4. Patients with tooth loss are at increased risk for poor/inappropriate dietary intake. Clinicians should counsel patients regarding ways to maintain good nutrition and minimize softer calorie-dense foods with low nutritional value. Pureed or shredded fruits and vegetables may serve as a means of ensuring adequate intakes of these food groups. A multivitamin should be considered in this group as well.
5. Patients with oral cancer and radiation-induced xerostomia should be counseled to use sugar-free mints and gums and routinely apply fluoride to teeth to prevent dental caries.

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Chapter 6
Loss of Muscle Mass and Muscle Strength in Obese and Nonobese Older Adults

Danielle R. Bouchard and Ian Janssen

Key Points

- *Sarcopenia* refers to the process of age-related skeletal muscle mass loss, and *dynapenia* refers to the process of age-related muscle strength loss. These terms are often used to describe older adults with unhealthy skeletal muscle mass and muscle strength levels, respectively.
- Well-designed longitudinal studies show little or no association between sarcopenia and the risk of impaired physical function, falls, and mortality.
- Conversely, dynapenia is consistently associated with these outcomes.
- The combination of sarcopenia or dynapenia with obesity among older adults (sarcopenic obesity and dynapenic obesity) is highly prevalent. The best treatment for these conditions is unknown, as weight loss is associated with both muscle mass and muscle strength loss.
- Physical activity, particularly resistance exercise, is one of the most promising approaches for preventing and treating both sarcopenia and dynapenia in obese and nonobese older adults.

Keywords Skeletal muscle • Muscle strength • Obesity • Physical function • Resistance exercise • Dietary supplement

Introduction

The terminology used to describe age-related loss of muscle mass and muscle strength has evolved since 1989 (Fig. 6.1). In 1989, Irwin Rosenberg coined the term *sarcopenia* to refer to the process of age-related skeletal muscle loss [1]. Sarcopenia comes from the Greek words s*arx* (flesh) and *penia* (loss).

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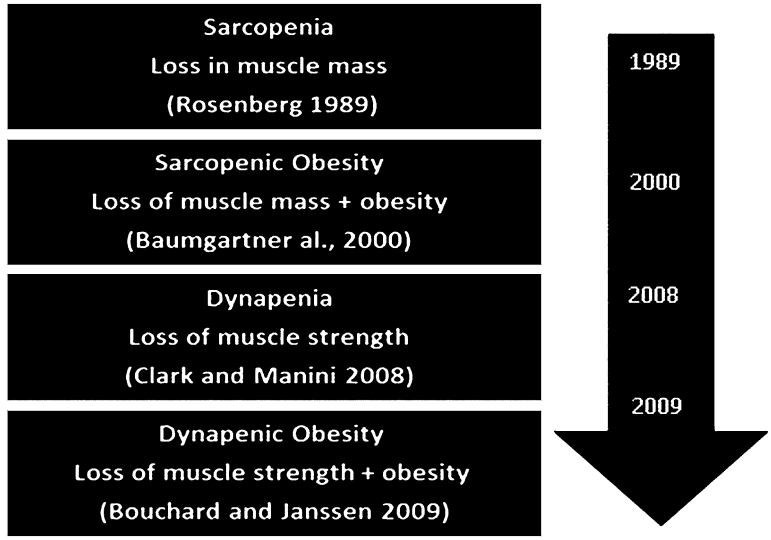

Fig. 6.1 Terms related to loss of muscle mass and muscle strength

The term *sarcopenic obesity* was introduced in 2000 to identify older obese adults that also presented with a low muscle mass [2]. Over time, the definition of sarcopenia as purely a loss in muscle mass evolved into one that included both a loss in muscle mass and muscle function [3, 4]. However, as discussed in more detail later on, the loss in muscle strength is not coupled to the loss in muscle mass. The term *dynapenia* was coined to refer specifically to the process of losing muscle strength with advancing age [5]. The term *dynapenia* is a translation from the Greek—poverty of strength, power, or force. In this chapter, sarcopenia (loss in muscle mass) and dynapenia (loss in muscle strength) will be considered as separate phenomenon. Finally, in 2009, *dynapenic obesity* was coined to identify obese older adults with low muscle strength [6]. This chapter discusses the prevalence, consequences, and possible prevention/treatment strategies of sarcopenia, dynapenia, sarcopenic obesity, and dynapenic obesity.

Sarcopenia

With few exceptions, cross-sectional studies have observed that muscle size remains relatively constant in the third and fourth decades, and then starts to decline noticeably at around the fifth decade [7, 8]. Longitudinal studies, with follow-up lengths of up to 12 years, have confirmed these observations [9, 10]. It has been estimated that skeletal muscle mass decreases by approximately 6 % per decade after mid-life [11].

Definition and Prevalence

Although all older adults have lost some muscle [12], there is a considerable variation in the amount of muscle within the older population. Older adults who had a high peak muscle mass and have lost muscle at a slow rate have reasonably healthy muscle mass values. Others may have had a low peak muscle mass and/or lost muscle quickly as they aged, and subsequently have a very low muscle mass. Many epidemiological studies have tried to identify this later group. Specifically, cut-points have

been used to identify which older adults have skeletal muscle values in the normal and unhealthy (i.e., sarcopenic) ranges. In 1998, Baumgartner and colleagues [13] proposed a process to determine which older persons have unhealthy values. Specifically, they determined the average and standard deviation of the height-adjusted appendicular skeletal mass (muscle mass of legs + arms/height^2) of a young and healthy reference population. Sarcopenia was then diagnosed if an older adult had an appendicular skeletal muscle mass value equal to or below two standard deviations of the mean of the young and health reference population. Using this approach, the prevalence of sarcopenia in participants in the New Mexico Elder Health Survey was 14 % in those aged 65–69 years, and over 50 % in those 80 years of age or older [13]. Since Baumgartner and colleagues [13], many other researchers have employed a similar approach for classifying sarcopenia [14, 15] and have reported a prevalence of 8.5 % [14] to 12.3 % [15] with populations aged 60 years and older. Besides this approach, another strategy has been employed to identify sarcopenia, namely using two standard deviations of skeletal muscle mass adjusted for body weight instead of height [16]. Using this approach, the prevalence of sarcopenia was similar for men (30.8 % vs. 29.5 %), but higher for women (30.3 % vs. 10.2 %), when compared with Baumgartner's approach [17].

Consequences of Sarcopenia

Functional Limitation and Physical Disability

The majority of the pre-2005 scientific literature on the health implications of sarcopenia focused on measures of physical function. These early studies were also cross-sectional in design [14] and, for the most part, demonstrated that sarcopenia is associated with functional limitation [13, 14]. These studies have used a variety of methods for measuring muscle size and for classifying sarcopenia. The strength of the association between sarcopenia and physical function in these cross-sectional studies would be considered moderate to strong by epidemiological standards. For instance, cross-sectional findings based on the Cardiovascular Health Study indicated that the likelihood of having physical disability at the start of the study (i.e., baseline exam) was 79 % greater in those with severe sarcopenia than in those with normal muscle mass.

More recently conducted longitudinal analyses have not supported the association observed in the initial cross-sectional studies. For example, in an 8-year follow-up of older adult participants in the Cardiovascular Health Study cohort, the risk of developing physical disability was 27 % greater in those with *severe* sarcopenia than in those with a normal muscle mass [18]. Thus, the effect of sarcopenia on disability risk was considerably smaller in the longitudinal analysis than in the cross-sectional analysis of the same cohort of participants, implying that the effects of sarcopenia on functional impairment and disability inferred from the cross-sectional studies published in the 1990s and early 2000s may have been overestimated. Other prospective studies [19, 20] have also reported no association between loss of muscle mass and functional limitation or physical disability.

Mortality

Studies of community-dwelling [21] and institutionalized [22] older adults have also shown that low muscle area in the upper arm is a good predictor of both short-term and long-term mortality risk. For example, in an 8-year follow-up of ~1,400 older Australians, Miller and colleagues [21] found that mortality risk was increased by twofold in those with an upper arm muscle area below ~21 cm^2. Studies have also used total fat-free mass (FFM) to predict mortality risk. In a landmark study of 57,053 adults aged 50–64 years, FFM, as measured with bioelectrical impedance, was associated with an ~25 % increased mortality risk over 6 years [23].

Metabolic Health

The metabolic effects of sarcopenia could be based on the fact that loss of muscle mass is associated with a decreased metabolic rate [24]. It has also been postulated that sarcopenia contributes to cardiometabolic diseases such as insulin resistance, type 2 diabetes [25], dyslipidemia, hypertension, and the metabolic syndrome [26]. However, the literature is mixed and in general does not support this postulation. For instance, a study of 22 obese postmenopausal women found that those with sarcopenia had a more favorable lipid and lipoprotein profile than those without sarcopenia [27]. Additional research on over 3,000 members of the Cardiovascular Health Study cohort found that sarcopenia per se was not a risk factor for the development of cardiovascular disease over an 8-year follow-up [28].

Dynapenia

A central belief of early research into the field of sarcopenia was that low muscle mass leads to low muscle strength [29], which in turn increases the risk of functional impairment and physical disability. However, the notion that a loss in muscle strength is tightly coupled to sarcopenia has been disproven. Longitudinal studies of older adults have reported that less than 5 % of the change in muscle strength is explained by the corresponding change in muscle mass [30]. Based on these and other findings, Clark and Manini proposed that the term sarcopenia be used to refer to the loss in muscle and that the term dynapenia be used to refer to the loss in muscle strength [31]. Muscle strength loss, or the process of dyanpenia, beings at around age 50 years, and proceeds at a rate of about 15 % per decade between 50 and 70, and is more accelerated in subsequent years [32].

Prevalence

Even if it is clear that older adults have a lower muscle strength than young people [33], the threshold or cut-point that denotes a critical loss in muscle strength is unclear. At present, researchers are using similar strategies to those that are being used to identify sarcopenia. In a recent study using a small sample ($n=46$) of healthy 50- to 75-year-old women, dynapenia was defined as muscle strength (measured with a handgrip dynamometer) equivalent to at least one standard deviation below the mean handgrip strength from a reference group made up of young adults [34]. Using this strategy, 50 % were dynapenic.

Consequences of Dynapenia

Functional Limitation and Physical Disability

Cross-sectional [19, 35] and longitudinal [19] studies have consistently reported that a low muscle strength, or dynapenia, is a risk factor for functional limitations and physical disability. For example, Visser and colleagues demonstrated there was an approximately 2.5 times greater risk of developing mobility limitations over 2.5 years in older adults in the lowest quartiles of muscle strength compared with the highest quartile [19]. Furthermore, Moreland and colleagues [36] reported, in a meta-analyses, that low muscle strength was associated with a 76 % increased risk of falling. Muscle strength is associated with functional limitations to a greater extent than muscle mass, implying that muscle function is more important than muscle quantity [37].

Mortality

Rantanen and colleagues reported that the risk of all-cause mortality was increased by 73 % in lowest grip strength tertile. Another study employing other measures of muscle strength (e.g., isokinetic quadriceps strength) made similar observations [38]. In addition, longitudinal studies have shown that rate of muscle strength decline is a strong predictor of mortality risk [39].

Metabolic Health

A comparison of lowest and highest muscle strength groups has shown low strength increases the risk of the metabolic syndrome [40], insulin resistance [41], and type 2 diabetes [42] by almost twofold. Furthermore, it has been reported that dynapenic postmenopausal women had a 24 % reduced maximum oxygen consumption [34].

Sarcopenic Obesity

Definition and Prevalence

The typical aging process is accompanied with an increase of body weight until about age 60 [43]. As a result, an increase in fat mass and a reduction in FFM occurs, but the changes in the two are not completely correlated [44]. As there is a lack of uniformity in the measurement and classification of sarcopenic obesity, the prevalence of this condition is unclear. The reported prevalence ranges from 2 % [45] to 48 % [46].

Consequences of Sarcopenic Obesity

Most of the literature examining the health implication of sarcopenic-obesity is based on cross-sectional study designs. Some studies report that sarcopenic obese people are more likely to have an impaired physical function [13, 47, 48], while others report no differences in function for those with sarcopenic obesity by comparison to those with sarcopenia or obesity alone [49–51].

Messier and colleagues [51] reported that sarcopenic obese older women do not have a more unfavorable metabolic profile compared with non-sarcopenic obese women. Baumgartner and colleagues [47] showed that sarcopenic obesity was a predictor of disability and even a higher mortality rate [52].

In short, it is not clear if being identified as both sarcopenic and obese is more harmful compared with being sarcopenic or obese alone.

Dynapenic Obesity

Definition and Prevalence

In 2009, Bouchard and Janssen defined dynapenic obesity as individuals (in this study aged 55 years or older) who were in the lowest tertile of muscle strength (measured by leg extension strength) and the highest tertile of fat mass (measured by dual-energy X-ray absorptiometry [DEXA]) [6].

Of the 2,039 people studied, 9.2 % of the men and 8.8 % of the women were considered to be dynapenic obese. Recently, Senechal and colleagues (2012) used two standard deviations below the mean strength in young healthy adults to recruit dynapenic-obese women to participate in a randomized controlled study [53]. Obesity was defined as 35 % of fat mass measured by DEXA. While the *dynapenic obesity* term is relatively new, for several years studies have been reporting on the negative consequences of having a poor muscle strength combined with extra body weight/fat.

Consequences of Dynapenic Obesity

Dynapenic obesity is associated with more functional limitations and a greater risk of type 2 diabetes and cardiovascular disease compared with dynapenia alone or obesity alone. For example, Bouchard and Janssen (2009) [6] concluded that dynapenic obese people have 2 % lower physical capacity compared with those who are obese, 7 % lower compared with those who are dynapenic, and 13 % lower compared with those who are nonobese and non-dynapenic. In a 9-year follow-up of almost 5,000 older adults who participated in the Cardiovascular Health Studies, dynapenia alone (poor grip strength) and obesity alone (high BMI) were not sufficient to increase cardiovascular risk; however, dynapenic obesity was associated with a 25 % increased risk of developing cardiovascular disease [28]. Senechal and colleagues [54] recently studied the impact of dynapenic obesity on metabolic health. They reported a higher risk of metabolic syndrome and type 2 diabetes in dynapenic obese adults compared with healthy counterparts.

Prevention and Treatment

The best prevention and treatment strategy for all four of the conditions discussed in this chapter is physical activity. Nutritional strategies, hormonal strategies, and medications have been explored to address muscle mass, but these have not been as successful as resistance training [3, 55].

Prevention and Treatment for Sarcopenia and Dynapenia

Resistance Training

Although most types of physical activity have a positive effect on muscle strength and muscle mass within older adults [56], resistance training is by far the optimal strategy. Based on many intervention studies reported in review papers, interventions have typically ranged from 8 to 16 weeks, and the vast majority have noted a significant increase in skeletal muscle size and muscle strength irrespective of the population group studied [57]. In fact, progressive resistance training has been shown to be effective in increasing muscle strength in frail older adults [58]. Resistance exercise leads to an increase in strength greater than what would be expected for the accompanying increase in muscle mass [59].

Current recommendations of the American College of Sports Medicine are: "*To maximize strength development, a resistance should be used that allows 10–15 repetitions for each exercise. The level of effort for muscle-strengthening activities should be moderate to high. On a 10-point scale, where no movement is 0, and maximal effort of a muscle group is 10, moderate-intensity effort is a 5 or 6 and high-intensity effort is a 7 or 8. Muscle strengthening activities include a progressive weight training program, weight bearing calisthenics, and similar resistance exercises that use the major muscle*

groups." Older adults should perform at least one set of 10–12 repetitions for 8–10 exercises that train the major muscle groups, and exercises for each of the major muscle groups should occur on 2 or 3 days a week [60].

A growing body of literature reports that resistance exercise that restricts blood flow stimulates muscle protein synthesis to a greater extent than traditional resistance training [61–64]. Blood flow restriction exercise consists of restricting blood flow by applying a wrapping or a blocking device near the muscle being exercised. Studies so far suggest that this strategy would increase muscle mass compared with traditional resistance training in older adults [62].

Resistance Training + Protein Supplements

Controversy exists as to whether protein supplements combined with resistance exercise have a greater impact on muscle hypertrophy than resistance exercise alone. The dose of protein required to increase skeletal muscle hypertrophy is unclear as one of the studies that demonstrated a beneficial effect [65] used a smaller dose of protein (10 g vs. 15 g) than a study showing no effect [66]. Symons and colleagues concluded that ingesting more than 30 g of protein in a single meal did little or nothing to enhance muscle protein synthesis [67]. The timing of protein intake around the exercise may be relevant in determining whether or not additional muscle hypertrophy occurs. Esmarck and colleagues [65] reported that a liquid protein supplement (10 g protein) ingested immediately post-exercise in older men increased skeletal muscle hypertrophy, whereas ingesting the protein supplement 2 h post-exercise did not.

Whole-Body Vibration

The whole-body vibration apparatus is a new tool that proposes to improve muscle mass, muscle strength, and bone mass. To utilize the machine a person stands, sits, or lays on a vibrating platform. As the machine vibrates, it transmits energy to the body and is forcing muscles to contract and relax dozens of times each second to maintain balance. Most intervention studies that have tested this apparatus, with intervention of up to 18 months long, reported increase in muscle strength and cardiorespiratory fitness but not changes in muscle mass [68]. However, when whole-body vibration is embedded in a standard exercise program, it appears to provide only minor effects above those obtained by exercise alone [69].

Supplements

Protein Supplements

Essential amino acids and milk-based proteins, creatine monohydrate, essential fatty acids, and vitamin D may all have beneficial effects on aging muscles [70]. An initial prevention strategy that may reduce the typical progression of sarcopenia in older persons is to ensure that they consume adequate protein in their diet. Data suggests that the average protein intake is lower in older adults than in young adults [71]. Protein supplements can be considered in addition to an individual's ad libitum diet. Protein-based nutritional supplements are attractive given their low cost, ease of administration, and they are well tolerated in older adults [72]. When used appropriately, protein/nutritional supplements may result in an increase in daily energy and protein intake in older adults [72]. The oral ingestion of intact whey protein stimulates muscle protein synthesis in older adults [73]. In a recent study,

Pennings and colleagues [74] demonstrated that whey protein stimulates more protein accretion than casein and casein hydrolysate, probably because of a faster digestion and greater leucine content. It is possible that the small increase in energy from a supplement of this nature would not be enough to decrease ad libitum food and protein consumption, as shown in other studies, which used protein/nutritional supplements with a considerably larger caloric content [75]. Although protein supplement studies have demonstrated promising results on short-term protein synthesis within skeletal muscle, the long-term effectiveness of protein supplements on muscle mass has yet to be demonstrated.

Other Supplements

Experimental studies have shown that 8 weeks of an omega-3 fatty acid supplement increased muscle protein synthesis (from 0.009 ± 0.005 %/h above basal values to 0.031 ± 0.003 %/h above basal values) [76]. Bicarbonate supplements have also shown promising results when taken during a 3-month exercise program, leading to reduced net acid excretion and increased leg press power by 13 % in women; although no positive effects were seen in men [77]. Bicarbonate is well-tolerated and inexpensive.

Hormones

The age-related decrease in anabolic hormones such as growth hormone, estrogen, ghrelin, testosterone, and dehydroepiandosterone (DHEA) have been linked to the development of sarcopenia [3]. A meta-analysis of 11 randomized controlled trials reported that testosterone replacement therapy produced a moderate increase in muscle strength in older men [78]. Although growth hormone administration increases muscle mass and strength in people with hypopituitarism [79], most of the initial studies conducted in older adults found that growth hormone therapy did not increase muscle mass and muscle strength [3, 79]. However, alternative strategies for stimulating the growth hormone and insulin-like growth factor pathway have shown promising results [3, 79]. For example, Nass and colleagues [80] have shown that ghrelin supplementation was well tolerated and resulted in an increase in growth hormone and muscle mass. Meanwhile, replacement studies of estrogen [81] and DHEA [29] have shown poor results.

Prevention and Treatment for Sarcopenic Obesity and Dynapenic Obesity

There is an ongoing debate as to whether weight loss should be recommended in older adults because of a risk of accentuated muscle mass loss, a risk of not meeting the recommended nutrients, or an increase in mortality risk [82]. However, in the last decade most reviews and meta-analyses have concluded that weight reduction in obese older adults has more advantages than disadvantages [83, 84].

Aerobic Exercise

It is possible for obese older adults to reduce their body weight by doing aerobic exercise [85, 86]. However, in older adults and especially obese older adults with low muscle mass and or muscle strength, it might be hard to create a sufficient energy deficit to cause a substantial weight loss. Nonetheless, irrespective of weight loss, aerobic exercise can improve health and functional capacity [87].

Caloric Restriction

Most of the debate in weight loss for older adults concerns caloric restriction as a single strategy to reduce body weight [84, 88]. However, a recent randomized controlled trial concluded that intentional dietary weight loss was *not associated* with increased all-cause mortality over 12 years [89]. However, when weight loss is also accompanied by a low muscle mass and/or strength, it is unclear if weight loss should be recommended considering that weight loss is associated with loss in muscle mass [84].

Specific to Sarcopenic Obese and Dynapenic Obese

The optimal treatment strategy for sarcopenic obesity and dynapenic obesity appears to be a combination of exercise and caloric restriction [82]. More specifically, an energy deficit of about 500 kcal/day with adequate protein and calcium, in addition to multicomponent exercise program, is recommended [83]. With that being said, only one study has specifically looked at the impact of caloric restriction, exercise, and caloric restriction + exercise in a sample of older people classified as being dynapenic obese. Senechal and colleagues [53] studied 38 dynapenic obese postmenopausal women randomized into four different groups (caloric restriction, resistance training, both, or control) for 12 weeks. After a body weight reduction of ~5 % in the caloric restriction group and combined group, the study concluded that caloric restriction with or without resistance training was effective in improving metabolic profile, whereas resistance training was the most effective strategy to improve physical capacity. Furthermore, they did not observe any significant reduction in muscle strength in any group using caloric restriction as part of the intervention.

Clinical Recommendations

1. Physical activity, and resistance training in particular, is the most promising approach for preventing and treating sarcopenia and dynapenia. To maximize muscle mass and strength development, 10–15 repetitions per set should be performed to the point of fatigue. Older adults should perform at least one set of repetitions for 8–10 exercises that train the major muscle groups, and exercises for each of the major muscle groups should occur on two or three nonconsecutive days of the week.
2. To help reduce the typical progression of sarcopenia in older people, ensure that their protein intake is at or slightly above the recommended dietary allowance. Protein supplements can be considered in addition to a person's ad libitum diet as these supplements are low in cost, are easy to administer, and well tolerated.
3. To treat obese older adults who have low muscle mass or low muscle strength, preliminary studies suggest that weight loss in combination with resistance training would be the best approach to improve metabolic health and functional limitations.

Conclusion

Sarcopenia, dynapenia, and obesity are a common part of the aging process. While the negative effects of sarcopenia were thought to be important, recent studies suggest that the effects of sarcopenia on functional impairment, mortality and metabolic health risks are modest. However, there is clear and consistent evidence that dynapenia is a risk factor for development of functional impairment, metabolic diseases, and mortality. While less is known about sarcopenic obesity and dynapenic obesity,

similar risk patterns are observed where dynapenic obese elderly people seem more affected than sarcopenic obese older adults. Resistance exercise is clearly the optimal treatment strategy for sarcopenia and dynapenia. Treatment, particularly for sarcopenia, can also include counseling on nutrition to ensure that dietary protein content is sufficient, and that there is pharmacological evaluation of anabolic hormones that tend to decline with old age. Finally, when sarcopenia or dynapenia is associated with obesity, preliminary data show that weight loss is safe and that greater results are obtained if moderate caloric restriction is prescribed in addition to regular exercise.

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Chapter 7
Muscle Metabolism, Nutrition, and Functional Status in Older Adults

Douglas Paddon-Jones and Aaron P. Russell

Key Points

- The progression of sarcopenia is often mirrored by a decrease in physical activity, which feeds into a vicious cycle of disuse and negative health outcomes.
- Despite the compelling image of elite endurance athletes with very little muscle mass, aerobic exercise is not an *anti-anabolic* activity. Endurance exercise can increase both mitochondrial and myofibrillar protein synthesis
- Anabolic resistance is characterized by an impaired response to stimuli such as protein ingestion or exercise. Over time, this can be a significant factor contributing to the age-related loss of muscle mass and function.
- Combining human clinical interventions with basic research will provide the greatest opportunity to enhance our understanding of the regulation and maintenance of muscle mass and function during aging.

Keywords Sarcopenia • Protein metabolism • Muscle mass • Nutrition • Strength and function

Introduction

In the last 50 years, the number of individuals over the age of 65 years in the United States has doubled. A further doubling is expected by 2030, dramatically increasing the number of adults at risk of sarcopenia, a condition characterized by an age-related loss of muscle mass with an associated reduction in physical function [1]. A reduction in muscle mass and functional capacity is typically viewed as an undesirable, yet inevitable, consequence of aging, and in its early stages, may be easily

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masked by subtle lifestyle adaptations. However, advanced sarcopenia is synonymous with physical frailty and is associated with an increased likelihood of falls and impairments in the ability to perform routine activities of daily living [2, 3]. In many instances, the progression of sarcopenia is mirrored by a decrease in physical activity, which feeds into a vicious cycle of disuse and negative outcomes, including impaired insulin action, accelerated loss of muscle and bone mass, fatigue, impaired motor control and functional capacity, and increased morbidity and mortality [4–6].

The inclusion of both muscle mass and function in the definition of sarcopenia has been stressed by several working groups as it provides a framework for understanding clinical consequences as well as potential interventions [1, 7]. While the trajectory of sarcopenia may be greatly accelerated by any number of catabolic events or crises (e.g., illness, injury, physical inactivity), an uncomplicated progression results in a 3–8 % reduction in muscle mass per decade, starting in the fourth or fifth decade of life [8]. Changes in muscle strength and functional capacity, while not directly proportional to changes in muscle mass in all instances, tend to follow a similar pattern with greater losses (approx. 3 % per decade) occurring after the age of 60 years [9].

An increasing number of translational research efforts continue to refine our understanding of sarcopenia and improve our ability to design and implement prevention and treatment-focused interventions. The goal of this chapter is to examine the opportunities and obstacles faced by clinicians and researchers seeking to understand or combat sarcopenia. To this end, we will focus on the regulation of muscle protein metabolism and the nutrition- and exercise-based strategies that provide the foundation for all other concomitant therapies.

Regulation of Muscle Mass with Age

Skeletal muscle represents approximately 40 % of the mass of the human body and plays a key regulatory role in metabolism, the maintenance of posture, and control of movement. Skeletal muscle is continuously being remodeled in response to loading and various metabolic stressors. Any progressive or unchecked reduction in muscle mass is a major health risk with the potential to compromise physical independence, reduce quality of life, and increase the reliance on professional or family care providers. Sarcopenia is the fifth leading cause of death in the United States' aged population and places significant socioeconomic pressure on family members and health care systems [3, 7, 10] (Fig. 7.1).

Skeletal muscle mass is maintained via the regulation of muscle protein synthesis and muscle protein breakdown [11, 12]. Considerable clinical research has focused on the implementation of exercise and nutrition interventions designed to stimulate muscle anabolism and ultimately preserve or increase muscle mass and function in young and aging adults alike [13–16]. While there have been successes, we continue to refine and improve prevention and treatment strategies for sarcopenia. To broaden our understanding of how nutrition and exercise may preserve muscle and function in older adults, recent attention has turned to understanding the regulation of intracellular signals that control muscle growth and breakdown [12, 17, 18]. An understanding of these regulatory signals is important, as very small alterations in the balance between muscle protein synthesis and breakdown (i.e., net balance) could facilitate a significant lean tissue loss over several years.

Signaling hormones including growth hormone (GH) and insulin-like growth factor-1 (IGF-1), as well as signaling pathways for Akt, mammalian target of rapamycin (mTOR) and striated muscle activator of Rho signaling/serum response factor (STARS/SRF), have been linked to sarcopenia (Fig. 7.2). Of particular interest is how these growth-regulating pathways are influenced by nutrition and muscle contraction in both young and older subjects. By understanding these key mechanistic events, we may be able to deliver targeted and effective exercise and nutrition strategies that may ultimately preserve muscle mass and functional capacity.

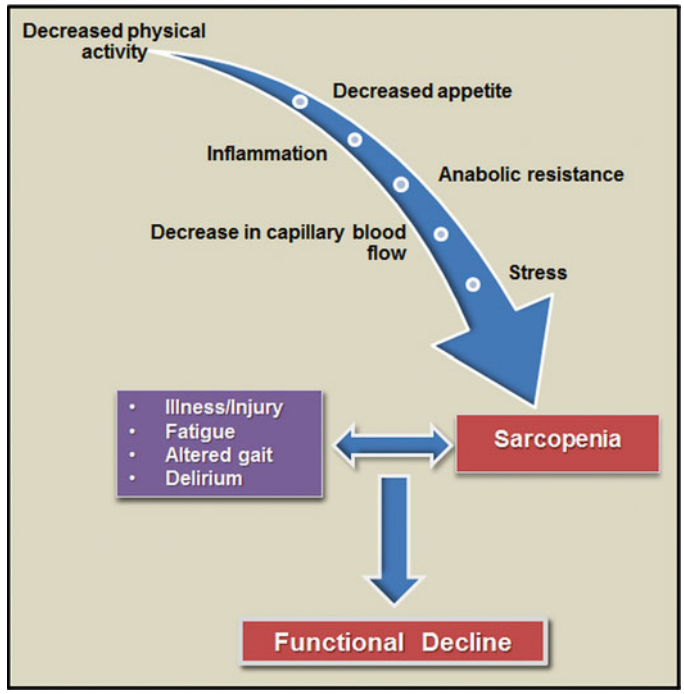

Fig. 7.1 The cascade of physiological changes leading to sarcopenic muscle loss and decreased physical function

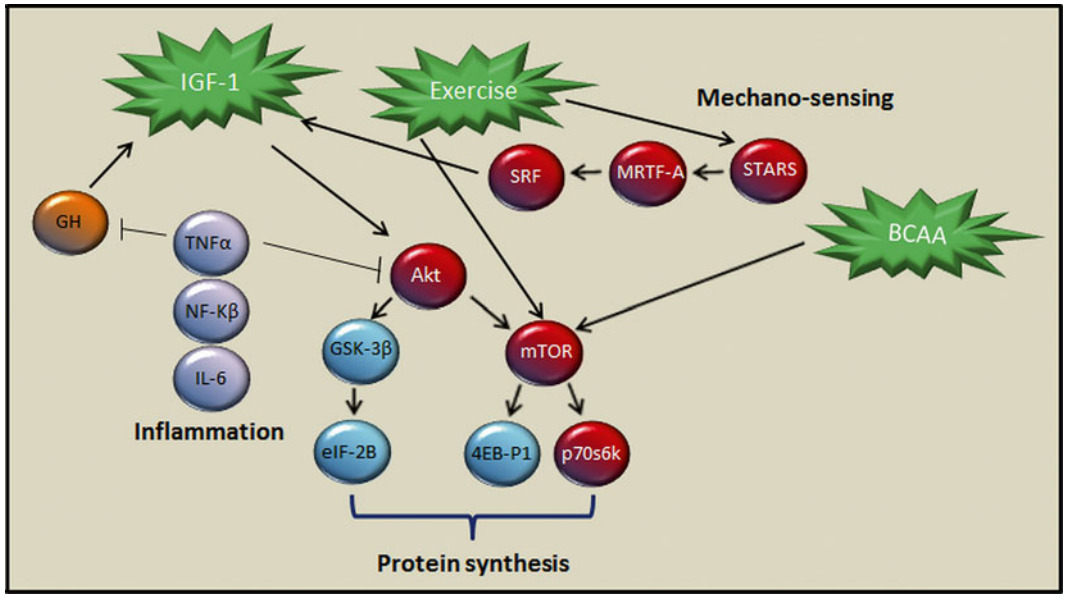

Fig. 7.2 Potential relationship between several molecular signaling pathways involved in skeletal muscle protein synthesis and their attenuation with age. IGF-1, exercise, and BCAA are potent activators of muscle protein synthesis in both younger and older subjects. These factors can activate several upstream targets, including Akt, mTOR, and STARS, that positively impact, directly or indirectly, muscle growth. The *red circles* indicate those known targets that are down-regulated in skeletal muscle from the elderly or that have attenuated activation in response to IGF-1, exercise and BCAA interventions. →, known activator; ⊣, known inhibitor

IGF-1/Akt-1 Signaling and Muscle Mass

IGF-1 activates a series of intracellular signaling cascades involving phosphatidylinositol 3-kinase (PI3K) and Akt-1 that regulate muscle growth [19–21]. Downstream targets of Akt-1 include glycogen synthase kinase-3β (GSK-3β) and mTOR. Phosphorylation of GSK-3β by Akt-1 [22, 23] releases its inhibition of the translation initiation factor eIF2B [24]. The phosphorylation and activation of mTOR results in further phosphorylation and activation of ribosomal $p70^{S6K}$, as well as phosphorylation of PHAS-1/4E-BP1 [24]. Phosphorylation of both $p70^{S6K}$ and PHAS-1/4E-BP1 activates pathways promoting protein synthesis and translation initiation, respectively. Hence, the Akt-1/GSK-3β and Akt-1/mTOR pathways are important for muscle growth and repair. Additionally, IGF-1/Akt can also reduce the activity of pathways involved in muscle protein breakdown [25]. Akt-1 phosphorylates the FoXO family of transcription factors where they remain sequestered to the cytoplasm. This inhibits the FoXO transcription of atrogin-1/MAFbx and MuRF1 [25], both important regulators of skeletal muscle atrophy [26, 27].

In aging human skeletal muscle, a reduction in IGF mRNA has been observed [28, 29]. Lower levels of IGF-1 may compromise that ability to activate Akt-1 in response to meals or exercise. Compared to young males, an elevated level of total Akt-1 protein has been observed in skeletal muscle from older men [28]. However, this was not matched by an elevated increase in phosphorylated Akt-1. This observation supports those made in older rat skeletal muscle [30] and suggests an age-related reduction in the efficiency to phosphorylate skeletal muscle Akt-1. Inefficient activation of the Akt-1 protein following an anabolic stimuli may contribute to impaired muscle protein synthesis and muscle growth.

The downstream GSK-3β and mTOR pathways, two axes independently stimulated by Akt-1, have also been measured and compared in muscle biopsies from young and older adults [28, 31]. Increased levels of total and phosphorylated GSK-3β have been observed in older subjects [28]. An increased pool of GSK-3β protein may be a result of increased protein translation or protein stability, aimed at providing the cell with a source to maintain protein synthesis. These observations suggest the existence of a mechanism that is able to phosphorylate GSK-3β, independently of Akt-1, an observation not without precedent [32]. Total and phosphorylated protein levels of mTOR and its downstream targets $p70^{S6k}$ [31], but not 4E-BP1 [28], have also been observed to be reduced in the elderly, when compared with younger muscle.

STARS/SRF Signaling

STARS is a muscle-specific actin-binding protein that binds to the I-band of the sarcomere and to actin filaments [33]. STARS increases actin polymerization by increasing the binding of free G-actin to F-actin filaments [33]. As a consequence the G-actin inhibition of the transcriptional coactivator, myocardin-related transcription factor-A (MRTF-A) is removed, permitting the nuclear translocation of MRTF-A and its enhancement of SRF transcription [34] (see Fig. 7.2). STARS also enhances smooth muscle cell proliferation [35], and in unpublished work, we have observed the same effect in C2C12 myoblasts. Following 8 weeks of hypertrophy-stimulating resistance training, STARS, MRTF-A, and SRF mRNA as well as RhoA and nuclear SRF protein levels are increased [36]. This is associated with increases in several SRF target genes: the structural protein α-actin [37], the motor protein myosin heavy chain type IIa (MHC IIa), and the insulin-like growth factor-1 (IGF-1) [38]. STARS mRNA and protein levels are also increased 3 h following an acute bout of single-leg endurance exercise [39]. STARS has been suggested to play a role in stabilizing the sarcomere, protecting it from mechanically induced damage [33]. This transient increase in STARS following contraction-induced mechanical stress may provide a protective mechanism to reduce the risk of contractile damage to the sarcomere or be required to activate intracellular signals responsible for muscle adaptation to exercise.

Recently, STARS, MRTF-A, and SRF have been shown to be reduced in skeletal muscles from aged 24-month-old mice [40]. SRF protein levels are also reduced in mice at 15 months of age with an associated decrease in the SRF target gene, α-actin [41]. Similarly, SRF protein levels are also reduced in muscle biopsies form elderly subjects [41]. Combined, these results suggest that the loss of members of the STARS signaling pathway, in particular SRF, may contribute to the loss of muscle mass and function in older adults. As IGF-1, a transcriptional target of SRF, is also reduced in aged muscle a compromised STARS/SRF signaling pathway may contribute to reduced IGF-1 levels and associated age-related muscle wasting. It is noteworthy that SRF activity is reduced in aged liver [42] and the transgenic disruption of hepatic SRF results in impaired liver function and IGF-1 production [43]. This aging-associated decline in SRF activity may influence the reduction in circulating IGF-1 and therefore perturb the pathways involved in muscle growth and regeneration.

Nutrition and Muscle Metabolism

Many factors that contribute to sarcopenia are precipitated by subtle negative changes in behavior and/or physiology and may require several years to facilitate a significant loss of lean tissue or muscle function [7]. To this end, one area that continues to attract considerable research and lay attention is the potential change in the metabolic response to meals in older adults. In both fasting and fed states, muscle protein synthesis and breakdown are regulated by various molecular switches that in turn control a series of intracellular signaling cascades. Identifying and understanding the activation of these molecular switches complements ongoing efforts to optimize dietary strategies to preserve muscle mass and function.

Anabolic resistance is characterized by an impaired or blunted cellular response to anabolic stimuli, such as protein ingestion [31, 44]. Over time, a chronically diminished capacity to stimulate net muscle protein anabolism is likely to be a significant factor contributing to the age-related loss of muscle mass and function. Until quite recently, most studies exploring changes in muscle protein synthesis in response to nutrition interventions used isolated amino acid cocktails [45–49] or, if they were more translational in design, whey [50, 51] or soy protein [50–53]. Many of these well-controlled, single macronutrient studies clearly demonstrated acute, age-related differences in the magnitude, time-course, and regulation of muscle protein anabolism. However, an increasing number of studies using protein-rich foods (e.g., beef, dairy products) as the anabolic stimulus suggest that ingestion of a moderate-to-large serving of protein in a single meal robustly stimulates muscle protein synthesis and markers of anabolism similarly in young and older adults [54–56]. In practical terms, the threshold for an age-independent increase in muscle protein anabolism appears to be a meal containing approximately 25–30 g of protein. However, older adults, particularly those who are sedentary, experience a blunted anabolic response to lower protein meals, or perhaps even meals containing a mix of protein and carbohydrate [57, 58]. This potential protein "threshold" response is consistent with the concept of anabolic resistance in older adults and is the focus of much ongoing research.

Essential amino acids, or specifically the branched chain amino acids (BCAA) and especially leucine, directly activate the mammalian target of rapamycin (mTOR) signaling pathway [59]. The mTOR complex consists of mTORC1 and mTORC2 that have distinct roles in the regulation muscle protein synthesis. mTORC1 activates several kinases including S6 kinase (S6K) and eIF4E [60, 61]. Activation of this signaling cascade increases cellular protein translation and initiation resulting in increased protein synthesis. As noted, in some older adults there is a blunted anabolic response to insulin and amino acids resulting in reduced mTOR phosphorylation and a decreased ability to initiate protein translation [57, 62, 63]. Similar observations have also been made in animal models (e.g., 20-month- vs. 8-month-old rats) [64]. An attenuated vasodilatory response to insulin in the elderly may also reduce the amount of available amino acids to the muscle [65].

Inflammation and Oxidative Stress

An increasing number of older individuals are at risk of sarcopenic obesity, an increase in fat mass with a concomitant reduction in muscle mass. Lipid accumulation has well-described negative effects on anabolic signaling via its activation of pro-inflammatory factors such as tumor necrosis factor alpha (TNF-α) and nuclear factor kappa-light-chain enhancer of activated B cells (NFκB) [66]. TNF-α, NFκB, and interlukin-6 (IL-6) are increased in muscle from older individuals [31, 67]. TNF-α may negatively influence muscle mass and function by reducing muscle protein synthesis and/or increasing protein degradation [68]. The inflammation-induced loss of muscle mass and function is complex and yet to be completely understood. However, TNF-α is a key signaling molecule activating apoptosis in skeletal muscle and it has been shown that apoptosis, inflammation, and oxidative damage play a role in age-related loss in muscle mass and strength [69, 70]. TNF-α also synthesizes ceramide [71], which is elevated in muscle from older individuals [72]. Ceramide reduces amino acid availability and inhibits the activation of Akt, mTOR, and ribosomal S6 protein [73, 74] as well as blunting muscle cell protein synthesis [73] (see Fig. 7.2).

Nutrition is a key modifiable factor with the potential to positively and negatively influence inflammation, apoptosis, and oxidative damage as well as ceramide levels. Consequently, understanding how nutrient ingestion can impact the molecular signals influencing muscle mass and function is important for the development of appropriate nutritional interventions. A TNF-α-dependent mechanism has been shown to reduce muscle protein synthesis during sepsis, an extreme model of systemic inflammation. This was facilitated/accompanied by reductions in mTOR, S6K, and 4E-BP1 [75]. Inflammation and TNF-α may also negatively influence skeletal muscle by decreasing growth hormone (GH) and IGF-1 [76] (see Fig. 7.2). IGF-1 gene transcription is controlled by GH via a Janus kinase-2 (JAK2)/signal transducer and activator of transcription-5b (STAT5b) signaling pathway [77, 78]. Reduced IGF levels in aged muscle may be linked to reduced circulating levels of GH [79], GH-receptor content [28] or GH sensitivity [80]. TNF-α regulates the transcription of suppressor of cytokine signaling-3 (SOCS3) [81], with the latter able to inhibit GH signaling to JAK2 and STAT5b [82, 83]. SOCS3 levels are increased in elderly males, although this is not associated with reduced STATb phosphorylation [28]. This suggests that the age-related reduction in IGF-1 mRNA may be influenced by a GH/SOCS3 pathway but independent of STAT5b transcriptional perturbation.

Exercise

To understand the benefits of exercise, it is useful to first consider the consequences of its absence. A sedentary lifestyle is undoubtedly a key precipitating factor contributing to sarcopenia [84]. Taking a lack of physical activity to an extreme, bed-rest studies clearly show that significant muscle mass and functional capacity can be lost in a very short period of time. Further, the rate of loss appears to be much greater in older adults, compared to a younger study population [48, 85] (e.g., >1 kg muscle loss during 10 days bed rest vs. 0.5 kg during 28 days bed rest). Two of the key negative adaptions are motor unit denervation and the preferential loss of fast twitch/type II muscle fibers. Both of these changes have the potential to reduce the ability to generate muscle power (i.e., the ability to rapidly apply force), which is necessary to successfully perform many activities of daily living and protect against unexpected events such as tripping or falling [86].

Intracellular stress induced by exercise can obviously be a potent anabolic stimulus. While basal (i.e., fasted and rested) muscle protein synthesis rates are similar in healthy young and older adults, like nutrition, some older subjects may also experience a blunted anabolic response to exercise. The age-related factors contributing to this are not precisely known; however, investigations into the molecular regulation of exercise-induced protein synthesis have shed some light.

Resistance Exercise

Resistance exercise training can effectively increase muscle mass and strength in older populations [87, 88]. Looking at the early adaptations that may ultimately contribute to phenotypic change; it has been demonstrated in cell culture models [20], rodents [89], and humans [90] that muscle protein synthesis requires activation of the mTORC1 pathway. Following an acute bout of resistance exercise, protein synthesis increases in both younger and older adults in a dose (i.e., intensity) -dependent manner [91, 92]. However, in many instances the duration or magnitude of the increase in protein synthesis appears to be slightly lower in the older subjects [92]. A similar age-related response has been observed following 4 months of resistance training [93]. The attenuated protein synthesis in the elderly following acute resistance exercise is associated with an impaired activation of mTORC1 (96), p70S6K and 4E-BP1 [92] (see Fig. 7.2). Similarly, a blunted activation of Akt/mTOR signaling has been observed in aged rat skeletal muscle following contractile stimulation known to induce muscle growth [94].

Endurance Exercise

Despite the compelling image of elite endurance athletes (e.g., marathon runners) with very little muscle mass, aerobic exercise per se is not an *anti-anabolic* activity. Endurance exercise can increase mitochondrial and myofibrillar protein synthesis [95], while chronic endurance training has been shown to activate mTOR and stimulate muscle hypertrophy [96]. These positive adaptations are important as mitochondrial mass and function tend to decrease with age [97]. Peroxisome proliferator-activated receptor-gamma (PPAR-γ) coactivator 1 alpha (PGC-1α) is a key regulator of mitochondrial biogenesis [98] and is reduced in aging muscle [99]. PGC-1α suppresses production of reactive oxygen species (ROS) [100], and its overexpression in mice protects against the on-set of sarcopenia [101]. Endurance exercise up regulates PGC-1α [102], and this may play a role in maintaining aging muscle mass as PGC-1α also inhibits lysosomal and proteasomal protein degradation via suppression of transcriptional activity of Forkhead (FoXO) transcription factors [103], the latter known to be increased in muscle from aging humans [104] and rats [105].

Low-Intensity Activities

Despite the concern that some types of physical activity may be impractical or medically contraindicated in frail older adults or patient populations, it is nonetheless clear that almost any form of physical activity is preferable to inactivity or bed rest. Numerous studies have reported robust improvements in muscle mass and strength following higher-intensity resistance exercise training programs in older adults [106]. In contrast, in a NASA-supported 21-day bed-rest study, we demonstrated that low-intensity muscular activity can also largely prevent the typical decline in muscle mass and function observed with physical inactivity. Specifically, spending as little as 1 h each day on a specially designed human centrifuge (2.5× gravity at the feet) was sufficient to maintain muscle protein synthesis [107] and partially preserve lower extremity muscle function [86]. In a clinical setting, this supports the growing consensus that even brief periods of very low intensity activity, such as walking or simply weight-bearing, may provide health benefits.

Combining Exercise and Nutrition

In almost every acute muscle metabolism study, the combination of physical activity and protein/amino acid ingestion has a positive, additive-like effect on skeletal muscle protein synthesis [58]. In a series of recent studies, we reported a 50 % increase in mixed muscle protein synthesis in cohorts of young and older adults following ingestion of a single protein-rich meal (i.e., lean beef). When subjects completed a simple bout of resistance exercise (i.e., leg extension exercise) immediately following the same meal, we observed a further 50 % increase in muscle protein synthesis during the same time frame.

This observation that aging does not necessarily impair the ability to stimulate muscle protein synthesis in response to exercise and an actual protein-rich meal is certainly encouraging news for older adults. However, as noted earlier, it is clear that in some instances the magnitude and/or time course of changes in muscle protein anabolism may differ with age. For example, in young adults, ingestion of 20 g of essential amino acids 1 h following a bout of resistance exercise has been shown to maximally increase muscle protein synthesis during a 1–3-h post-exercise period. In a cohort of older adults, the magnitude of the increase in muscle protein synthesis was similar; however, the peak did not occur until 3–6 h post-exercise [91]. Thus, it appears that while many elements of the signaling pathway (e.g., mTOR, S6K1, 4E-BP1, eEF2) are not directly affected by age, others (e.g., ERK1/2 signaling and AMPK activation) may be less responsive, thereby contributing to the delayed increase in muscle protein synthesis in older adults.

Finally, while carefully controlled, acute research studies can provide a great deal of useful mechanistic data [51, 52, 54], they often fail to reflect a realistic exercise and/or eating experience or predict a longer term outcome (e.g., a change in muscle mass or strength). Further, due to the invasive nature of clinical trials that involve procedures such as stable isotope infusions, muscle biopsies, and rigorous exercise testing, participation is often limited to older adults who are in remarkably good health, and perhaps not representative of the larger aging population. There is clearly a need to adopt a more translational research approach to current acute/mechanistic feeding studies by linking them to longer duration outcome studies.

Conclusion

Sarcopenia has debilitating consequences for the elderly community and considerable impact on health-care systems. As our society ages and continues to demand higher living standards and quality of life, identifying lifestyle and/or therapeutic interventions to maintain skeletal muscle mass and function remains a key focus for biomedical and health research. A multidisciplinary research approach, combining human clinical interventions, with molecular interventions in animal models and cells, will harness the minds and diverse research strengths of scientists interested in healthy aging. This approach will provide the greatest opportunity to enhance our understanding of the regulation and maintenance of muscle mass and function during aging.

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Chapter 8
Nutrition in the Prevention and Treatment of Cognitive Decline

Grace E. Giles, Kristen E. D'Anci, and Robin B. Kanarek

Key Points

- Epidemiological studies suggest that nutrients including B vitamins, vitamin D, polyphenol, and omega-3 fatty acid intake are associated with enhanced cognitive function in older adults.
- Randomized controlled trials provide mixed evidence that nutritional manipulations slow the progression of age-related cognitive decline.
- Diets such as the Mediterranean diet may be beneficial in slowing cognitive decline.

Keywords Aging • Cognitive function • Alzheimer's disease • B vitamins • Vitamin D • Polyphenols • Fruit • Tea • Chocolate • Omega-3 polyunsaturated fatty acids • Mediterranean diet

Introduction

Aging is often accompanied by cognitive changes, the direction of which depends on the specific cognitive domain. For instance, knowledge and procedural memory remain relatively unimpaired, whereas selective attention, processing speed, working memory, and episodic memory frequently decline with age [1–3]. Cognitive decline not only goes along with normal aging, but also can serve as an early indicator of more severe cognitive problems, including Alzheimer's disease and other forms of dementia [4]. In elderly individuals, the estimated prevalence of mild cognitive impairment is 16 %, while the estimated prevalence of Alzheimer's disease is 13 %, and all forms of dementia is 46 % [5–7].

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Cognitive decline, however, is not an inevitable consequence of aging. Rather, cognitive functioning may be influenced by a number of lifestyle variables, including nutrient intake [8]. For example, as reviewed in the present chapter, there is evidence that individual nutrients (e.g., vitamin B_6, vitamin B_{12}, folic acid, and vitamin D) as well as foods containing phytochemicals and fatty acids may moderate age-related cognitive decline.

Three types of study designs have been employed to evaluate the influence of nutrition on cognitive aging: cross-sectional, prospective, and randomized controlled trials. Cross-sectional studies evaluate the association between nutrition and cognition at one time point. Thus, these studies provide a momentary picture of the association of nutrient intake on cognitive behavior; however, they cannot provide information on the important question of the long-term consequences of nutrition on cognitive abilities. In comparison, prospective studies determine the role of initial nutritional status on later cognitive outcomes. Using this methodology, the effect of nutrient intake on changes in mental abilities across time can be evaluated [9, 10]. As an example of these methodologies, Kalmijn and colleagues (1997) employed both a cross-sectional study, which evaluated the association between baseline polyunsaturated fatty acid intake and cognitive function in elderly men, and a prospective study, which assessed whether baseline fatty acid intake predicted cognitive decline 1–3 years later [11].

Findings from epidemiological studies are informative because they offer clues to potential associations between nutrition and cognitive behavior. However, as epidemiological designs are correlational by nature, they cannot be used to draw causal conclusions about the effect of a specific nutrient or food on behavior. For example, a positive association between fish intake and cognitive performance cannot be interpreted as meaning that increased fish consumption will improve mental functioning or prevent cognitive decline in the elderly. It is just as possible that elderly individuals who consume more fish have a healthier diet, a greater level of education, and/or are more physically active than those who consume less fish. Second, epidemiological studies often quantify food intake using food frequency questionnaires (FFQ) or 24-h food recalls. However, it is well known that there are wide variations in day to day food intake, and that memory problems, especially in the elderly, may impair accurate recollections of food intake [12, 13]. For this latter reason, some studies have used blood levels of a nutrient or other biomarkers as a measure of nutrient status.

In contrast to epidemiological studies, randomized double-blind, placebo-controlled trials (RCTs) that directly assess the effect of a dietary supplement on behavior have the potential to identify causal links between diet and cognition. However, these studies also have limitations. For example, determining the appropriate amount of a nutrient to study (e.g., vitamin B_6 or folic acid) is often difficult. Very low levels of a nutrient may be associated with difficulties in performing cognitive tasks. As the level of nutrient intake increases, mental functioning improves until optimal performance is achieved. Further, increases of the nutrient may have no effect, or in some cases, may actually lead to toxicity and impairments in performance of cognitive tasks [14]. The duration of the nutrient manipulation, as well as whether the nutrient is given alone or in combination with other nutrients, can also influence the outcomes of RCTs [14].

The study population must also be considered when comparing RCTs assessing the role of a nutrient on cognitive performance in elderly individuals. Across studies, populations vary with respect to a variety of factors, including overall health, medication use, age, degree of cognitive decline, duration of cognitive problems, and the presence of illnesses (e.g., gastrointestinal disorders) or medications that may interfere with nutrient absorption. Another factor to consider when conducting RCTs is the baseline nutritional status of the participants. Some RCTs have investigated the effects of a particular nutrient on cognitive performance in individuals whose intake of the nutrient is at optimal levels, while others have examined the effect of the same nutrient in individuals with suboptimal intakes.

It is important to emphasize that cognitive function is not a unitary concept, but rather can be divided into a number of domains, including attention, episodic memory, semantic memory, spatial orientation, decision making, and executive functioning. Unfortunately, there is little consistency across studies with respect to either the cognitive domains studied, or the specific cognitive tests used [15].

Indeed, in a recent systematic review of 39 RTCs assessing the effects of flavonoids and micronutrients on cognitive performance, Macready and colleagues (2010) reported that 121 different cognitive tests were used. They also noted that while some cognitive domains (e.g., working memory; executive functioning; and global cognitive impairment) were well represented in RCTs, other domains (e.g., psychomotor processing speed; perception; episodic memory; and procedural memory) received much less attention. Additionally, while some researchers explored the effect of a nutrient on only one cognitive domain, others measured nutrient effects on multiple domains using one or more cognitive task [15].

The most common behavioral measure used to assess global cognitive impairment and quantify age-related cognitive decline is the Mini-Mental State Examination, which combines a number of cognitive domains, including memory, attention, and consciousness among others, into one composite score [16]. This score ranges from 0 to 30, and averages 27 among adults over 65 years old. It is estimated that scores decrease 3–4 points per year following onset of Alzheimer's disease [17]. Although the MMSE has been used extensively in RCTs examining nutrient intake and cognitive functioning, questions have been raised whether the test is sensitive enough to reveal subtle cognitive changes that may be associated with dietary manipulations [15]. Other frequently used cognitive tests include the forward and backward digit span test; Stroop color test; trails test; and the Ray figure task; see [15, 18] for a summary of cognitive measures utilized in geriatric psychiatry.

Finally, it should be remembered that damages to the areas of the brain mediating cognitive behavior may occur much earlier than outward signs of cognitive decline and that by the time the effects of a nutrient are assessed, the brain may be irreversibly altered.

B Vitamins

Support for the importance of the B vitamins, especially vitamin B_6, vitamin $B_{12,}$ and folate, for normal brain activity was initially provided by research demonstrating that severe deficiencies of these vitamins were associated with impairments in neurological and psychological functioning. While severe B-vitamin deficiencies are rare in the United States, milder, subclinical B-vitamin deficiencies are not uncommon in the elderly due to poor appetite, interactions with medications, and age-related decrements in the absorption of these vitamins [19–23]. It has been hypothesized that these subclinical B-vitamin deficiencies may contribute to age-related decrements in cognitive abilities and the eventual development of dementia by impairing methylation reactions which are critical for normal brain functioning [22, 24–26].

More specifically, vitamins B_6 and B_{12}, and folate are critical components of the one-carbon metabolism cycle. In brief, the essential amino acid methionine is converted to S-adenosyl-methionine (SAM). SAM is the primary methyl donor in a number of reactions, including creatine synthesis, neurotransmitter synthesis and catabolism, and DNA synthesis, and is the sole methyl donor for reactions in the brain [27–29]. Once SAM yields its methyl group, it is converted to S-adenosyl-homocysteine (SAH), which is subsequently hydrolyzed into the sulfur-containing amino acid homocysteine. Homocysteine is then recycled into methionine, a methylation reaction requiring both folate and B_{12}, or catalyzed into the amino acid cysteine via B_6-dependent reactions. In folate or vitamin B_{12} deficiency, remethylation of homocysteine to methionine and its subsequent conversion to SAM are impaired. Vitamin B_{12} and folate are closely linked in the methylation process, such that a B_{12} deficiency can lead to a secondary folate deficiency. To convert homocysteine to methionine, vitamin B_{12} binds to methionine synthase, and accepts a methyl group from folate (as 5-methyl tetrahydrofolate [5-methyl THF]). Without vitamin B_{12}, 5-methyl THF becomes "trapped" and is not available for reactions (i.e., DNA synthesis) further downstream [30]. With vitamin B_6 deficiency, homocysteine clearance is also impaired. Thus, high levels of homocysteine are seen with deficiency of folate, vitamin B_6 and/or B_{12}.

It has been hypothesized that an elevated level of homocysteine can be neurotoxic and can contribute to the etiology of cerebrovascular disease, including stroke and vascular dementia (e.g., [25, 31, 32]). In support of this hypothesis, a number of studies, but not all (e.g., [33]), have found that individuals with high levels of homocysteine display greater age-related cognitive deficits and a higher risk of dementia than those with lower levels [25, 34–37]. Moreover, several cross-sectional studies have found that patients with Alzheimer's disease have significantly higher total homocysteine than either age-matched hospitalized controls or healthy community-dwelling elderly individuals [38–40]. For example, in one longitudinal study, higher levels of homocysteine in Alzheimer's patients were associated with a greater progression of hippocampal atrophy and a greater decline in Mini Mental State Evaluation scores [41]. Additionally, recent studies using magnetic resonance imaging of healthy participants have found an inverse relationship between plasma homocysteine levels and brain size [42].

Initial epidemiological evidence supporting a relationship between vitamin B status and cognitive function in older individuals was provided in 1983 by Goodwin and colleagues who reported that healthy elderly individuals with low intakes or blood levels of vitamin B_{12}, folate, vitamin E, and riboflavin did more poorly on tests of memory and abstract thinking than elderly individuals with higher intakes or blood levels of these vitamins [43]. A number of subsequent cross-sectional studies have confirmed this initial finding, with individuals with low vitamin B status with or without high homocysteine levels, performing more poorly on cognitive tasks than their more adequately nourished counterparts [34, 44–47]. Additionally, other cross-sectional studies have observed that patients with Alzheimer's disease have lower serum concentrations of B vitamins than those without the disease and further that the severity of the deficiency is associated with the severity of the disease [25, 26, 35, 48–55].

Results of several prospective studies point to an inverse relationship between vitamin B status and cognitive decline with individuals with initially lower blood levels of B vitamins displaying a greater risk of subsequent cognitive impairment and dementia than those with higher blood levels of the vitamins [26, 35]. For example, Tucker and colleagues (2005) reported that over a 3-year period, low baseline levels of B vitamins predicted cognitive decline [47]. However, other studies have found no association between vitamin B status and the risk of subsequent dementia [56–58].

It is important to stress that it is difficult to compare the effects of B vitamin supplementation in mediating age-related cognitive decline across studies as studies have varied widely in a number of variables such as the exact composition of the vitamin supplements; the duration of supplementation; the cognitive tests used; the participant's age, health, nutritional status, and other confounding variables (e.g., socioeconomic status; smoking and physical activity) [58]. Additionally, recent work has suggested that genetic factors may moderate the interaction between cognitive performance and B vitamin status. For example, Vogiatzoglou et al. (2013) found that among well-nourished healthy elderly, the detrimental effects of low levels of vitamin B_{12} on cognitive performance were more pronounced in individuals with the ApoE $\varepsilon 4$ allele, which is the first identified genetic risk factor for Alzheimer's disease [59].

While it has yet to be determined whether homocysteine is causative in cognitive decline, the relationship between B vitamins, homocysteine, and cognition has been intensively studied and reviewed elsewhere [25, 31, 32]. Generally, low B vitamin status with or without high homocysteine is associated with poorer cognitive outcomes [34, 44–47] as well as Alzheimer's disease [52–55] Although a number of studies have shown an inverse relationship between B vitamin status and homocysteine levels, and a positive relationship between B vitamin status and better cognitive performance in older individuals, not all studies show a clear relationship (for review see [57]). However, newer work examining gene–nutrient interactions has cast new light on factors that play an important role in the relationship between B vitamin status and cognitive performance. Discussed below are some of the more widely studied gene–nutrient interactions, but the field continues to evolve.

Interaction Between APOE ε4 Genotype and B Vitamins

Carriers of the apolipoprotein E (APOE) $\varepsilon 4$ allele have an increased chance of developing Alzheimer's disease. Presence of the APOE $\varepsilon 4$ allele is also associated with earlier onset of cognitive impairment. However, presence of the APOE $\varepsilon 4$ allele does not guarantee that an individual will inevitably develop Alzheimer's disease. Lifestyle factors such as diet, exercise, and smoking can influence the etiology and progression of the disease.

More recent work has examined the relationship between the APOE $\varepsilon 4$ genotype, B vitamin status, and Alzheimer's disease. Some of these studies suggest that there is an interaction between APOE $\varepsilon 4$ status and B vitamin status in cognitive performance such that carriers of the APOE $\varepsilon 4$ allele may be at greater risk for the negative consequences of high homocysteine or low B vitamin status. It is not clear, however, whether the relationship between APOE $\varepsilon 4$ status, B vitamin status, and cognitive performance is directly related to brain function, or if the relationship is more indirectly a result of increased risk for cardiovascular disease [60, 61].

Cross-sectional data show that in carriers of the APOE $\varepsilon 4$ allele, higher vitamin B_{12} status is more strongly associated with cognitive performance relative to noncarriers [62] and that high homocysteine in APOE $\varepsilon 4$ carriers is more strongly associated with poorer cognitive function relative to noncarriers [63]. In the Hordaland Homocysteine Study [59], vitamin B_{12} status was positively associated with cognitive performance. In particular, higher levels of vitamin B_{12} were associated with better global cognition in APOE $\varepsilon 4$ carriers relative to noncarriers. However, longitudinal studies show a much weaker outcome dependent upon APOE $\varepsilon 4$ genotype. While Brown et al. (2011) showed a cross-sectional relationship among APOE $\varepsilon 4$ status, B vitamin status, and cognitive function, after 7 years follow-up, there was only a significant relationship between APOE $\varepsilon 4$ carriers, low vitamin B_6 status, and a verbal cognitive task [64]. Other research demonstrated that although presence of the APOE $\varepsilon 4$ allele, elevated homocysteine, and low folate status were more frequently observed in patients with mild cognitive impairment relative to matched controls, these factors were not predictive of subsequent progression to dementia [61]. Presence of the MTHFR C677T polymorphism, discussed in more detail below, may also play a significant role in the relationship between APOE $\varepsilon 4$ genotype and B vitamin status. While the distribution of MTHFR genotype does not appear to be related to APOE $\varepsilon 4$ genotype, some research suggests that presence of both the APOE $\varepsilon 4$ allele and MTHFR TT polymorphism may aggravate the impact of B vitamin deficiency. For example, in comparison with patients with mild cognitive impairment or matched controls, patients with Alzheimer's disease have higher levels of homocysteine, and this observation is stronger in the presence of the MTHFR TT genotype and low folate status [65]. Additionally, some research shows that while total homocysteine may be elevated in patients with Alzheimer's disease, there may be a stronger relationship between high LDL cholesterol levels and cognitive performance in Alzheimer's disease than B vitamin levels [60]. These studies indicate a need for further elucidation of the nature of the relationship between APOE $\varepsilon 4$ genotype, nutritional status, and progression of cognitive decline.

Methylenetetrahydrofolate Reductase (MTHFR) Genotype

Recent research examining the gene–nutrient interaction between folate status and polymorphisms in the methyltetrahydrofolate reductase (MTHFR) gene has shown that individuals with the MTHFR 677T allele (CT or TT) are less efficient in utilizing available folate, specifically in the reduction of 5,10-methylene THF to 5-methyl THF, and thus may have higher folate requirements than those with

the MTHFR 677 CC genotype. In the United States, where folic acid fortification is mandatory, rates of folate deficiency are relatively low. However, carriers of the TT polymorphism have impaired homocysteine clearance that is strongest in the presence of low folate status [66].

A number of epidemiological studies provide data suggesting that poor vitamin B status could contribute to the development of age-related dementias. However, results of randomized-controlled trials comparing the cognitive consequences of vitamin B supplementation to placebo have shown limited utility of the use of B vitamin therapy in combating age-related cognitive decline. Moreover, although the links between high-homocysteine and cognitive impairment have been extensively examined, the evidence is incomplete. At present the data support the idea that high-homocysteine, rather than being causative in the etiology of disease, may serve instead as a biomarker for other pathological processes. Finally, as the science evolves, we are gaining a better understanding about the importance of genetic factors in the larger arena of B vitamins.

Vitamin D

Vitamin D, sometimes known as the "sunshine vitamin," is a fat-soluble steroid hormone naturally synthesized from 7-dehydrocholesterol when ultraviolet-B rays from the sun reach the skin. Small amounts of vitamin D are also obtained from the diet from fatty fish (e.g., salmon, mackerel, and tuna), fish oils, beef liver, and egg yolks, and from dairy foods and cereals specifically fortified with the vitamin. In addition, many individuals obtain vitamin D in the form of dietary supplements [67]. Whether obtained from sunlight or intake of food or supplements, vitamin D is physiologically inert until it is converted to 25-hydroxyvitamin D[25(OH)D] in the liver, and subsequently to the active form of the vitamin 1,25-dihydroxyvitamin D[1,25$(OH)_2$D], primarily in the kidney. As it represents a reliable and relatively stable measure of bioavailability, serum level of 25(OH)D expressed as either ng/mL or nmole/L is typically used as an indicator of vitamin D status. However, it should be noted that techniques for measuring vitamin D have not been consistent across countries, which has confounded efforts to develop international guidelines for the vitamin [68].

Currently, there is no clear consensus on the optimum serum level of 25(OH)D. However, most experts have concluded that a minimum level of between 50 and 75 nmol/L 25(OH)D is needed for good health [69–71]. Using these values, a significant proportion of the world's population has lower than the recommended levels of vitamin D (hypovitaminosis D). Older individuals are particularly at risk for hypovitaminosis D as a result of (1) consuming a diet with less than adequate vitamin D, (2) having a reduced capacity to metabolize the vitamin, and (3) having limited exposure to sunlight [67, 69, 71, 72].

Vitamin D is best known for its role in building and maintaining strong bones. The vitamin facilitates calcium absorption from the gastrointestinal tract and maintains sufficient serum levels of calcium and phosphate for normal mineralization of bone. In children, vitamin D deficiency is associated with rickets, a disease characterized by soft bones and skeletal abnormalities while in adults, deficiency of the vitamin can result in osteomalacia whose symptoms include bone pain as well as bone and muscle weakness [67, 71]. Recent research has highlighted the fact that vitamin D deficiency also increases the risk for a number of age-related diseases, including cardiovascular disease, metabolic syndrome, type 2 diabetes, stroke, and cancer [70, 73, 74].

Of particular import to the present chapter, is the mounting evidence demonstrating that vitamin D is critical for the normal functioning of the nervous system, and that vitamin D deficiency may contribute to age-related decrements in cognitive behavior. Initial indications of the importance of vitamin D in modulating nervous system activity came from research describing vitamin D receptors (VDR) and the enzymes necessary for the synthesis of the active form of the vitamin throughout the brain and spinal cord. VDR expression is found in both neurons and glial cells particularly in areas of the brain associated with cognitive behavior including the cortex, hippocampus, thalamus, basal ganglia, hypothalamus, and amygdala [75].

Support for the importance of VDR for brain functioning is provided by studies demonstrating that animals born to mothers who were vitamin D deficient during pregnancy displayed morphological changes in the brain including larger brains, cortical layer thinning and larger than normal lateral ventricles relative to control animals [76]. These alterations in brain structure were associated with discrete changes in learning and memory such as impaired latent inhibition and reduced habituation [77]. Similarly, VDR knockout mice display abnormalities in brain function and cognitive behavior including high anxiety, abnormal grooming behavior, impaired nest building, and aberrant maternal behaviors [78, 79].

Vitamin D plays a variety of roles within the nervous system. For example, the vitamin is important for mediating the synthesis of a number of neurotransmitters (e.g., dopamine, serotonin, catecholamines, and acetylcholine) and for up-regulating the synthesis of several neurotrophic factors (e.g., nerve growth factor and glial cell line derived neurotrophic factor) which promote the development and survival of neurons and glial cells [75, 80]. Studies in experimental animals demonstrating that vitamin D administration (1) decreases neuronal injury resulting from neurological trauma, and (2) protects against stress-induced apoptosis in hippocampal neurons have helped to establish a neuroprotective role for the vitamin. Additionally, vitamin D has both antioxidant and anti-inflammatory properties. With respect to aging, it has been proposed that vitamin D protects against age-related inflammatory changes in the hippocampus and reduces hippocampal biomarkers of aging [81, 82]. Moreover, recent work has demonstrated that injections of vitamin D not only mitigate age-related changes in inflammatory state, but also decreases the memory impairments seen in aged animals [83]. Vitamin D also strongly stimulates phagocytosis and augments the removal of amyloid β, one of the characteristic pathological biomarkers found in the brains of individuals with Alzheimer's disease [75, 80, 83, 84].

Results of a number of cross-sectional studies have found that low serum vitamin D levels are associated with impairments in cognitive functioning in older individuals (e.g., [85–89]). For example, Annweiler and coworkers (2010) observed that older community-dwelling French women with lower levels of serum 25(OH)D displayed more cognitive deficits than women with higher serum 25(OH)D levels [90]. In a subsequent study, the same research group, noted that older men and women with mild cognitive impairment (MCI) had lower serum 25(OH)D concentrations than their cognitively healthy counterparts [91]. Further support for the potentially detrimental cognitive effects of hypovitaminosis D is provided by a recent systematic review by van der Schaft and colleagues (2013) who reported that in 18 out of 25 cross-sectional studies, individuals with low vitamin D levels did more poorly on tests of cognitive functioning or displayed a higher frequency of dementia than individuals with higher serum levels of the vitamin [92]. Research demonstrating that individuals with Alzheimer's disease have lower serum levels of 25(OH)D than suitably matched individuals without the disease suggest that hypovitaminosis D could ultimately play a role in the etiology of Alzheimer's disease [93–98].

Prospective studies have examined whether initial vitamin D status predicts later development of cognitive deficits and the risk of suffering from dementia. In the majority of these studies, over time, participants with initially low vitamin D intake or serum levels of 25(OH)D displayed significantly greater declines in performance on cognitive tasks and/or a higher frequency of dementia than participants who began the study with better vitamin D status [92, 97, 99, 100].

While the results of cross-sectional and prospective studies suggest that impaired vitamin D status may contribute to cognitive decline in elderly individuals, as noted above, these types of studies cannot verify causality. Rather than contributing to the development of age-related cognitive decline and Alzheimer's disease, it is possible that vitamin D deficiency represents a consequence, rather than a cause, of cognitive deficits in elderly individuals. Age-related degenerative illnesses, such as Alzheimer's disease are often marked by a reduction in mobility and outdoor activity, and thus a decrease in exposure to sunlight. Moreover, as these diseases progress many patients experience feeding difficulties leading to a decrease in dietary intake of vitamin D, or are taking medications which interfere with absorption of the vitamin [97].

While a number of epidemiological studies suggest a relationship between vitamin D levels and mental functioning, the results of RCTs investigating the effects of vitamin D on cognitive behavior have been more mixed. In an early RCT, Dhesi and colleagues (2004) found that relative to a placebo injection, a single intramuscular injection of 600,000 IU vitamin D increased serum levels of the vitamin and improved reaction time in a choice situation in individuals who had a history of falling and a low baseline serum level of 25(OH)D [101]. More recently, Annweiler et al. (2012) observed that older outpatients given vitamin D_3 supplements for 16 months had significantly higher serum levels of 25(OH)D and better cognitive performance, particularly executive functioning, than controls given a placebo [102]. In contrast, Przybelski and coworkers (2008) reported that while oral administration of 50,000 IU of vitamin D three times a week for 4 weeks increased serum 25(OH)D levels in nursing home residents, vitamin D supplementation did not lead to improvements in either cognitive or motor behavior [103]. As intranasal insulin can acutely improve cognition and vitamin D enhances insulin actions in the brain, Stein et al. (2011) explored the effects of a high dose of vitamin D_2 followed by intranasal insulin in community dwelling participants with mild to moderate Alzheimer's disease [104]. All participants received a low-dose of insulin (1,000 IU) for 16 weeks, followed by either a high-dose of vitamin D or placebo for 8 weeks. While serum levels of 25(OH)D increased following the high dose of vitamin D, the high dose of vitamin D provided no benefits in cognitive behavior relative to the low dose of the vitamin. In the largest study to date, healthy, elderly women from 40 Women's Health Initiatives clinics were randomized to receive either 400 IU vitamin D in combination with 1,000 mg calcium or placebo. After a mean follow-up of 7.8 years, no differences in the incident of mild cognitive impairments or in cognitive functioning on a number of domain-specific cognitive functions were found between the two groups [105].

While RCTs have not consistently supported the concept that vitamin D supplementation has a positive effect on cognitive functioning in the elderly, these types of studies should not be ignored. Rather, more studies systematically assessing variables such as the dose and duration of supplementation, and sex and age should be conducted. Moreover, these studies should begin by investigating the effect of a nutrient in individuals with less than adequate nutrient intake [14].

Polyphenols

Polyphenols are organic compounds found in a variety of foods most notably fruits, vegetables, and beverages. Among others actions, these compounds have antioxidant, antibiotic, and anti-inflammatory properties [106]. The fact that polyphenols reduce oxidation within the nervous system is of particular interest to cognitive aging, as oxidative stress is believed to play a role in the etiology of Alzheimer's disease [107]. Additionally, these compounds stimulate neurogenesis and neuronal regeneration and can protect neurons from injury induced by neurotoxins [2, 108].

There is growing evidence that fruits and vegetables containing polyphenols can counteract age-related declines in cognitive functioning [109, 110]. Indeed, a recent cross-sectional study found that older adults with "questionable dementia," whose cognitive scores fell between cognitively normal and mild dementia, reported lower appetite and lower intakes of total food, fruits and vegetables, and fluids than cognitively normal older adults [111]. A second cross-sectional study evaluating the relationship between plant food consumption and performance on a number of cognitive tests, including the Mini-Mental State Examination as well as tests measuring memory, executive function, perceptual speed, and visuospatial skills found that older adults who ate more vegetables performed better on tasks measuring executive function, perceptual speed, and semantic memory while those who ate more fruit performed better on tasks measuring visuospatial skills and both episodic and semantic memory. Both fruit and vegetable consumption conferred benefit on Mini-Mental State Examination scores [112].

Unlike cross-sectional studies which are limited to one time point, prospective studies allow us to determine whether higher intake of fruits and vegetables predicts cognitive performance over time. In support of a positive role for foods containing polyphenols in preventing the development of age-related cognitive decline, two studies found that although total fruit intake was unrelated to cognitive decline, higher intake of vegetables, especially green leafy vegetables, predicted reduced cognitive impairment over 6 years [113, 114]. Similar results were found in a 5-year prospective study, in which vegetable intake, particularly root vegetables and cabbage, was associated with a reduced decline in information processing speed. Again, no effect was found for fruit intake [115]. However, other studies have found conflicting results. For example, Peneau and colleagues (2011) reported that while higher combined intake of fruits and vegetables, as well as total intake of fruit at baseline predicted enhanced verbal memory 13 years later, in contrast, however, they found that higher combined intake of fruits and vegetables and total vegetable intake actually was associated with lower scores on tests of executive function [116].

Together the previous studies provide preliminary evidence that global polyphenol intake may relate to cognitive performance in older individuals, but the cross-sectional and prospective nature of the studies makes it impossible to determine whether polyphenols play a causal role in cognitive aging. This limitation pertains not only to the aforementioned studies, but also to the majority of those in the subsequent sections, as most research on polyphenols and aging has utilized epidemiological designs. However, a number of RCTs have assessed the efficacy of polyphenol-rich foods including blueberries, grapes, and ginkgo biloba extract on cognitive aging, including Alzheimer's disease.

Berries and Grapes

There is now substantial evidence that consuming foods containing phytochemicals such as those found in berries can help to reduce age-related memory loss. Initial support for this idea came from preclinical studies demonstrating that prolonged intake of blueberries reduced a number of the cognitive impairments typically seen in older laboratory animals [117]. It has been hypothesized that these beneficial effects are related to the polyphenolic compounds found in blueberries and other fruits. These compounds, such as the anthocyanins, which are responsible for the color of these fruits, cross the blood brain barrier to become localized in areas of the brain related to learning and memory (e.g., hippocampus). In the brain, these phytochemicals decrease vulnerability to the oxidative stress that occurs with aging, reduce inflammation, and may increase neuronal signaling [2, 118].

Recent studies indicate that intake of berries may have positive effects on cognitive aging in humans as well as laboratory rodents. For example, Devore et al. (2012) reported that higher consumption of blueberries and strawberries over a 6-year period predicted a slower decline in global cognitive and verbal function in older women [118].

Randomized controlled trials evaluating the efficacy of fruit juice, specifically cranberry, blueberry, and grape juice, on cognitive performance in older adults offer promising evidence for a beneficial effect of fruit juice on cognitive function. For instance, 6 weeks of blueberry juice supplementation in older adults showing signs of memory decline but not dementia resulted in improvement in associative learning and recall relative to placebo [119]. Similarly, 12 weeks of grape juice supplementation in individuals with memory decline but not dementia enhanced verbal learning and retention relative to placebo [120]. The same group found no differences in learning and retention as a result of 16 weeks of grape juice supplementation, but did find reduced semantic interference during recognition memory in individuals with mild cognitive impairment [121]. However not all studies have found beneficial effects of juice consumption on behavior. In particular, 6 weeks of cranberry juice supplementation in healthy older adults had no influence of cognitive measures of memory, intelligence, attention, or executive function [122]. Taken together, epidemiological studies and RCTs provide preliminary support for concluding that fruit, especially berries and grapes, impede cognitive aging (for review, see [2]).

Green Tea

Green tea is a rich source of another class of polyphenols, called flavanols. Catechins, a subclass of flavanols, comprise approximately 30 % dry weight of the tea leaf [123]. Green tea contains a higher concentration of polyphenols than black or oolong tea because unlike black or oolong tea, its preparation does not result in oxidation of leaf polyphenols. In Japanese adults over the age of 70 years, intake of green tea, but not black or oolong tea, was associated with less cognitive impairment, evidenced by higher scores on the Mini Mental State Examination [124]. In comparison, green, black, and oolong tea all were associated with higher Mini Mental State Examination scores, but only black and oolong tea predicted a slower reduction in scores over a 1- to 2-year follow-up, possibly owing in part, to greater consumption of black and oolong tea than green tea among older individuals [125]. Green tea consumption was also associated with lower psychological distress [126]. Thus, epidemiological evidence suggests that green tea consumption may reduce the risk of cognitive decline, yet RCTs are necessary to verify the causal nature of this relationship.

Chocolate

Chocolate and other cocoa products are becoming recognized as a rich source of flavanols with potent antioxidant and anti-inflammatory actions [127]. While most research has concentrated on the effects of chocolate on the cardiovascular system, there are a growing number of RCTs aimed at appraising the effects of chocolate intake on cognitive functions. The majority of these RCTs have focused on healthy young adults. These trials provide conflicting results, with some showing no impact of chocolate on cognitive behavior [128, 129] and others finding improvement in mental fatigue, sustained attention, and working memory [130, 131]. Research in older adults is similarly inconsistent. Flavanoid- and procyanidin-rich dark chocolate had no effects on a wide range of neuropsychological tests in healthy older adults [132]. However in older adults with mild cognitive impairment, flavanol-rich cocoa improved executive function, verbal memory, and processing speed [133], suggesting that cocoa may have more beneficial effects in individuals who have experienced cognitive impairments than those who are cognitively healthy.

Total Polyphenol Intake

Although most studies have focused on individual classes or sources of polyphenols, recent work has evaluated the association between cognition and polyphenol intake across multiple classes of polyphenols. The first study used a cross-sectional design to assess the correlation between flavanoid intake and cognitive performance among older men and women [134]. Flavanoid intake was determined using a food frequency questionnaire. Cognitive measures, including the Moray House Test, a measure of intelligence and verbal reasoning, the National Adult Reading Test, the Wechsler Adult Intelligence Scale-III, and the Mini-Mental State Examination, were grouped into three factors: memory, intelligence, and processing speed. Intake of a number of flavanoid-rich foods was associated with improved cognitive performance, including total fruit, citrus fruit, total vegetable, red wine, and chocolate. However, these effects were no longer significant after adjusting for childhood IQ and socioeconomic status.

The second study evaluated the relationship between polyphenol consumption at age 66 and cognitive performance 13 years later [135]. Analysis of all cognitive measures factored into two cognitive components: (1) language and verbal abilities, which were positively associated with intake of total polyphenols and total flavanoids, as well as with a number of specific classes of these compounds

including catechins and flavanols and (2) executive function, which was not correlated with total polyphenol or flavanoid intake and inversely associated with intake of foods containing catechins, proanthocyanids, and flavanols.

One final study sought to determine the association between chocolate, wine, and tea intake and cognitive function on a number of cognitive tasks including the Mini-Mental State Examination as well as others assessing episodic memory, attention, perceptual speed, and visuospatial skills [136]. Chocolate, wine, and tea intake, alone and together, were associated with enhanced cognitive function across all measures, and wine intake conferred the strongest protection against poor cognitive performance.

Monounsaturated and Polyunsaturated Fatty Acids

Omega-3 (*n*−3) and omega-6 (*n*−6) fatty acids comprise the family of polyunsaturated fatty acids. *n*−6 PUFAs include linoleic acid (LA) and arachidonic acid (ARA) whereas *n*−3 fatty-acids include alpha linolenic acid (ALA), eicosapentaenoic acid (EPA), and docohexaenoic acid (DHA) [137]. Our current western diet is comprised of a ratio of between 10:1 and 17:1 *n−6* to *n−3* PUFA. These ratios represent a shift in our diet from consumption of *n*−3 PUFA rich foods to *n*−6 PUFA r rich foods. Foods containing *n*−3 PUFAs include fish, fish oil, wild game, wheat germ, walnuts, and plants. Foods high in *n*−6 PUFAs include common vegetable oils, including corn, safflower, sunflower, and soybean oil [138, 139].

A host of research has been dedicated to determining whether polyunsaturated fatty acids (PUFA) influence cognitive aging [140–143]. Epidemiological studies assessing the influence of *n*−3 PUFAs on cognitive decline in older adults generally measure dietary intake of foods containing fatty acids and/or plasma or erythrocyte levels of the fatty acids. Associations with cognitive performance are then determined at one or more time points. The most common behavior measure used in these studies has been the Mini Mental State Exam, which is often used to characterize mild cognitive impairment or cognitive decline on a discrete yes-or-no basis.

The majority, although not all, of epidemiological studies have found positive relationships between intake of *n−3* PUFA and/or plasma erythrocyte levels of *n−3* fatty acids and cognitive function in older adults [144, 145]. For instance, intake of fish (especially nonfried fish, fatty fish, and tuna fish), fish oil, and *n*−3 PUFA supplements has been related to reductions in age-related cognitive impairments [11, 146–150]. This relationship is particularly strong in individuals who do not carry the *APOE* ε4 allele, a primary risk factor for Alzheimer's disease [147].

Other studies have computed *n*−3 and *n*−6 PUFA intake from dietary records and found that higher total *n*−3 PUFAs, EPA and DHA and lower total *n*−6 PUFAs and *n*−6:*n−3* ratios are associated with reduced cognitive decline [151–153]. Only one study thus far has found *n*−3 PUFA intake to be unrelated to cognitive function [145].

Several researchers have reported that lower levels of plasma and/or erythrocyte *n*−3 fatty acids were related to poorer cognitive performance and increased risk of cognitive decline or dementia [154–157], again with evidence suggesting that the association is particular to individuals without the *APOE* ε4 allele [157]. Further support for a relationship between PUFAs and mental functioning is provided by research demonstrating that erythrocyte EPA was lower and *n*−6 PUFAs were higher in older adults with mild cognitive impairment than in healthy individuals [158]. Although another study found no associations between plasma *n*−3 and global cognitive decline, higher plasma *n−3* levels were associated with a reduced decline in verbal fluency in individuals with higher hypertensive and dyslipidemic markers and lower depressive symptoms [159]. It should be noted that a few studies have failed to find relationships between PUFAs and cognitive performance [160–162].

RCTs assessing the influence of *n*−3 PUFA supplementation on cognitive function in healthy older adults have shown that DHA (800–900 mg/day) can improve verbal, visuospatial, and episodic

memory, and higher serum and plasma DHA were generally associated with improved cognitive scores on these measures [163, 164]. However a lower dose of DHA (i.e., 252 mg/day) did not influence cognitive function [165]. Two doses of EPA and DHA (226 mg EPA + 176 mg DHA and 2,093 mg EPA + 847 mg DHA) improved attention relative to placebo, but this effect was limited to *APOE ε*4 carriers [166]. Thus randomized controlled trials in healthy older adults generally suggest that *n*−3 PUFAs improve cognitive function.

n−6 PUFAs can augment β-amyloid deposition, a primary neurological symptom of Alzheimer's disease, while *n*−3 PUFAs (or low *n*−6 to *n*−3 ratios) may reduce the effects of *n*−6 PUFAs on β-amyloid deposition [167]. These findings suggest that supplementation with *n*−3 PUFA may have beneficial cognitive functions in individuals with mild cognitive deficits or Alzheimer's disease. In support of this section, *n*−3 PUFAs reduced memory and attention decrements in older adults with mild Alzheimer's disease and reduced memory impairments in individuals with more severe Alzheimer's disease [168]. Similarly, *n*−3 PUFA supplementation improved global clinical status in individuals with mild to moderate Alzheimer's disease. Moreover, the higher proportion of red blood cell membrane EPA, the greater the reduction in cognitive deficits [169]. DHA-rich fish oil enhanced verbal fluency in older adults with mild cognitive impairment, and both EPA- and DHA-rich fish oil improved depressive symptoms [170]. In contrast, other work showed no influence of *n*−3 PUFA supplementation in individuals with mild to moderate Alzheimer's disease [171].

Whereas the majority of studies focus on polyunsaturated fatty acids, and generally use monounsaturated fatty acids as controls, one study evaluated the relationship between olive oil use and cognitive decline, including tests of global cognitive decline, visual memory, and verbal fluency [172]. At baseline, high or moderate olive oil intake was correlated with better visual memory and verbal fluency but not related to global cognitive function. Across 4 years, "intensive" olive oil intake (i.e., using olive oil both in cooking and dressing foods, rather than one or the other) predicted reduced cognitive decline in visual memory and verbal fluency, but again no effect on global cognitive function.

Epidemiological results showing that higher *n*−3 PUFA intake and plasma levels are associated with reduced overall cognitive decline are supported by some RCTs showing that *n*−3 PUFA supplementation, particularly DHA, reverses age-related cognitive decline in otherwise healthy individuals [163, 164, 166], but there is less evidence to suggest such an effect in individuals with mild cognitive impairment and Alzheimer's disease. Alzheimer's disease risk factors included history of depression and carrying the *APOE ε4* gene may influence *n*−3 PUFAs' efficacy in preventing cognitive decline in older adults [147, 152, 157].

Mediterranean Diet

Dietary consumption of polyphenols varies geographically, ranging from approximately 800 mg/day in Finland and Spain [173, 174] to 1,000 mg/day in Poland [175]. Polyphenol intake may be particularly high in Mediterranean countries [174, 176] which rely heavily on polyphenol-rich foods including fruits, vegetables, and legumes. These foods, along with cereals, low-fat dairy products, olive oil, spices, onions, fish, and white meat, as well as wine in moderation, constitute the "Mediterranean Diet," which may confer health benefits over diets with less emphasis on plants and unsaturated oils [177]. Studies that examined the relationship between the Mediterranean Diet and cognitive aging typically utilize a 0–9 point scale, with higher scores indicating greater adherence to the Mediterranean diet [178]. Beneficial food groups, including fruits, vegetables, legumes, cereals, and fish are assigned a 0 for intake below the median and 1 for intake above the median, whereas detrimental food groups, including meat, full-fat dairy, and ratio of monounsaturated to saturated fat, are assigned a 1 for intake below and 0 for intake above the median. Moderate alcohol intake is assigned a 1 while low and high alcohol intake is assigned a 0.

In individuals free of cognitive impairment at baseline, overall adherence to the Mediterranean diet was not associated with developing mild cognitive impairment over a 4 year period. Indeed, counter to expectation, higher intake of monounsaturated fats and fish predicted greater cognitive decline [179]. However, analyses did not take into account fish type or preparation. Other studies have evaluated cognitively healthy individuals at high cardiovascular risk. In a cross-sectional analysis, high consumption of olive oil, coffee, walnuts, and wine as well as total urinary polyphenol excretion was associated with enhanced memory and global cognitive function [180]. In contrast, a prospective study carried over a 5-year period found no evidence that adherence to the Mediterranean diet predicts cognitive decline among individuals with vascular disease or at risk for vascular disease [181].

Results of studies assessing the effects of the Mediterranean diet on cognitive behavior in individuals with Alzheimer's disease have been inconsistent. For example, Scarmeas and colleagues (2007) reported that in older adults with Alzheimer's disease at baseline, adherence to the Mediterranean diet was associated with reduced mortality over a 4-year period [182]. Moreover, higher Mediterranean diet scores were associated with slower global cognitive decline on the Mini-Mental State Examination in older adults with dementia, but not with tests of specific cognitive domains including verbal fluency and episodic memory [183]. It is important to note that in studies which assess adherence to the Mediterranean diet in non-Mediterranean subjects, diet may not completely reflect the true Mediterranean diet and, thus, results may not be representative of older adults who fully follow the Mediterranean diet. For example, despite similar overall adherence to the Mediterranean diet, individuals in France [183] consumed more fruits and vegetables than those in the United States [184].

In a comparison of older adults cognitively healthy at baseline to those with mild cognitive impairment, greater adherence to the Mediterranean diet was associated with reduced progression from mild cognitive impairment to Alzheimer's disease, as well as marginally significant reduction in procession from healthy cognition to mild cognitive impairment [184]. Also in older adults with and without mild cognitive impairment, higher intake of vegetables, unsaturated to saturated fatty acid ratio and moderate alcohol was associated with reduced risk of mild cognitive impairment, specifically in individuals with impairment in memory, but not individuals with impairments in nonmemory cognitive domains [185]. Finally, the Mediterranean diet but not another measure of healthy diet, i.e., Healthy Eating Index, which is based on recommendation from the Dietary Guideline for Americans, was protective against cognitive decline [186]. Thus the majority of studies found some protective effect of the Mediterranean diet against age-related cognitive decline in healthy older adults [180, 186] as well as those with cognitive impairment or Alzheimer's disease [183–185, 187].

Thus, together with evidence that individual components of the Mediterranean diet, including polyphenol-rich fruits, vegetables, and red wine and *n*−3 PUFA-rich fish, enhance cognitive function, adherence to the Mediterranean diet may slow the progression of age-related decline. However, the timeline with which nutrition may influence cognitive aging remains relatively unexplored, as the majority of evidence for such a relationship stems from epidemiological studies. Future research should seek to better understand whether adherence to the Mediterranean diet and intake of other macro- and micronutrients discussed in this chapter are necessary in early adulthood to protect against cognitive decline, or whether these nutritional manipulations can slow cognitive decline beginning in old age.

Conclusion

As noted in the introduction, a number of variables should be considered when evaluating the role of vitamins and other nutrients on cognitive behavior in the elderly: age, nutrient status, combination of nutrients, amount of nutrients in RCTs, cognitive tasks, number of participants, and measurements of vitamin status [58]. Additionally, variables in cohort studies, including physical activity, socioeconomic status, comorbid diseases, and genetic factors such as the *APOE* ε4 allele, may confound results.

Nevertheless, the evidence reviewed here that nutrition may influence cognitive function in older adults, and in some cases slow the progression of cognitive aging, as in the case, for example of the Mediterranean diet. Nutrition is of particular interest in older adults, as food intake generally declines with age, often resulting in poor protein, vitamin, and mineral consumption [188].

For instance, high homocysteine and/or low vitamin B status was associated with reduced cognitive scores and increased risk of cognitive decline, particularly in individuals with the *APOE ε*4 allele [34–37, 43–47, 59–61]. However, results from RCTs do not present such convincing evidence, suggesting that elevated homocysteine may serve as a biomarker, rather than cause, of age-related cognitive decline. Likewise, serum vitamin D levels and intake have been associated with reduced cognitive decline (for review, see [92]). But, whereas some RCTs found beneficial cognitive effects of vitamin D supplementation [101, 102], others did not [103–105].

Polyphenols, *n*−3 PUFA, and diets heavy in polyphenol-rich fruits and vegetables, i.e., Mediterranean diet, are also associated with reduced cognitive decline in older adults [183–187]. Polyphenol-rich fruit and vegetable intake, particularly berries and grapes, is correlated with and stimulates improved global cognitive function as evidenced by both epidemiological and randomized controlled trials [118–120]. The same is true for *n*−3 PUFA plasma and erythrocyte levels [146–150] and intake [163, 164], particularly in healthy older adults rather than those with Alzheimer's disease [166].

Thus, across the vitamins and foods reviewed in this chapter, a consistent finding was that intake was associated with higher cognitive scores across cross-sectional and prospective studies, while the relationship was less clear in randomized controlled trials. Thus future research should focus on determining whether a causal relationship exists between diet and cognitive function, including pinpointing particular populations who may benefit most from improved nutrition (e.g., individuals with versus without heightened risk for Alzheimer's disease) and determining optimal intake values among older adults.

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Chapter 9
Food Insecurity and Hunger Among Older Adults

David R. Buys and Julie L. Locher

Key Points

- Food insecurity is a pressing public health issue for older adults.
- Older adults may be less likely than some other segments of the general population to experience food insecurity, but those who are food insecure are likely to remain food insecure and to experience its effects to a greater degree.
- Dealing with food insecurity among older adults requires a multi-pronged approach, including continued support for government programs, such as the Nutrition Services provided for by the Older Americans Act and the Supplemental Nutrition Assistance Program, and private sector programs, such as food banks.

Keywords Food insecurity • Hunger • Undernutrition • Obesity

Introduction: Food (In)Security, Hunger, and Undernutrition

Meeting nutritional needs is necessary for optimal health across the lifespan and especially for older adults [1, 2]. However, it is not always feasible to access the foods needed to obtain desirable health outcomes. Therefore, it is important to understand what factors enable, constrain, or are associated with individuals' ability to access and consume healthful foods. This is especially true for older adults who may be susceptible to irreversible changes in their diet as they encounter illnesses and changes in their eating behaviors with advancing age [3, 4]. Food (in)security is a helpful construct in trying to understand forces that may promote or impede how people obtain and consume nutrition.

The World Health Organization (WHO) defines food security as existing "when all people at all times have access to sufficient, safe, nutritious food to maintain a healthy and active life" [5]. WHO posits that food security has three pillars: availability, access, and use of food. *Availability* refers to

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having an adequate amount of food to feed all people; this is not currently a problem in the United States or most other nations as there is a large enough food supply for most persons around the world. *Access* is more of a problem in the United States, however, and refers to individuals "having sufficient resources to obtain appropriate foods for a nutritious diet." Finally, *Use* refers to "appropriate use based on knowledge of basic nutrition and care, as well as adequate water and sanitation." Proper food use requires adequate access to food and education about what dietary practices are appropriate for a healthy lifestyle [5]. When availability, access and use are not in equilibrium, a state of food insecurity is present. Combating food insecurity and working toward a state of food security is important, so much so that it has been called the "linchpin of healthful living" [6].

Measurement and Definition of Food (In)Security in the United States

The term food (in)security was first operationalized for use in the US context in 1989 by an expert panel of the Life Sciences Research Office (LSRO) as having "access to enough food for an active, healthy life" [7]. Similar to the WHO definition, food security requires availability of and access to nutritionally appropriate foods without food assistance from emergency food supplies, illegal means, or other coping strategies. *Food insecurity*, in contrast, exists "whenever the availability of nutritionally adequate and safe foods or the ability to acquire acceptable foods in socially acceptable ways is limited or uncertain" [8]. Food insecurity specifically refers to a condition stemming from poverty or other factors, not voluntary nutritional modifications such as fasting. While in the general population, poverty is the most likely factor to cause food insecurity, among older adults it may be caused by physical impairments or disabilities that limit their ability to procure, prepare and/or consume the food [9, 10].

After the LSRO conceptualized food (in)security, in 1990, the United States Congress mandated that trends in nutrition and food security in the US be monitored; and these new measures of food (in) security were to be focused on whole households, rather than on individuals. This led to funding for the first administration of the Food Security Supplement (FSS) to assess prevalence rates of food insecurity in 1995. Initially sponsored by the Economic Research Service of the United States Department of Agriculture (USDA), measures of food insecurity have since been collected annually by the Census Bureau's Current Population Survey. Early categories of food security included three categories, from most to least severe: "food insecurity with hunger," "food insecurity without hunger," and "food security." In 2006, a National Academy of Sciences panel made recommendations for updated categories of food (in)security that would distinguish between food insecurity and hunger [11, 12] and ensure that the categories were conceptually and operationally sound and able to relay pertinent and actionable information to policy makers [13]. Questions from the current Core Food Security Module (CFSM) used to assess food (in)security are presented in Table 9.1.

The categories of food insecurity that emerged from these questions are high, marginal, low, and very low food security. *High food security* is a "state in which there are no reported indications of food-access problems or limitations." *Marginal food security* is a state of "one or two reported indications—typically of anxiety over food insufficiency or shortage of food in the house." There would be little or no indication of changes in diets or food intake. Households with *low food security* (formerly "food insecurity without hunger") report "reduced quality, variety, or desirability of diet." They also report little or no indication of reduced food intake. Households with *very low food security* (formerly "food insecurity with hunger") report "multiple indications of disrupted eating patterns and reduced food intake" [13]. Households that indicate three or more of any of these conditions of food insecurity are classified as food insecure, including that individuals in households: (1) worried their food would run out before getting more money; (2) bought food that didn't last and didn't have money for more; and (3) couldn't afford to eat balanced meals. Additionally, households with adults who indicated that they

Table 9.1 Survey questions in the FSS that assess household food security

1. "We worried whether our food would run out before we got money to buy more." Was that often, sometimes, or never true for you in the last 12 months?
2. "The food that we bought just didn't last and we didn't have money to get more." Was that often, sometimes, or never true for you in the last 12 months?
3. "We couldn't afford to eat balanced meals." Was that often, sometimes, or never true for you in the last 12 months?
4. In the last 12 months, did you or other adults in the household ever cut the size of your meals or skip meals because there wasn't enough money for food? (Yes/No)
5. (If yes to question 4) How often did this happen—almost every month, some months but not every month, or in only 1 or 2 months?
6. In the last 12 months, did you ever eat less than you felt you should because there wasn't enough money for food? (Yes/No)
7. In the last 12 months, were you ever hungry, but didn't eat, because there wasn't enough money for food? (Yes/No)
8. In the last 12 months, did you lose weight because there wasn't enough money for food? (Yes/No)
9. In the last 12 months did you or other adults in your household ever not eat for a whole day because there wasn't enough money for food? (Yes/No)
10. (If yes to question 9) How often did this happen—almost every month, some months but not every month, or in only 1 or 2 months?

(*Questions 11–18 were asked only if the household included children age 0–17*)

11. "We relied on only a few kinds of low-cost food to feed our children because we were running out of money to buy food." Was that often, sometimes, or never true for you in the last 12 months?
12. "We couldn't feed our children a balanced meal, because we couldn't afford that." Was that often, sometimes, or never true for you in the last 12 months?
13. "The children were not eating enough because we just couldn't afford enough food." Was that often, sometimes, or never true for you in the last 12 months?
14. In the last 12 months, did you ever cut the size of any of the children's meals because there wasn't enough money for food? (Yes/No)
15. In the last 12 months, were the children ever hungry but you just couldn't afford more food? (Yes/No)
16. In the last 12 months, did any of the children ever skip a meal because there wasn't enough money for food? (Yes/No)
17. (If yes to question 16) How often did this happen—almost every month, some months but not every month, or in only 1 or 2 months?
18. In the last 12 months did any of the children ever not eat for a whole day because there wasn't enough money for food? (Yes/No)

Source: Food Insecurity in the US: Measurement: United States Department of Agriculture: Economic Research Service; 2012 [cited 2012]. Available from: http://www.ers.usda.gov/topics/food-nutrition-assistance/food-security-in-the-us/measurement.aspx#.UV35bKKG3eA

ate less than what they felt they should and that they cut the size of their meals or skipped meals in at least 3 months were classified as having very low food security. Because the U.S. Household Food Security Scale asks about hunger over the previous year, it is sensitive to rare, occasional, or episodic occurrences of food insecurity [14], not just recent episodes or occasions. When a household contains one or more persons responding affirmatively to the questions about food insecurity, the full household is considered food insecure [12].

Communities, likewise, may be considered food (in)secure; that is, they may be in "A situation in which all community residents [are unable to] obtain a safe, culturally acceptable, nutritionally adequate diet through a sustainable food system that maximizes self-reliance and social justice," [15] without resorting to emergency food sources [16]. In contrast, communities that are food secure have conditions in place that enable their residents to access healthy foods that support complete well-being [17]. While community food security is relatively easily defined, measuring it is not so easy; Cohen and colleagues proposed an assessment tool for community food insecurity, but uptake has been slow because of its complexity [18]. Food (in)security is a measure at the household, community, or higher-level, but it has implications for more individual-level challenges like hunger and malnutrition, including undernutrition and obesity.

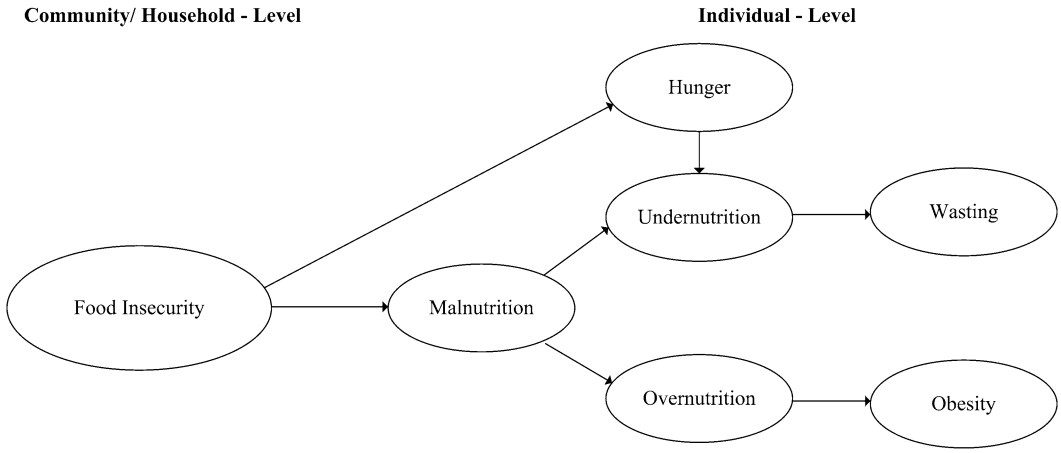

Fig. 9.1 Conceptual model of the association of food insecurity with individual nutrition-related outcomes

Hunger

Hunger is "a potential consequence of food insecurity that, because of prolonged, involuntary lack of food, results in discomfort, illness, weakness, or pain that goes beyond the usual uneasy sensation" [13]; furthermore, it "may produce malnutrition over time" [7]. Hunger is distinct from food insecurity, though sometimes, it is an indicator or consequence of it. Furthermore, hunger is an individual-level condition that should be assessed at that level, in contrast to food insecurity, which is usually assessed at the household or community level [12, 19]. Hunger, as a social problem, has been recognized by society for much longer than food insecurity [12]. However, even given the longstanding recognition that hunger is a problem, older adults may experience unrecognized hunger and consequently be less likely to benefit from efforts to combat hunger through government services and private organizations like SNAP or food banks [20]. This is likely because older adults may have subclinical nutrient deficiencies such as iron, folic acid, and vitamin A, but not demonstrable clinical indications of undernutrition such as wasting or other signs that would indicate the presence of hunger to the naked eye [21].

Malnutrition

Malnutrition is "a condition brought about by insufficient intake of nutrients to meet biological requirements" [12] and may manifest itself as either undernutrition, leading to wasting or as overnutrition, leading to obesity [22]. Both of these will be described further in the next sections (Fig. 9.1).

Undernutrition

Undernutrition is a specific nutritional state which has been characterized by unintentional weight loss, low anthropometric measurements, abnormal biochemical markers, poor nutritional intake as indicated by nutrition screening instruments [23]. Undernourishment has also been defined by the

FAO as a state "when caloric intake is below the minimum dietary energy requirement," and is considered to be "an extreme form of food insecurity" [24]. The specific causes of weight loss in older adults include anorexia, cachexia, malabsorption, hypermetabolism, dehydration, and sarcopenia. The prevalence rates of these conditions are estimated to be 5–10 % of persons in nursing homes and up to 50 % of persons discharged from hospitals [25]. More information on definitions and measurement of undernutrition, malnutrition, and nutritional risk is presented in Chap. 3.

Overnutrition and Obesity

Food insecurity has historically been associated with undernutrition, and older adults have been stereotyped as underweight and frail. However, in the past decade, there has been a rise in the proportion of obese older adults, and food insecurity has become increasingly recognized as a factor contributing to overnutrition and obesity [19, 25–27]. "Overnutrition" [or consumption of excess calories] may stem from access to and use of foods of high calorie/low nutrient density that exceed the caloric needs of those needed for the individual consuming them [21]. Habits of excess kcal consumption that may have existed over a lifetime become exacerbated in older age with the loss of lean muscle mass, with the net effect of sarcopenic obesity [28, 29]. Thus, ironically, it is possible to be both overnourished according to one measure (i.e., calories consumed), yet undernourished according to another (i.e., macro- and micro-nutrients consumed).

It is also the case that persons who are food insecure may be more likely to live in poorer neighborhoods with less access to stores that sell nutritious foods or those for special dietary needs [30], limiting their ability to buy foods necessary for a healthy lifestyle. They may resort to purchasing low nutrient-dense foods with higher energy that are more convenient and affordable for them [35]. Ultimately, the overabundance of inexpensive and nutritionally-depleted foods contributes to obesity among persons in food insecure communities or households [19]. This may cyclically exacerbate food insecurity in older adults who become unable because of mobility restrictions to travel beyond their own neighborhoods to shop for more nutritionally dense foods.

The Distribution of Food (In)Security in the Population

Individual and Household Characteristics of Food (In)Security

The characteristics of individuals and households living with food insecurity vary across the population. In 2011, 14.9 % of all US households were food insecure (living with low or very low food security), an increase from 10.5 % in 2000 [31]. Figure 9.2 demonstrates current rates of food (in) security in the United States.

Among the total population, 5.7 % were living with very low food security in 2011, up from 5.4 % the previous year, which was a statistically significant increase. Those numbers were as low as 3 % in 2000, increasing to 4 % in 2004, and remaining unchanged through 2007 when they began to increase to current levels. Factors associated with food (in)security among the general population, were low social capital, rural residence, lower income, lower education, and minority status [32].

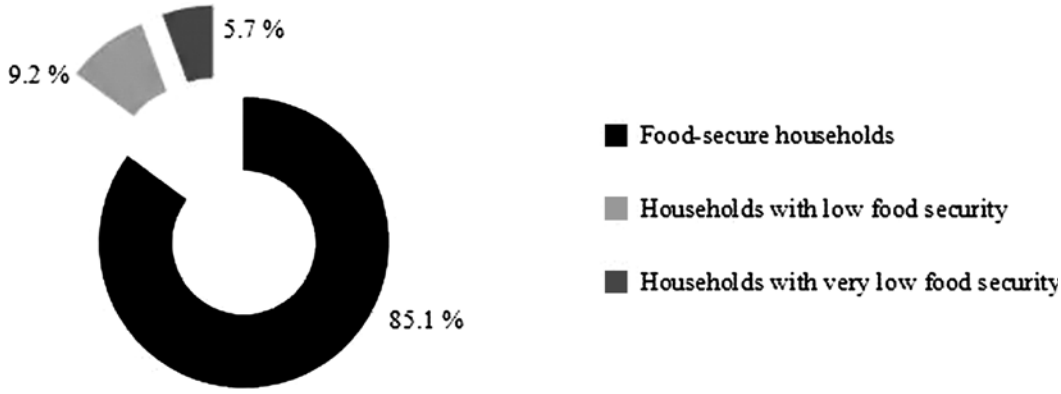

Fig. 9.2 U.S. households by food security status, 2011. Reprinted from [33]

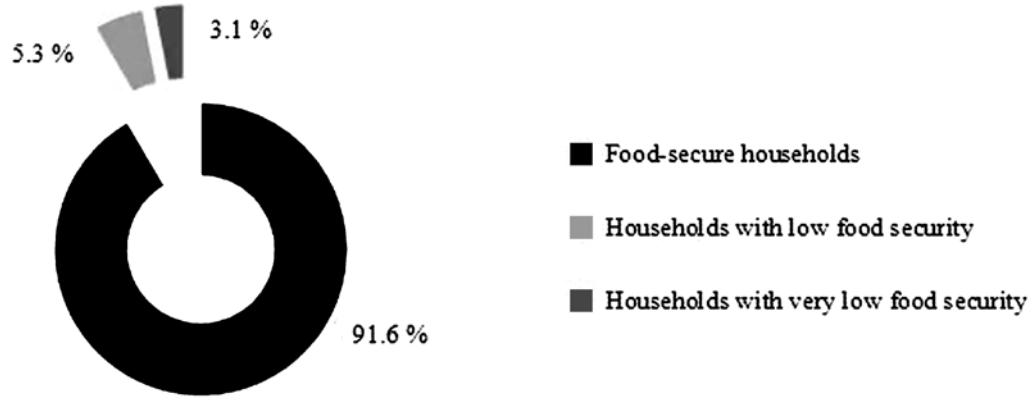

Fig. 9.3 U.S. households with older adults by food security status, 2011. Reprinted from [33]

Food (In)Security Characteristics for Middle and Older Adults

In 2011, among households with older adults (65+), 8.4 % were food insecure (Fig. 9.3).

Among this older adult population, 5.3 % lived with low food security, and 3.1 % lived with very low food security [33]. Also, about 19 % of households with adults ages 60 and over who were living below 185 % of the poverty line were food insecure [22].

Prior to 2011, between 2007 and 2009, when the US economy was under duress, food insecurity among middle and older adults saw some notable changes. Persons 40–49 years old experienced a 68 % increase between 2007 and 2009, compared to 38 % increases for 50–59 year olds, and a 25 % increase among those 60 and older. Overall however, older individuals were less likely to be food insecure than younger ones. Yet, food insecurity was more prevalent in larger households of older adults (with two or more persons) and among individuals that had less than a high school diploma, had disabilities related to work, or were in rented homes [34, 35].

Between 2006 and 2008, the number of poor and near poor older adults who did not know where their next meal would come from doubled from 4.7 to 10.1 % [36]. This rate is projected to increase to nearly 13 % by 2025, when the youngest Baby Boomers turn 65. Factors predictive of food

insecurity among older adults, include living with a grandchild, living alone, being African American or Hispanic, living in or near poverty, having less than a high school education and being a renter. Specifically, food insecurity among older adults with a grandchild in the home is at least twice that of older adults without a grandchild living in their home [37]. Furthermore, food insecurity among the poor and near poor are two to three times greater for persons over age 50 than for the general population. Notably, though, after 2007, food insecurity did not increase at the same rate among the poor and near poor as it did for persons in higher income brackets. This is indicative that the economic recession had the greatest impact for food insecurity among those with higher incomes [31].

In general, food insecurity is strongly linked with poverty and may be either transitory [i.e., varying throughout the year or through the lifecourse] or chronic. Unlike children and/or young and middle-aged adults, older adults with limited resources are more likely to experience chronic poverty and food insecurity because they are less likely to acquire new, additional resources and move out of poverty. Whereas younger persons experience seasonal or temporary food insecurity [e.g., that which may be associated with an economic downturn or job loss], older adults who are dependent upon Social Security or Supplemental Security Income for the rest of their lives are not able to break out of poverty, and, thus are likely to remain food insecure without assistance.

Geographic Variation in Food (In)Security

Regional differences in food insecurity among older adults were significant in 2011, ranging from 16 % in the South to 15.8 % in the West, to 13.5 % in the Midwest, and the Northeast [33]. The disparity in food insecurity between states is also substantial, with the lowest rate of food insecurity at 1.5 % in North Dakota and climbing to over eight times greater in Mississippi, with a rate of 12.3 %. Furthermore, persons living with very low food security ranged from 2.6 % in North Dakota to 6.8 % in Alabama [35]; with regards to older adults, eight of the states with the highest rates of food insecurity are in the South.

Large cities and rural areas have more food insecure older adults than suburban areas and other outlying areas around large cities [33]. Food insecurity differs, as well, for those older adults in metropolitan versus nonmetropolitan areas. For example, married persons are less likely to be food insecure than unmarried persons in metro areas, but not nonmetro areas. Also, older adults living alone in metropolitan areas are twice as likely to be food insecure as those not living alone, but there is no relationship in nonmetro areas [36].

Health Implications of Food (In)Security

Food insecurity, hunger, and undernutrition represent different health-related challenges for all individuals and specifically for older adults. Risk factors associated with inadequate nutritional intake include poverty, race, living alone, chronic diseases, cognitive status, dentition, location of residence, polypharmacy, and household food sufficiency [2]. Among the general population, an association has been observed between food insecurity, hypertension, hyperlipidemia, and diabetes. Among persons living in households with very low food security, there was a twofold increase in diabetes risk compared to those in food-secure households. Furthermore, adults with diabetes in food-insecure households had higher hemoglobin A1c values relative to persons in food-secure households, indicating that people in food insecure homes may not be managing their diabetes well through diet [27]. Additionally, food insecurity has been associated with poor physical and mental health status, including depression in women [6]. Specifically, anxiety, feelings of alienation and deprivation, distress, and adverse changes in family and social interactions sometimes occur as a result of food insecurity [12].

Food (In)Security and Health Among Older Adults

Food insecurity poses specific health-related challenges for older adults. Among persons 60–69 years old who live at less than 200 % of the poverty level and who are food insecure, 28 % of them have diabetes, compared to 19 % of persons who are food secure. Among all persons 60–69 who are food insecure, 10 % report depressive symptomology compared to 4 % of those who are food secure. Of those who are food insecure, 87 % indicated at least one activities of daily living limitation, compared to 72 % of those who are food secure. Finally, among persons food insecure, 42 % reported having excellent, very good, or good health, compared to 61 % of persons who are food secure [35, 36]. Older adults 65+ who were food insecure reported greater health services utilization [38], and those who presented at emergency departments from food insecure contexts had greater comorbidities than those who came from food-secure ones [39]. Also, Lee et al. [9] found that food insecure older adults were more likely to have poorer dietary intake, nutritional status, and health status than food-secure persons. Finally, food insecure persons ages 60 years and older have statistically significant lower nutrient intakes; and food insecure persons ages 50 years and older are less likely to be in excellent or very good health [40].

Among slightly younger persons, those 50–59, 19 % of food insecure people had diabetes compared with 10 % food-secure people. Among persons who were food insecure, 16 % reported depressive symptomology compared to 3 % of those who were food secure. Of those who were food secure, 52 % indicated at least one activities of daily living limitation, compared to 21 % of those who were food secure. After adjusting for income, race, and education, food insecurity affected activities of daily living, such that, a food insecure person had a rating like that of a food-secure adult 14 years older. These food-insecure adults were also more likely than food-secure persons to have diabetes. Furthermore, prevalence of food insecurity was nearly twice as high for persons with multiple physical impairments (29 %) than those with none (15 %). Finally, among these food insecure persons, only 48 % reported having excellent, very good, or good health, compared to 78 % of persons who were food secure [31].

Malnutrition and Health Among Older Adults

Malnutrition may manifest itself differently among people of different ages. Undernutrition, one aspect of malnutrition, varies for older adults according to the setting in which it is measured. Undernutrition is prevalent among 5–12 % of the community-dwelling older adult population; 5–10 % of the nursing home population; 32–50 % of hospitalized patients, and 70–92 % of homebound persons [25, 41]. Undernutrition has been shown to be a cause of pressure ulcers, hip fractures, falls, weakness, fatigue, anemia, edema, cognitive abnormalities, infections, immune dysfunction, thymic atrophy, decreased delayed hypersensitivity, decreased mitogen lymphocytes, and decreased response to immunizations, and death [25]. Furthermore, undernutrition has been associated with functional decline and increased health care utilization, including nursing home placement, and costs of care [42–44]. Weight loss stemming from undernutrition may accelerate functional decline, loss of muscle mass, balance impairment, and decreased strength and power and walking speed [2]. Also among older adults, weight loss of 5 % or more doubles the risk of death [25, 45]. Other possible causes of undernutrition are polypharmacy, which may alter desire for food; poor dentition, which may alter a person's ability to chew food; and functional status, which may impede people from shopping for and preparing food. Additionally, psychosocial issues, including mental and cognitive impairment may lead to lower nutritional status. Specifically, depression may lead to a loss of motivation to consume

enough or appropriate foods [30]. In a study of urban homebound older adults, 29 % of the women and 37 % of the men were underweight; and 38 % consumed inadequate amounts of protein and energy. Age, educational status, and oral symptoms were all predictors of lower BMI. Wearing of dentures was positively associated with BMI [46].

Overnutrition may also stem from food insecurity, as described above. Overnutrition leads to obesity, a condition affecting approximately 30 % of all older adults. Obesity-related conditions include hypertension, hyperlipidemia, and diabetes. Costs for obese versus nonobese older adults among Medicare beneficiaries are projected to be 34 % greater. In one study of older adults receiving Medicare home health services, nutritional risk among overweight and obese patients was associated with nursing home placement within 1 year of follow-up [44]. Nutritional risk, including undernutrition, is described in greater detail in Chap. 3, and obesity is discussed in Chaps. 6 and 10.

Interventions for Food Insecurity

The public health response to the food and nutritional needs of food insecure older adults may have an influence on health outcomes for many years to come [47]. By 2030, it is projected that there will be over 72 million persons over 65 years of age in the United States, nearly double that of 1996. With this shifting population, it is imperative that society address the need for appropriate nutritional health. On average, older adults reported spending 12.4 % of their income on food [48]. One report on older adults observed that while income for making food purchases was not a problem, obtaining and preparing food was challenging due to limited transportation, functional limitations, or other health impairments [10]. Because of the increasing numbers and proportion of older adults in the United States, it is especially important to consider what interventions on food insecurity may be effective.

Food Assistance for Older Adults

Because adequate nutrition is necessary for health, functionality, and the ability of older adults to remain at home in the community, it is imperative that researchers, practitioners, and advocates consider what programs exist and what needs remain for ensuring food security for older adults. Food and nutrition programs for community-residing older adults have been well described in a position paper issued jointly in 2010 by the American Dietetic Association, American Society for Nutrition, and Society for Nutrition Education [30]. In the U.S., nutrition assistance programs designed for older adults include the Older Americans Act (OAA) Nutrition Program, Senior Farmers' Market Nutrition Program, Commodity Supplemental Food Program (CSFP) for adults age 60 years and older who meet income eligibility requirements, and the Child and Adult Care Food Program (CACFP) for chronically impaired disabled adults and adults age 60 years and older in adult day care centers. Programs designed for all citizens, including older adults, include Supplemental Nutrition Assistance Program (SNAP), the Emergency Food Assistance Program, and the Emergency Food and Shelter National Board Program. Among food-insecure households, only 57 % participated in one or more of the three largest Federal food and nutrition assistance programs during the month prior to the 2011 survey [33].

Among Older Americans Act programs, there are three primary nutrition services for nutrition assistance: Home-Delivered Nutrition Services (HDN), Congregate Nutrition Services (CN), and a Nutrition Services Incentive Program. In 2010 the HDN program provided approximately 145 million meals to more than 880,000 older adults; and the CN program provided over 96.4 million meals to more than 1.7 million older adults in different community settings. These services are crucial for their

recipients as nearly 90 % of AOA clients have multiple chronic conditions, which can be combated through proper nutrition. Furthermore, nearly 35 % of older adults receiving HDN meals were unable to perform three or more activities of daily living, while 69 % were unable to perform three or more instrumental activities of daily living; these impairments are also associated with nutritional needs which were being met through the Administration on Aging (AOA) programs, and possibly preventing or delaying their need for institutional care.

In 2010, however, approximately 89 % of food-insecure older adults did not receive home-delivered or congregate meals. It was estimated that eligible persons may not participate in the OAA programs such as HDN or CN offerings for a number of potential reasons—they may have limited awareness of available services; live in areas with limited available services; receive informal services through friends, family, or other organizations; choose not to obtain government assistance; or receive nutrition assistance through other federal programs, such as SNAP. However, a recent report found that only 7 % of CN participants and 16 % of home-delivered meal recipients also received SNAP benefits [49].

While participation rates in HDN and CN program seems to be low, there is an increasing demand for OAA Elderly Nutrition Program Services. The Government Accountability Office reported that in 2010 requests for HDN and CN services have increased 79 % and 47 %, respectively, since 2007. This may reflect the increasing rates of older adults who stay in their homes rather than moving to institutional settings; it is important because the growing number of individuals eligible for HDN services are those most vulnerable for poor dietary intake, poor nutritional status, and physical disability [2].

Because, the chronic diseases that are the major causes of death among older adults include heart disease, cancer, stroke, influenza, and pneumonia, all of which are impacted by diet and nutrition, it is important to consider how to maintain food security among this population. Similarly, preventing malnutrition in older adults—including undernutrition and overnutrition—through healthy nutrition may delay or prevent the disablement process, reducing fall risk and hip fractures. Reducing these conditions may also increase functional capacity and reduce medical costs to individuals and the Medicare system [19].

One of the most frequently used programs among the general population is SNAP; not only is the SNAP program helpful for relieving individual food insecurity and hunger, the USDA found that for every $5 in new food stamp benefits, individuals spent $9 in their communities, indicating that there is an economic ripple effect [19]. Older adults have the lowest participation rates in SNAP; therefore, food access may be improved among older adults through greater participation in the program. However, the USDA's research in 2004 on why individuals who may qualify, including older adults, do not apply for benefits found that "one-third [of non-participants] did not think they were eligible, 18 % were unsure whether or not they would qualify for benefits, and a small % had never heard of the [program]." Some older adults who were aware of the process reported that they believed SNAP benefits are too low. Furthermore, the application process for SNAP may be too long and complicated for older adults, especially those with cognitive or physical impairments, who may be even less likely to apply for SNAP.

Private and community initiatives to promote food security among individuals in communities should focus on improving access to healthy and nutritious food items, increasing the self-reliance of communities in providing their own foods, and developing cross-disciplinary, inter-institutional responses to food and nutrition-related needs. These goals may be accomplished through farmers markets, community-supported agriculture programs and economic development activities [50]. Innovative programs partnering farmers markets with low income older adults to provide seasonal vegetables may be useful toward this end [51]. Further research on the effectiveness of the existing programs would also bolster the evidence-base for the continuation of these programs.

Conclusion

The evidence presented here indicates that food insecurity is hazardous to the health of the general population and older adults, alike, because of its association with malnutrition, including under- and overnutrition; physical and mental health problems; health services utilization; chronic disease management; medication management; and poor food and nutrition intake leading to malnutrition [52]. Continuing to combat food insecurity with programs like the OAA Nutrition Services and finding new ways to connect food insecure persons with resources through the OAA and SNAP is important. These programs that promote food security need to be emphasized because they have the potential to promote health, reduce disease risk, and cultivate effective disease management [30].

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Part III
Common Clinical Conditions

Chapter 10
Obesity in Older Adults and Strategies for Weight Management

Dennis T. Villareal and Krupa Shah

Key Points

- The increasing prevalence of obese older adults is a major public health issue.
- Obesity causes frailty in older adults by exacerbating the age-related decline in physical function.
- Treatment plans for obese older adults should include lifestyle interventions such as weight loss, behavior modification, and exercise therapy to improve physical function and quality of life and reduce medical complications associated with obesity.
- While treatment of obesity may improve a number of health parameters, the potential for adverse effects of weight loss on bone and muscle mass must also be taken into consideration.

Keywords Obesity • Older adults • Frailty • Weight loss • Exercise • Behavior modification • Sarcopenia

Introduction

Obesity is defined as an unhealthy excess of body fat, which increases the risk of morbidity and premature mortality. Obesity is a growing concern among adults. It has not only increased in prevalence, but it has also been associated with significant morbidity and mortality. Some of its medical risks include hypertension, diabetes, hyperlipidemia, coronary artery disease, and osteoarthritis. More so in older adults, obesity exacerbates the age-related decline in physical function, impairs quality of life, and leads to frailty. The current therapeutic and management tools designed for weight management in older persons include lifestyle intervention (diet, physical activity, and behavior modification), pharmacotherapy, and surgery. Current evidence suggests that weight-management strategies in obese

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older adults improves physical function, quality of life, and reduces medical complications. The treatment must consider the potential adverse effects of weight loss on bone and muscle mass.

This chapter will review the clinical issues related to obesity in older adults and provide health professionals with the appropriate weight-management guidelines on the basis of current evidence.

Obesity: An Epidemic

Obesity among older adults continues to grow in prevalence in the United States. Data from the National Health and Nutrition Examination Survey (NHANES) indicate that approximately one-third of United States adults are obese [1]. Likewise, in developed countries, the prevalence of obesity is increasing among older adults. The underlying reasons for the increased prevalence are an increase in the older person population, and an increase in the percentage of obesity in that population. Past studies have compared point-in-time statistics of the American older adult population and highlighted the increase in prevalence of obesity. For example, in a 10-year period between 1991 and 2000, obesity was found to grow from 14.7 to 22.9 % in the 60–69-year age group, while obesity grew from 11.4 to 15.5 % in the >70-year age group. This represents an increase of 56 and 36 % in the respective age groups [2]. More recent estimates suggest that 37 % of adults 65 years of age or older are obese (Body Mass Index, BMI $\geq$ 30 kg/m^2), and such prevalence is expected to become even more evident with the aging of "baby boomers" [3]. The prevalence of obesity in older adults will continue to challenge our health care systems [4]. Furthermore, obesity poses an increasing problem for long-term care facilities [5]. On a positive note, obesity is less likely to develop in the very old population (>80-year-olds). In this age group, the prevalence rate of obesity is considerably lower than for younger cohorts. The relatively low prevalence of obesity after 80 years of age could be due to the survival advantage of being lean [6]. Nonetheless, overall, more than 15 % of the older American population is obese, and obesity is more common in older women than in men [2]. Moreover, concern about the prevalence of geriatric obesity is not contained to the United States. It is an increasing problem of older populations throughout the world [7].

Pathophysiology of Obesity

Aging is associated with marked changes in body composition. After 30 years of age, fat-free mass (FFM), which is comprised predominantly of muscle, progressively decreases, whereas fat mass increases. FFM reaches its peak during the third decade of life, while fat mass (FM) reaches its peak during the seventh decade [8]. Subsequently, after about age 70, both indices (FFM and fat mass) decrease. Aside from quantitative changes of FFM and fat mass, aging is also associated with a redistribution of body fat and FFM. The intra-abdominal fat increases, while the subcutaneous fat and total body fat decrease [9].

Body fat is accumulated when energy input exceeds energy expenditure. The intake of energy does not change or may even decline with aging. Energy output comprises the resting metabolic rate (accounts for ~70 %), the thermal effect of food (~10 %), and physical activity (20 %). Aging is associated with a decrease in all major components of energy output. Resting metabolic rate decreases by 3 % every decade after 20 years of age. About three-fourths of this decline can be accounted for by a loss in FFM [10]. The thermal effect of food is 20 % lower in older men than in younger men [11]. Physical activity decreases with increasing age, and it accounts for about one-half of the decrease in energy output that occurs with aging [12].

As one ages, the growth hormone and testosterone production decreases, which results in a reduction in FFM and increased accumulation of fat mass [13]. Thyroid hormone-induced oxidative bursts are decreased with aging. Changes in neurohumoral modulators of appetite and body composition such as leptin and ghrelin have also been implicated as causes of obesity in later life. Resistance to leptin could result in a diminished ability to downregulate appetite [14]. These changes in hormone levels with aging could play an important role in the pathogenesis of obesity.

Measuring Overweight and Obesity

It is difficult to accurately measure body fat mass in most clinical settings because such assessments require the use of sophisticated technologies that are not readily available. Two measures for assessing overweight and total body fat content are widely used and accepted as simple methods to classify medical risk with regards to body fat; they are the body mass index (BMI) and waist circumference.

Body Mass Index

BMI is calculated as weight (kg)/height squared (m^2). The BMI is used to assess overweight and obesity and to monitor changes in body weight status. It allows meaningful comparisons of weight status within and between populations. However, in older adults, age-related changes in body composition and loss of height caused by compression of vertebral bodies and kyphosis alter the relationship between BMI and percentage body fat. Therefore, at any given BMI value, changes in body composition tend to underestimate fatness, whereas the loss of height would tend to overestimate fatness.

Waist Circumference

The presence of excess fat in the abdomen out of proportion to total body fat is an independent predictor of comorbidities such as cardiovascular disease, diabetes, and hypertension [15]. Men with a waist circumference of >40 in. and women with a waist circumference of >35 in. are considered to have increased disease risk.

Table 10.1 incorporates both BMI and waist circumference in the classification of overweight and obesity and provides an indication of relative disease risk [16].

Health Implications of Obesity

Adverse Effects of Obesity

Obesity is associated with a number of health hazards. Some adverse effects include increased mortality, health complications, poor quality of life, and disability. These hazards are discussed in detail below.

Table 10.1 Classification of overweight and obesity by BMI, waist circumference, and associated disease risk

			Disease risk[a] (Relative to normal weight and waist circumference)	
	BMI (kg/m^2)	Obesity class	Men <40 in. Women <35 in.	Men >40 in. Women >35 in.
Underweight	<18.5		–	–
Normal[b]	18.5–24.9		–	–
Overweight	25.0–29.9	I	Increased	High
Obesity	30.0–34.9	II	High	Very high
	35.0–39.9		Very high	Very high
Extreme obesity	≫40	III	Extremely high	Extremely high

[a]Disease risk for type 2 diabetes, hypertension, and CVD
[b]Increased waist circumference can also be a marker for increased risk even in persons of normal weight

Mortality

Obesity was associated with significantly higher all-cause mortality relative to the normal weight BMI in both younger and older adults [17]. Although the relative risk of death associated with obesity is greater for younger adults than for older ones [18, 19], a high BMI increases absolute mortality and health risks linearly up to 75 years of age [20]. That is, from a clinical standpoint, the health complications associated with obesity increase linearly with increasing BMI until the age of 75. The relationship of obesity in >75 years of age with total mortality is unclear. Some previous epidemiological studies do not show that excess body weight is detrimental to mortality in advancing age [21, 22]. However, underlying diseases that can themselves increase the risk of early mortality may cause the underestimation of the relation between obesity and mortality in older adults. Since those who are susceptible to the effects of obesity die at a younger age, the surviving group of obese older adults are said to be the "resistant" survivors. Furthermore, waist circumference, an indicator of central adiposity, is identified as a potentially good risk factor for mortality in obese elderly adults [23].

Comorbid Disease

Obesity and increased visceral fat are associated with increased morbidity and poor quality of life. Most studies evaluating obesity-related complications focus on middle-aged and younger adults. The prevalence of the medical complications associated with obesity, such as hypertension, diabetes, cardiovascular disease, and osteoarthritis, increases with age. Therefore, obesity and weight gain during middle age may contribute to medical complications and development of obesity-associated chronic disease, and subsequent increased health care expenditures that occur during old age [24].

Metabolic Abnormalities

There is an age-related increase in the prevalence of all of the components of the metabolic syndrome. Relative to those who are 20–34 years of age, the odds of having metabolic syndrome for those who are over 65 years of age were reported to be 5.8 in men and 4.9 in women [25]. Additionally, increased abdominal fat is independently associated with metabolic syndrome in adults aged 70–79 years [26]. Fasting plasma glucose increases by 1–2 mg/dL and postprandial glucose by 10–20 mg/dL for each decade of age after 30 years. Accordingly, the prevalence of type 2 diabetes mellitus based on standard criteria is highest in older persons [27]. The age-related increase in fat

and, more importantly, visceral fat, could be the main causative factor for the increased prevalence of diabetes mellitus and insulin resistance in the elderly. At the age of 65, there is a strong influence of BMI on the remaining lifetime risk of diabetes, with the increased risk ranging from ~3 % with BMI < 18.5 kg/m^2, 10 % with BMI 18.5–25 kg/m^2, 14 % with BMI 25–30 kg/m^2, 29 % with BMI 30–35 kg/m^2 and 35 % with BMI ≥ 35 kg/m^2 [28].

Hypertension is extremely prevalent in the older population, affecting 65 % of all persons aged >60 years [29]. Obesity and high blood pressure continue to be correlated, even in old age [30]. Obesity-related dyslipidemia (i.e., low HDL cholesterol and high serum triglyceride concentrations) is seen in both younger and older adults. In the United States, 35–42 % of white men and women who are over 65 years of age with metabolic syndrome have low HDL cholesterol (<40 mg/dL in men and <50 mg/dL in women) and high triglyceride (>150 mg/dL) concentrations [25]. Data from longitudinal studies suggest that obesity increases the risk of cardiovascular disease in older men. Elevated BMI in older 70-year-old men and women was associated with an increase in new cases of coronary artery disease, fatal and nonfatal myocardial infarction, and cardiovascular disease mortality during 12–15 years of observation [31] in older men but not in older women.

Arthritis

Osteoarthritis (OA) is the most common type of arthritis and its prevalence increases progressively with age in both sexes in parallel with the increase in body weight and fat observed with aging. The age-related increase in prevalence of OA presumably reflects bodily changes as a result of a lifetime of being overweight, which results in chronic mechanical strain on weight-bearing joints [32, 33]. In a population-based study of older adults, with a mean age of 73, the relative risk of developing knee OA increased from 0.1 for a BMI lower than 20 kg/m^2 to 13.6 for a BMI of 36 kg/m^2 or higher [34].

Pulmonary Abnormalities

Obesity is associated with obstructive sleep apnea (OSA), obesity-hypoventilation syndrome, and pulmonary function abnormalities [35]. Increased fat on the chest wall decreases lung compliance, increases the work of breathing, and reduces ventilation [36]. The prevalence of OSA increases with age. Both waist circumference and waist changes were the most powerful predictors of OSA in older obese and normal-weight men in a 30-year follow-up study [37].

Urinary Incontinence

The prevalence of urinary incontinence increases after the age of 65 and affects 15–30 % of that population. Obesity further exacerbates the high prevalence of urinary incontinence in older adults, which has been shown to be directly associated with elevated BMI [38, 39].

Cancer

Obesity is a risk factor for several types of cancer, including breast, colon, gallbladder, pancreas, and bladder amongst both men and women, more so in older than younger adults [40]. A study in older women has shown that breast cancer occurs more frequently in obese older women than all older women [40]. Obese postmenopausal women are also at higher risk of developing malignant melanoma and endometrial cancer than their nonobese counterparts [41].

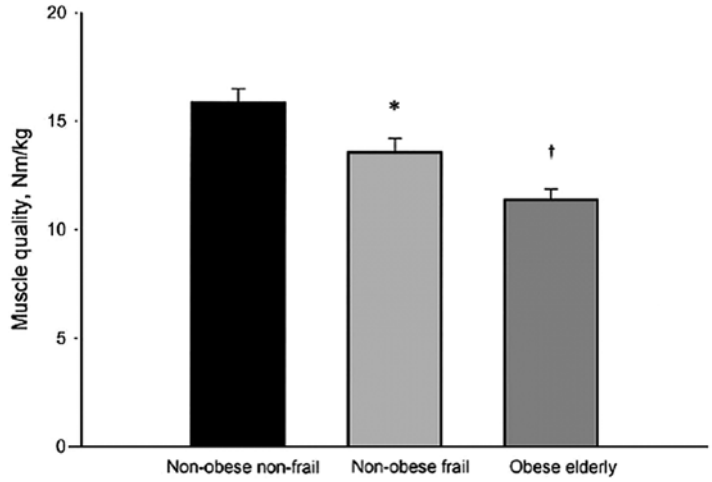

Fig. 10.1 Muscle quality (strength per muscle mass) in nonobese nonfrail, nonobese frail, and obese elderly subjects. Reprinted by permission from Macmillan Publishers Ltd: Obesity. Villareal DT, Banks M, Siener C, Sinacore DR, Klein S. Physical frailty and body composition in obese elderly men and women, 12(6), copyright 2004

Functional Impairment and Quality of Life

Aging causes a progressive decline in physical function because of a continued decline in muscle mass, strength, and power, and an increase in joint instability and arthritis [42]. These functional impairments affect activities of daily living, decrease quality of life, and lead to an increased utilization of health care services. Obesity has important functional implications in older adults because it worsens their age-related decline in physical function. Data from both cross-sectional [43–45] and longitudinal studies [46–48] have consistently demonstrated a strong link between increasing BMI and worsening physical function in older persons. High BMI is associated with self-reported impairment in ADLs, limitations in mobility, decreased physical performance, and increased risk for functional decline [45–50]. Moreover, obesity is associated with increasing nursing home admissions [51, 52].

Although obesity is associated with increases in FM, aging is associated with a decline in FFM (primarily skeletal muscle) and function, referred to as sarcopenia [53] and obesity does not appear to protect against sarcopenia. In one study [54], the prevalence of sarcopenia in obese persons increased with age, suggesting that many obese persons maintain a constant fat mass while losing muscle mass. In another study [55], obese older adults were found to have sarcopenia based on lower relative muscle mass and low muscle strength per muscle area (low muscle quality, Fig. 10.1), despite having more than adequate body weight, which is opposite of the stereotypical frail older adult. Their functional performance, aerobic capacity, strength, balance, and walking speed were as severely reduced as the frail nonobese adults [55]. Thus, obesity in older adults acts synergistically with sarcopenia (sarcopenic obesity; see also Chap. 6) to augment disability. Accordingly, the "sarcopenic-obese" individual has two problems that lead to frailty: (1) decreased muscle mass and strength, which occur with aging, and (2) a need to carry greater weight due to excess body fat [55, 56]. Figure 10.2 is a cross-sectional MRI image from the mid-thigh in a frail obese older adult. This figure demonstrates the excessive adipose tissue infiltration of skeletal muscle mass with obesity.

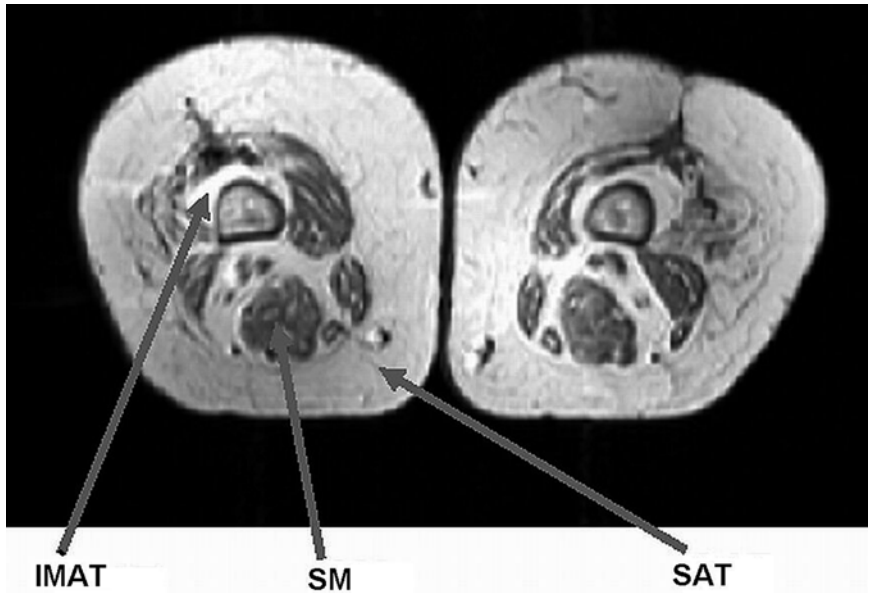

Fig. 10.2 Cross-sectional MRI image from the mid-thigh in a frail obese female participant (76 years of age). *IMAT* intermuscular adipose tissue, *SAT* subcutaneous adipose tissue, *SM* skeletal muscle

In one study [55], 96 % of community-living older adults with BMIs >30 were frail, as determined by physical performance test scores [57], peak oxygen consumption [58], and self-reported ability to perform activities of daily living [59]. Data from another study [60] also demonstrated that obesity was associated with a marked increased risk of frailty (odds ratio = 3.5), determined by weakness, slowness, weight loss, low physical activity, and exhaustion. In another study [61] obesity was identified as one of the five modifiable risk factors that predict functional decline in both vigorous and basic activities among older women. Recently in a study of community dwelling older adults, frailty was related to BMI in a U-shaped manner (i.e., increased frailty in people with extremes of low or high BMI). However, in people with large WC (≥35 in. in women and ≥40 in. in men), frailty was shown to exist in all BMI categories [62].

Beneficial Effects of Obesity

Increased body weight is associated with increased bone mineral density (BMD) and decreased osteoporosis and hip fracture in older men and women, whereas the converse is true for being of low body weight. Both body fat mass and FFM are directly correlated with BMD. Although the increase in BMD has been attributed to mechanical stress on the weight-bearing skeleton, the protective effects have also been observed in non-weight-bearing bones [63]. Therefore, hormonal factors that are increased in obese persons, such as circulating estrogens, insulin, and leptin, might contribute to the osteoprotective effects of obesity, by stimulating bone formation and inhibiting bone resorption. The increase in both BMD and the extra cushioning effect of the fat surrounding crucial areas such as the hip might provide protection against hip fracture during a fall in obese older adults [64]. On the other hand, recent studies also suggest that excess adiposity could be detrimental to bone and also increases fall risk [65, 66].

Effects of Intentional Weight Loss in Older Adults

Body Composition

Loss of body weight is accompanied by a decrease in both FM and FFM. Therefore, it is possible that weight loss in obese older persons could increase sarcopenia by worsening the age-related loss of muscle mass. In younger adults, ~75 % of diet-induced weight loss is composed of fat tissue and ~25 % is composed of FFM [67]. The relative amount of diet-induced weight loss as FFM and fat mass in older men and women is similar to that observed in younger adults [68]. Therefore, diet-induced weight loss does not produce a disproportionate loss of lean tissue in old persons. Despite much evidence linking high body fat to functional disability [45, 47, 48], weight loss has not been typically instituted in obese older persons because of the fear that it will exacerbate sarcopenia. Additionally, it is a general belief among many geriatricians that some "reserve" of body fat is advantageous in the older people particularly if they are hospitalized [69].

In a randomized controlled trial conducted in obese older subjects, there was no significant difference in loss of FFM after a diet-induced weight loss plus regular exercise compared with the control group who did not lose weight. These encouraging findings suggest that regular exercise can attenuate a diet-induced loss of FFM in older persons [70].

Medical Complications

Data from young and middle-aged adults show that weight loss improves or normalizes metabolic abnormalities associated with obesity. Similarly, it has been shown that moderate weight loss in obese older adults simultaneously decreases an array of metabolic coronary heart disease risk factors [71].

Physical Function and Quality of Life

Moderate weight loss in conjunction with physical activity improves physical function and health-related quality of life in obese older persons. Data from studies conducted in overweight and obese older persons with or without joint disease have shown that the combination of moderate diet-induced weight loss and exercise therapy improved both subjective and objective measures of physical function and health-related quality of life and had a greater beneficial effect than did either diet or exercise interventions alone [70, 72–74]. These findings suggest that obesity is a reversible cause of frailty and impaired quality of life in older adults.

Recently, in a 1-year randomized controlled clinical trial, 107 obese adults aged 65 years and older were recruited to investigate the independent and combined effects of weight loss and exercise on physical function, body composition, and quality of life [75]. Participants were randomized into a weight management program, exercise training program, weight management plus exercise training program, and a control group. The weight management program consisted of a balanced diet producing an energy deficit of 500–750 kcal/day in participants' daily requirements. The exercise intervention included both aerobic and resistance training components. Results demonstrated that while physical function improved in all of the intervention groups compared to the control group, the group simultaneously adopting the weight management and exercise training programs demonstrated a significantly higher physical function compared to the other interventions. Moreover, the group that received the combined intervention also tended to demonstrate more benefits in terms of reduced loss of lean body mass and bone mineral density, as well as improved aerobic capacity, strength, balance,

and gait speed. These findings suggest that the combination of weight loss and exercise programs is more effective at preventing frailty and preserving quality of life for obese older adults compared to interventions focused on one single modality.

In this context, it is important to underline that the combination of weight loss and exercise programs is safe, and the exercise benefits may effectively compensate the reduction of lean mass due to the weight loss program [76] (see also Chap. 22). Further studies are needed to determine whether weight loss can be maintained beyond 1 year and may be able to prevent major health-related outcomes (including mortality and nursing home admissions) in obese older adults. These studies should focus on evaluating whether long-term weight maintenance is likely to produce the most meaningful changes in health outcomes in obese older adults.

Mortality

It has been observed in several population-based studies that community-dwelling older adults who lost weight, or who experienced weight variability, had an increased relative mortality risk compared with those who were weight stable [37].

However, most studies have inherent weaknesses, such as not reporting whether the observed weight changes were intentional or unintentional, relying upon self-reported weight change, or not distinguishing between weight loss in obese and lean subjects. Moreover, a recent randomized controlled clinical trial demonstrated that intentional dietary weight loss was not significantly associated with increased all-cause mortality over 12-year of follow-up in older overweight or obese adults [77].

Bone Mineral Density

Weight loss can have adverse effects on bone mass. Previous interventional studies conducted in young and middle-aged adults reported that weight loss causes bone loss that may be proportional to the amount of weight loss [78–80]. However, it is not known whether the bone loss associated with intentional weight loss increases the risk of osteoporotic fractures in obese persons. One study showed that diet-induced weight loss, but not exercise-induced weight loss, is associated with reductions in BMD at weight-bearing sites, suggesting that exercise should be an important component of a weight-loss program to offset adverse effects of diet-induced weight loss on bone [81]. In a more recent study, regular exercise was able to attenuate weight-loss-induced bone loss [76]. It is thought that this beneficial effect may be specific for sites involved in weight-bearing exercise [82], mediated by prevention of weight-loss-induced increase in sclerostin (Sclerostin is a secreted Wnt antagonist that inhibits osteoblastic proliferation and differentiation, thus reducing bone formation, an inhibitor of bone formation secreted by osteocytes) [83]. Therefore, including exercise as part of a weight-loss program is particularly important in older persons to reduce bone loss.

Interventions and Treatment

Weight loss in obese persons of any age can improve obesity-related medical complications, physical function, and quality of life. In older adults, improving physical function and quality of life may be the most important goals of therapy. The current therapeutic tools and recommendations available for weight management in older persons are (1) lifestyle intervention involving diet, physical activity, and behavior modification; (2) pharmacotherapy; and (3) surgery.

Weight Management Intervention

Weight management intervention is just as effective in older as in younger subjects [70, 72–74]. The combination of an energy-deficit producing diet, increased physical activity, and behavior therapy causes moderate weight loss and is associated with a lower risk of treatment-induced complications. Weight-management therapy that minimizes muscle and bone losses is recommended for older adults who are obese and who have functional impairments or metabolic complications that can benefit from weight loss.

Diet Therapy

In order for weight loss to be successful, an energy deficit must be achieved. A low-calorie diet that reduces energy intake by 500–750 kcal/day results in a weight loss of 0.4–0.9 kg (about 1–2 lb)/week and a weight loss of 8–10 % by 6 months. The diet should contain 1.0 g/kg high-quality protein/day [70], and multivitamin, and mineral supplements to ensure that all daily recommended requirements are met, including daily intakes of 1,500 mg calcium and 1,000 IU vitamin D to prevent bone loss. Very low-calorie diets (<800 kcal/day) should be avoided because of an increased risk of medical complications. Also, depending on the patient's cardiovascular risk status, the diet therapy should be consistent with the National Cholesterol Education Program Expert Panel (Adult Treatment Panel III)'s Therapeutic Lifestyle Changes Diet and or possibly the Dietary Approaches to Stop Hypertension (DASH diet) [84].

Referral to a registered dietitian, who has weight-management experience, is often necessary to ensure that appropriate nutritional counseling is provided. Patients should be educated on food composition, preparation, and portion control and their food preferences should be supported to improve compliance.

Successful weight loss and maintenance program should be based on a sound scientific rationale. The program should be safe and nutritionally adequate, as well as practical and applicable to patient's social and ethnic background.

Physical Activity

Introducing an exercise component early in the treatment course can improve physical function and can ameliorate frailty in the older adult [70]. The exercise program should be individualized according to a person's medical conditions and disability (again, see Chap. 22). The program should start at a low-to-moderate intensity, duration, and frequency to promote adherence and avoid musculoskeletal injuries. If possible, the program should be gradually progressed over a period of several weeks or months to a longer, more frequent, and more vigorous effort. The goals of regular exercise in obese older persons are to increase flexibility, endurance, and strength; therefore, a multicomponent exercise program that includes stretching, aerobic activity, and strength exercises is recommended. Even very old or frail persons can participate in these types of physical activities.

Behavior Modification

Clinicians should help obese older adults set personal goals, monitor progress, and use motivational strategies to improve adherence to the weight-loss program (see also Chap. 1). The cognitive behavioral therapy strategies that should be considered include goal setting, self-monitoring, social support, stimulus control techniques, and problem-solving skills. Lifestyle and behavior modification can be

facilitated by counseling from a behavioral therapist, exercise specialist, or dietitian who has weight-management experience.

Implementation of changes in the diet and activity habits of older adults may be challenging. An increased burden of disease, adverse quality of life, depression, hearing and visual difficulties, and cognitive dysfunction may make it difficult to change one's lifestyle. This increase in chronic disabilities with aging reduces physical activity and exercise capacity. Common geriatric situations, such as depression, cognitive impairment, dependency on others, institutionalization, widowhood, loneliness, and isolation should be addressed, because these factors can make it more difficult to adopt or adhere to lifestyle changes designed to lose weight. Lifestyle-change programs should also encourage participation by family members and care providers for better compliance.

Pharmacotherapy

Since most clinical trials that evaluate the use of pharmacotherapy excluded older adults or included only a small number of older adults, the available data are insufficient to determine the efficacy and safety of pharmacotherapy in this population.

The use of pharmacological agents to treat obesity can add an additional burden on older persons. Many obese older patients are already taking multiple medications for other diseases, which can increase the chances of nonadherence, drug–drug interactions, and errors with obesity pharmacotherapy.

Moreover, potential side effects can have more serious consequences in older adults. Some examples of weight loss drugs that are FDA approved include phenteramine, orlistat, and a recently approved drug Qysmia (combination of phentermine and topiramate extended-release). These drugs are seldom covered by health insurance or Medicare, which can add an additional financial burden in older patients who have a fixed income. A thorough review of all the medications should be conducted for older adults who are obese, because some medications may cause weight gain (e.g., antipsychotic, antidepressants, anticonvulsants, or steroids). Furthermore, weight- loss-induced clinical improvements might require changes in medications to avoid iatrogenic complications.

Weight-Loss Surgery

A few studies have provided information on the effectiveness and safety of bariatric surgery among older adults. Data from case series that evaluate the effect of bariatric surgery in patients who are over 60 years of age suggest that the relative weight loss and improvement in obesity-related medical complications are lower, whereas the perioperative morbidity and mortality are greater, in older compared to younger patients [85]. However, bariatric surgery can result in considerable weight loss and marked improvements in obesity-related physical impairment and medical complications in the older patients such as reversal of diabetes. The laparoscopic-adjustable gastric band is associated with fewer serious complications and a lower mortality rate; therefore the gastric band may be a better choice than the Roux-en-Y gastric bypass for older patients. However, it should be emphasized that the efficacy and safety of these procedures have not been compared in randomized trials in older adults. Therefore, careful patient selection, intensive preoperative education, and expert operative and perioperative management are advised. Surgery should be considered in selected older adults who have disabling obesity that can be ameliorated with weight loss and who meet the criteria for surgery. The preoperative evaluation should include an assessment for depression, which is common amongst older adults and could influence outcome. Postoperative management should include monitoring for nutritional and metabolic problems; particularly, vitamin B_{12} deficiency, iron deficiency, and osteoporosis.

Conclusion

The increasing prevalence of obese older adults is a major public health issue. Decreased muscle mass with aging and the burden of extra body mass due to obesity make it particularly difficult for obese older adults to function independently and may lead to the secondary complication of frailty. Treatment plans for obese older adults should include comprehensive lifestyle interventions such as dietary changes that promote weight loss, behavior modification, and exercise therapy to improve physical function, quality of life, and the medical complications associated with obesity. Finally, the treatment must consider the potential adverse effects of weight loss on bone and muscle mass, as well as physical function and quality of life. Randomized controlled trials to determine health benefits and risks from long-term weight management in obese older adults are necessary.

Clinical Recommendations for Older Adult Weight-loss Therapy

1. Initial assessment
   - A thorough medical history, physical examination, appropriate laboratory tests, and review of medications should be conducted to assess the patient's current health and comorbidity risks.
   - Additional information such as the patient's readiness to lose weight, previous attempts at weight loss, and current lifestyle habits should be collected before initiating weight-loss therapy.
   - Clinicians should help obese older adults set their personal goals and welcome participation by family members and care providers.
   - Clinicians should individualize the weight-loss plan after taking into account the special needs of this population.
2. Diet therapy
   - Advocate a modest reduction in energy intake (500–750 kcal/day) containing 1.0 g/kg high-quality protein/day, multivitamin, and mineral supplements (including 1,500 mg calcium and 1,000 IU vitamin D/day).
   - Consider referrals to a registered dietitian for appropriate nutritional counseling and education.
3. Behavior therapy
   - Behavior therapy should highlight both diet and exercise—the integral parts of weight loss therapy and weight maintenance. The self-monitoring of nutrient intake and better understanding of physical activity accomplishes this task.
   - Consider referring to a behavioral therapist for counseling.
   - Stress management, stimulus control, problem solving, contingency management, and social support should be addressed.
4. Exercise therapy
   - Clinicians should assess the need for stress test before any physical activity.
   - Advocate an exercise program that is gradual, individualized, and monitored.
   - A multicomponent exercise program including stretching, aerobic activity, and strength exercises is recommended.

5. Additional recommendations

   - Advocate a combination of energy deficit–producing diet, increased physical activity, and behavior therapy. Such combinations are associated with the low risk of treatment-induced complications.
   - Bariatric surgery may be an option for patients who have failed multiple weight-loss attempts.
   - Weight maintenance efforts should be implemented once weight-loss goals have been achieved.

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Chapter 11
Nutrition and Lifestyle Change in Older Adults with Diabetes Mellitus and Metabolic Syndrome

Barbara Stetson, Holly M. Knight, and Sri Prakash L. Mokshagundam

Key Points

- In the United States, 22–33 % of adults >65 years of age have diabetes and constitute 44 % of persons with self-reported diagnosed diabetes [1].
- The aim of diabetes intervention is to prevent or delay the development of long-term complications of high blood glucose and related metabolic abnormalities and improve the quality of life.
- "Metabolic syndrome" refers to a cluster of abnormalities that includes hypertension, dyslipidemia, abnormal blood glucose, and abdominal obesity. Over 40 % of adults over the age of 70 have metabolic syndrome.
- Hypoglycemia is a major limiting factor in the management of diabetes. Factors that may play a role in the increased risk of hypoglycemia in older adults include poor nutritional status, cognitive dysfunction, poly-pharmacy, and comorbid illnesses.
- Diabetes-related comorbidities such as diabetic retinopathy, cardiovascular disease, peripheral vascular disease, and congestive heart failure may result in decreased usual activity and limit activities of daily living, including transportation, shopping for food, and ability to read food labels and restaurant menus.
- Given the high rates of depression in the diabetes population, careful assessment of depressive symptomology and its impact on dietary intake, diabetes self-care, and health outcomes and provision of support is critical.

Keywords Blood glucose • Metabolic syndrome • Hypoglycemia • Depression • Quality of life

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Introduction

Diabetes mellitus (DM) (diabetes) is a major health problem in the United States. The estimated number of individuals with diabetes is approximately 25.8 million, of whom 7 million are undiagnosed [2]. In older adults type 2 diabetes disproportionately affects minority populations, with higher prevalence in African Americans and Hispanics, who also have poor blood glucose control and more comorbidities and complications relative to non-Hispanic whites [3]. The prevalence of obesity is rising so rapidly in so many countries that the World Health Organization has declared that there is now a global epidemic of obesity. Internationally, emergence of new cases of diabetes parallels the increases seen in Western countries and incidence is are rapidly increasing in low and middle income countries and global prevalence is at an all-time high [4].

Diabetes in Older U.S. Adults

The graying of America is contributing to the increasing number of U.S. cases of diabetes, as prevalence increases with age. In developing countries, the majority of people with diabetes are between 45 and 64 years of age. In developed countries, the majority of people with diabetes are age 65 or older. The aging population has and will continue to contribute to the now evident diabetes epidemic and the resultant burdens of increased functional impairment, intensive care, and mortality [3].

Health Consequences of Diabetes

Diabetes is a chronic disease that leads to a variety of micro (e.g., nephropathy, retinopathy, and neuropathy) and macrovascular (e.g., coronary artery disease, peripheral vascular disease, and stroke) complications that affect almost all bodily systems. While the primary abnormality, elevated blood glucose level, remains largely asymptomatic, the consequences of sustained elevation are potentially devastating. Diabetes is the leading cause of blindness, chronic renal insufficiency, peripheral neuropathy, and nontraumatic limb amputations in the United States.

Type 2 diabetes exerts a tremendous economic burden and substantial impact on comorbidities such as visual impairment, end stage renal disease, cardiovascular disease, and events such as myocardial infarction and amputations, particularly in older adults [3]. Older adults have a particularly high prevalence of diabetes-related conditions, approximately three-quarters living with diabetes or prediabetes. It is estimated that 30 % of older adults have diabetes, with almost half of these individuals as yet undiagnosed [5]. A recent review of diabetes and diabetes complications in older adults indicates that older adults with diabetes have higher rates of falling, incontinence, and psychiatric comorbidities such as depression and dementia relative to younger adults with diabetes [5].

Cardiovascular disease (CVD) is the most frequent and costly complication of type 2 diabetes. When cardiovascular events are stratified by diabetes status, relative risk for men is twice that of gender-matched non-diabetics and for women is threefold. Among all CVD events, diabetes accounts for 56 % of events in men and 78 % of events in women. A number of diabetes-related risk factors, as well as post-glucose challenge hyperglycemia in nondiabeteic individuals, have been associated with CVD [6].

General Aims of Diabetes Treatment

The management of diabetes requires a combination of lifestyle interventions and medications, with dietary approaches to maintaining optimal glycemic control as a key component. The aims of diabetes treatment are to: (1) decrease/prevent the development of long-term complications of high blood glucose and related metabolic abnormalities, (2) improve quality of life, and (3) treat or prevent the development of symptoms of high or low blood glucose.

Diagnosis and Classification

Diagnosis

The American Diabetes Association (ADA) recommends the following criteria for the diagnosis of DM [7]:

- Hemoblobin A1c ≥6.5 %.
- The Hemoblobin A1c test should be performed in a laboratory using a method that is National Glycohemoglobin Standardization Program (NGSP)-certified and standardized to the Diabetes Control and Complications Trial (DCCT) assay; or
- Fasting plasma glucose (FPG) ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h; or
- 2-h plasma glucose ≥200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test (OGTT); or
- In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).

In the absence of unequivocal hyperglycemia, the result should be confirmed by repeat testing. The ADA diagnostic criteria were developed for general use, and apply broadly to all age groups. No specific ADA guidelines exist for older adults.

Typologies of Diabetes in Older Adults

The proper classification of diabetes is important in setting goals for nutritional management of individuals with diabetes, with broad classification of type 1 and type 2 diabetes.

Type 1 Diabetes

Type 1 diabetes is an autoimmune disorder resulting from cell mediated and antibody mediated destruction of beta-cells of the islets [8]. Although type 1 diabetes most commonly occurs in the first three decades of life, it can develop at any age, even in older adults. An additional contributor to the population of older individuals is that the number of individuals with type 1 diabetes living into old age has increased [9]. Research investigating potential nutritional influences on the development and progression of diabetes has led to a widespread interest in the role of vitamin D. Several studies indicate that in type 1 diabetes the role of vitamin D is in prenatal or early life vitamin D deficiency. Vitamin D deficiency has been gaining increasing attention as a potential factor in the development of both type 1 and type 2 diabetes. Several epidemiological studies have indicated that vitamin D deficiency could be a factor in risk of development of type 1 and type 2 DM [10]. Vitamin D has

been shown in animal models to be associated with both insulin resistance and insulin secretion, abnormalities of which play a key role in the development of type 2 DM [11]. The NIH has recently funded a multicenter trial to assess the role of vitamin D supplementation in prevention of type 2 DM. Vitamin D has also been shown to play an important role in the regulation of both innate and reactive immune system [12]. In animal models of type 1 DM, 1–25 dihydroxyvitamin D has been demonstrated to delay development of type 1 DM [13]. Definitive human trials are awaited. The complex interaction between vitamin D and DM has been recently reviewed by Van Belle et al. [14].

Type 2 Diabetes

The majority of older adults with diabetes have type 2 diabetes, which is characterized by two defects: insulin resistance and defective insulin secretion [15]. The majority of individuals with type 2 diabetes are obese. However, in the older population the proportion of subjects with type 2 diabetes who are underweight increases and could be as high as 20 %. This is particularly true in the nursing home population due to sarcopenia and frailty [16].

The exact mechanism of insulin resistance in type 2 diabetes is unclear. A variety of genetic and environmental factors lead to decreased insulin sensitivity. Obesity and decreased physical activity are known to decrease insulin sensitivity [17]. Aging is associated with body composition changes of increased fat and decreased muscle mass [18, 19]. This could be partly responsible for the increase in insulin resistance with aging. Aging is also associated with a decline in insulin secretion, particularly a blunting of the first-phase insulin secretion [20]. Age-related increases in sedentary lifestyle may also further compound these changes. Vitamin D deficiency has been linked to increased insulin resistance and higher prevalence of type 2 diabetes.

Establishing Medication and Nutritional Management Goals

Once the type of diabetes is established, medication and nutritional management goals should be developed. In addition to tailoring the nutritional recommendation to assist glycemic control, consideration of other important CVD risk factors is critical. Obesity, dyslipidemia, hypertension, and insulin resistance are important and often overlapping factors warranting consideration when planning dietary interventions for older adults with type 2 diabetes. Avoidance of hypoglycemia, particularly recurrent and/or severe hypoglycemia, is a major consideration in type 1 diabetes. Lifestyle interventions that have been recommended for the management of diabetes have positive effects on both insulin secretion and insulin resistance. Aggressive lifestyle intervention can prevent the progression of impaired glucose tolerance to diabetes and could decrease the dose and number of medications for the management of type 2 diabetes.

Medication Use and Glycemic Control in Older Adults with Diabetes

Goals of Diabetes Treatment in Older Adults

The major aim of treating diabetes is to decrease the rate of micro and macrovascular disease associated with elevated blood glucose. Two landmark trials have served as the basis for the recommendations for the management of blood glucose levels in DM until 2012. Neither of these trials enrolled individuals over age 65 years. The DCCT was conducted in adults with type 1 diabetes and compared

intensive insulin treatment using multiple insulin injections or an insulin pump to conventional treatment using twice daily injections of intermediate- and short-acting insulin [21, 22]. The results showed significant reduction in risk of all microvascular disease endpoints in the intensively treated group. The United Kingdom Prospective Diabetes Study (UKPDS) was a long-term study of a variety of treatment options in adults with type 2 diabetes [22]. Major UKPDS findings were that: (1) a reduction of 1 % in hemoglobin A1c resulted in ~22 % reduction in microvascular complications, (2) glycemic control in type 2 DM worsened over time and necessitated changes in medication, and (3) in a subgroup of subjects treated with metformin there was a significant reduction in macrovascular disease. Ten-year follow-up noted persistent microvascular benefits [23]. While the DCCT and UKPDS informed earlier guidelines, three new studies that included older participants [24–26] have raised questions about the role of intensive glycemic control in reducing macrovascular events in older adult subjects. This has been reviewed extensively in a combined ADA—AHA review [27].

Current ADA goals are to aim for HbA1c levels ≤7.0 %. In addition the ADA recommends individualization of glycemic control goals with an HbA1c of <6 % when feasible. The new guidelines by the ADA recognize the uncertainty arising from the newer trials and the need to consider multiple factors in determining glycemic goals for each individual such as duration of diabetes, risk of hypoglycemia, presence of comorbidities, and age [28]. This is particularly true for older adults. The 2003 California Healthcare Foundation/American Geriatric Society (AGS) guidelines [29] have helped clarify some of these concerns, and several concepts, including cognitive function, social support, and presence of comorbidities, have been subsequently incorporated in the ADA guidelines. The AGS guidelines also recognize the importance of comorbidities that are common in the older adult with diabetes that influence ability to maintain strict glycemic control [29]. Approaches to the management of hyperglycemia may be seen in Fig. 11.1.

In addition to glycemic goals, several metabolic and cardiovascular risk factors must also be considered due to the higher rates of cardiovascular disease and its substantial impact on morbidity and mortality. The high risk of cardiovascular morbidity and mortality in diabetes is likely due to a variety of factors, including overall blood glucose control, glycemic fluctuation, postprandial blood glucose levels, high LDL cholesterol, low HDL cholesterol, elevated serum triglycerides, blood pressure, and altered coagulation profile. In addition, inflammation, pro-oxidant state, and endothelial dysfunction play a significant role. Despite multiple trials that have shown benefits of statins in reducing CVD events, few have specifically addressed benefits of statins in individuals with diabetes aged 65 and over [30]. Based on these trials, it is reasonable to use statins in older adults <80 years age and exercise caution with older individuals. The benefits of fibrates in the older adult are not clear. Similarly, the benefits of blood pressure reduction have not been specifically addressed in older adults with diabetes; however, some subpopulation analyses indicate benefits of blood pressure reduction consistent with ADA goals [30]. Optimal implementation of the current guidelines may require changes in the way that risk-factor management is viewed by caregivers and patients [31]. Many providers emphasize the importance of patient awareness of their diabetes-related labs that reflect ADA goals, particularly their A1c, blood pressure, and lipids. A nationally representative sample of adults with type 2 diabetes from the NHANES survey found that knowledge was limited (48 % were able to report their last A1c level, 63 % their last blood pressure level, and 22 % their last LDL level) and was greatest among non-Hispanic whites and those with higher education and income [32]. In general, knowledge about personal diabetes-related labs was not significantly associated with meeting related clinical recommendations. This lack of a significant association between knowledge and meeting clinical recommendations suggests that an emphasis on awareness of these test values in and of themselves may not be a necessary priority, particularly in older adults with other competing demands [32].

Any nutritional approach to the management of DM must specifically address the issues related to cardiovascular risk. Cardiovascular risk reduction in DM is achieved through a combination of lifestyle changes and pharmacological interventions that address the multiple risk factors. Taken together, these lifestyle and pharmacological interventions can play a major role in cardiovascular risk reduction in persons with diabetes.

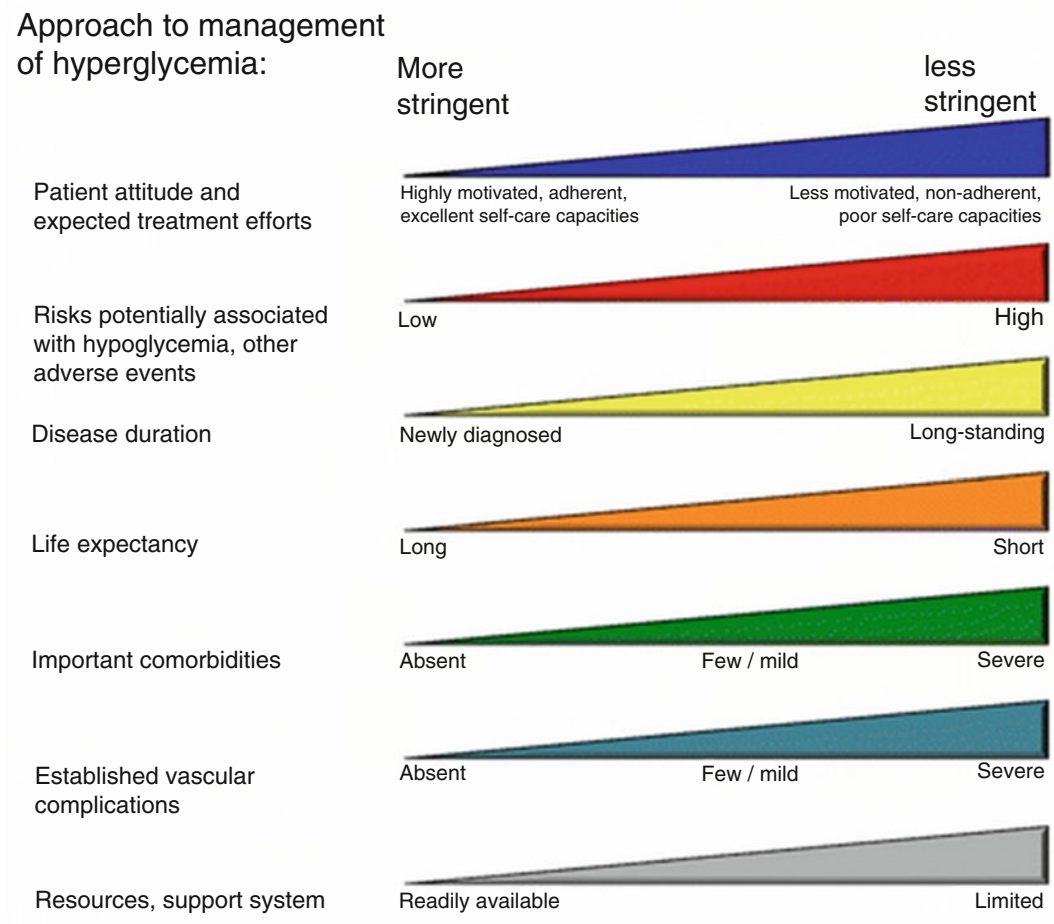

Fig. 11.1 Approach to management of hyperglycemia. Reproduced with permission from the American Diabetes Association, from Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care. 2012 Jun;35(6):1364–79; permission conveyed through Copyright Clearance Center, Inc.

General Diabetes Dietary Goals

The general goals of nutritional recommendations for the management of diabetes include:

1. Achieve and maintain blood glucose levels as outlined above.
2. Achieve and maintain optimum lipid levels.
3. Achieve and maintain reasonable body weight. This would include weight loss, if overweight, and weight gain, if undernourished.
4. Prevent acute complications.
5. Maintain overall health.

Macronutrient Recommendations

The carbohydrate composition (amount and type) of the diet has been a focus of many recommendations and subject of recent controversy. There are no well-designed studies that have compared

different dietary approaches. In a study of a high carbohydrate (60 %), low fat (25 %) diet, compared to a low carbohydrate (35 %), high monounsaturated fat (50 %) diet [33], plasma glucose, triglyceride, and VLDL cholesterol were lower in the subjects in the low carbohydrate/high monounsaturated fat diet group [33]. However, use of high-fat/low-carbohydrate diets could lead to more hypoglycemic episodes and ketosis, particularly in type 1 diabetes [34].

Higher protein diets have been recommended and have been popular for weight loss. However, the efficacies of these diets in persons with diabetes have not been well tested. Higher protein content has been shown to increase risk of development and progression of diabetic nephropathy (as discussed in Chap. 16 of this book), contraindicating this type of diet for persons with poorly controlled diabetes or complications.

Low-carbohydrate diets are not recommended in the management of diabetes. Dietary carbohydrate is the major contributor to postprandial glucose concentration, and foods containing carbohydrates are an important source of energy, water-soluble vitamins and minerals, and fiber. Thus, in agreement with the National Academy of Sciences-Food and Nutrition Board, a recommended range of carbohydrate intake is 45–65 % of total calories [35]. In addition, because the brain and central nervous system have an absolute requirement for glucose as an energy source, restricting total carbohydrate to <130 g/day is not recommended [36]. Monitoring carbohydrate intake, whether by carbohydrate counting, using the exchange system, or experience based estimation remains a key component of managing diabetes. Use of complex carbohydrates is preferred. The use of lower fat content in the diet is based on the need to restrict caloric intake, improve lipid levels, and assist weight loss. While use of vitamin supplements is not generally recommended for patients with type 2 diabetes, the ADA recommends using a multivitamin for older adults. There has been no convincing evidence to recommend the routine use of antioxidants, vitamin E, or C in individuals with diabetes.

Balancing Diet and Medication

The interaction of diet and medication is of particular importance in diabetes management. Insulin and drugs that increase insulin secretion are likely to induce hypoglycemia if meals are not taken at appropriate times. Erratic eating patterns might require readjustment of medications, dose, timing, or both. This may be of particular concern in the hospitalized older patient with diabetes. Poor eating habits might also necessitate change to medications that are less likely to cause hypoglycemia when used alone. Metformin (Glucophage), thiazolidenediones (Pioglitazone—Actos), and incretin-based therapies (Exenatide-Byetta; Liraglutide—Victoza; Sitagliptin—Januvia; Saxagliptin—Onglyza; and Linagliptin—Tradjenta) are least likely to cause hypoglycemia when used alone. The problem of unwanted weight gain is another issue for consideration for many individuals. Insulin and the thiazolidenediones, particularly when used in combination, are most likely to result in weight gain. Loss of appetite may occur with Metformin, Exenatide, Liraglutide (glucagon-like peptide 1 receptor agonists), and pramlinitide (Symlin, an amylin analog) and would be of concern in undernourished individuals.

Body Weight and Functional Status in Older Adults with Diabetes

Overweight and Obesity in Older Adults

Overweight and obesity are both important risk factors for the development of type 2 diabetes and are prevalent in older adults (as is discussed in Chap. 10 of this book). Obesity appears to be common in older adults until the eighth decade of life and then declines in the oldest old. Muscle mass and body strength decreases observed in aging may result in sarcopenia in normal, over-, and underweight older

adults. This may be further enhanced by inactivity, which may result from diabetes complications and comorbidities. Combining physical activity interventions with nutritional approaches may help to combat these difficulties while improving fitness and functional status [3].

Underweight and Malnutrition

While obesity is clearly a problem that greatly impacts diabetes in older adults, for many individuals, malnutrition may be the more pressing nutritional concern. Even with the problem of increasingly prevalent overweight, obesity, and diabetes, the prevalence of obesity in older persons with diabetes is still less than that in younger person with type 2 diabetes. This may be particularly true for the oldest old, and those who have impaired functional status [37]. Factors influencing undernourishment in older adults include changed sense of taste and/or smell, oral issues such as poor dentition or swallowing difficulties and functional difficulties resulting in problems in preparing food or feeding oneself [3]. Brief malnutrition screening with validated instruments such as the Mini-Nutritional Assessment [38] may help to streamline evaluation for determining the need for further specific nutrition therapy [3].

Special Nutrition Intervention Situations for Persons with Diabetes

Acute Illness, Hospitalization, Enteral and Parenteral Nutrition

Management of hyperglycemia in the hospital setting has gained increasing attention over the last few years. Hyperglycemia is common among hospitalized subjects and has been shown to be associated with higher mortality and morbidity in a variety of studies [39–44]. This is particularly relevant to the older population, since they are more likely to be admitted to the hospital and have higher rates of diabetes. The American Association of Clinical Endocrinologists (AACE) and ADA have recommended glycemic targets for patients with hyperglycemia [45]. Initial studies in the ICU setting suggested that tight blood glucose control to a level of <110 mg/dL would result in significant improvement in mortality and morbidity [46]. However, this was not confirmed by subsequent studies, which also pointed to a higher mortality with efforts to achieve goal blood sugar of <110 mg/dL, perhaps related to higher rate of hypoglycemia [47, 48]. Current recommendations are to achieve a glucose level of 140–180 mg/dL [49, 50].

Hospitalization

A variety of systemic problems have been identified that affect glycemic control in the hospital setting. Barriers that may impact an individual's nutrition status and subsequently affect glycemic control include poor appetite, inability to eat, increased nutrient and calorie needs due to catabolic stress, variation in diabetes medications, and the possible need for enteral or parenteral nutrition support. Proper timing of meals and the relation to medications is important. Insulin should be administered immediately before or after a meal. Due to the wide heterogeneity in the hospital population, individualization of nutrition recommendations is key to improving outcomes. The common practice of

ordering an "ADA Diet" is strongly discouraged, as the ADA does not endorse any specific diet. The consistent carbohydrate meal planning system is encouraged. For this system to be effective, it is important that nursing and nutrition services coordinate their services. The key areas of focus to improve inpatient glycemic control are:

1. Establishing screening criteria for appropriate referral to a registered dietitian.
2. Identifying nutrition-related issues in clinical pathways and patient care plans.
3. Implementing and maintaining standardized diet orders such as consistent carbohydrate menus.
4. Integrating blood glucose monitoring results with nutrition care plans.
5. Using standing orders for diabetes education and diabetes medical nutrition therapy (MNT) as appropriate.
6. Standardizing discharge follow-up orders for MNT and diabetes education post-discharge when necessary [51, 52].

Patients requiring clear or full liquid diets should receive 200 g carbohydrate/day in equally divided amounts at meal and snack times [53]. Liquids should not be sugar-free. Patients require carbohydrate and calories, and sugar-free liquids do not meet these nutritional needs. For tube feedings, either a standard enteral formula (50 % carbohydrate) or a lower carbohydrate content formula (33–40 % carbohydrate) may be used. Calorie needs for most patients are in the range of 25–35 kcal/kg every 24 h. Care must be taken not to overfeed patients because this can exacerbate hyperglycemia. After surgery, food intake should be initiated as quickly as possible. Progression from clear liquids to full liquids to solid foods should be completed as rapidly as tolerated [54].

Enteral and Parenteral Nutrition

Enteral and parenteral nutrition might pose additional challenges in the management of patients with diabetes. While the glycemic goals for individuals receiving enteral and parenteral nutrition are the same as glycemic goals for the general population with diabetes, achievement of normoglycemia may be more difficult in patients who are acutely ill. There is evidence that poor glycemic control in individuals on parenteral or enteral nutrition is related to poor outcomes. It is estimated that up to 30 % of patients who receive parenteral nutrition have diabetes, many of whom have no previous history of diagnosed diabetes and develop hyperglycemia due to stress-induced increases in counter-regulatory hormones and cytokines.

The relative value of high-carbohydrate versus high-fat enteral feeds for persons with diabetes has been debated [55]. The most widely used commercial enteral preparations for individuals with diabetes provide, 1 cal/mL, 40 % (CHOICEdmTF; Novartis Medical Nutrition) to 34 % (Glucerna; Abott Laboratories, Inc.) carbohydrate, and 43 % (CHOICEdmTF) to 49 % (Glucerna) fat. They also have high monounsaturated fatty acids (MUFA; 35 % of kcal in Glucerna). MUFA has been shown to be beneficial in improving lipid profile, glycemic control, and lowering insulin levels in both acutely ill and ambulatory individuals [56]. CHOICEdmTF has a higher content of medium-chain triglycerides and no fructose. The use of insulin or oral agents in persons receiving enteral nutrition should be tailored to match the timing of feeds. Parenteral nutrition fluids are high in carbohydrate and derive fewer calories from fat. In persons with diabetes, particularly in less severely stressed individuals, the proportion of carbohydrate may be decreased but is still very high. The usual rate of glucose infusion is 4–5 g/kg body weight and lipid infusion of 1–1.5 g/kg body weight. This requires adequate use of insulin to maintain normoglycemia [57]. Insulin infusion not only maintains glycemic control, but prevents protein breakdown and promotes protein synthesis.

Long-Term Care

Residents of long-term care facilities may face additional or unique problems. They tend to be underweight and do not necessitate any caloric restrictions. Low body weight has been associated with higher mortality and morbidity in these populations. Restricting food choices may lead to poor overall nutritional status and has not been shown to improve glycemic control [58]. Hence, the use of "no concentrated sugar," "no sugar added," or "liberal diabetic diet" is discouraged [59, 60].

Metabolic Syndrome

The term "metabolic syndrome" refers to a cluster of abnormalities that was initially described as including hypertension, dyslipidemia, abnormal blood glucose, and abdominal obesity. Insulin resistance was considered to be a central pathogenetic abnormality in this syndrome. In 2001, the National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III) [61] recommended the use of the metabolic syndrome in cardiovascular risk assessment. The NCEP-ATP III defined metabolic syndrome [62] is the most widely used definition. Prevalence of metabolic syndrome as defined by the NCEP-ATP III in the NHANES III cohort increases with age, with over 40 % of adults over the age of 70 having the metabolic syndrome [63]. NCEP-ATP III Criteria for Diagnosis of Metabolic Syndrome reflect presence of three or more of the following risk factors: abdominal obesity (waist circumference): men: >102 cm (>40 in.), women: >88 cm (>35 in.); triglyceride: >150 mg/dL; HDL cholesterol: men: <40 mg/dL, women: <50 mg/dL; blood pressure: <130/85 mmHg; fasting blood glucose: >110 mg/dL.

The exact significance of the metabolic syndrome has been controversial. A variety of clinical studies have demonstrated an association between metabolic syndrome and risk of heart disease, stroke, and development of diabetes [64, 65]. However, several other studies have shown a lack association between the "syndrome" and CVD risk that cannot be attributed to its individual components [66, 67]. Identification of individual risk factors related to the metabolic syndrome construct should prompt health care providers to look for other risk factors and resultantly, encourage the use of behavioral approaches such as diet and increased physical activity rather than always prescribing a different drug for each medical condition. The management of the cluster of risk factors represented in metabolic syndrome is primarily aimed at reducing cardiovascular risk by addressing the individual risk factors. In individuals with pre-diabetes, the aim is to prevent progression to type 2 diabetes.

The metabolic syndrome predicts a higher rate of progression to type 2 diabetes. The landmark Diabetes Prevention Program (DPP) evaluated the impact of intensive lifestyle intervention and pharmacological treatment on the delay or prevention of progression of individuals with high risk of diabetes (most of whom had metabolic syndrome) to type 2 diabetes. The DPP demonstrated the efficacy of both lifestyle and pharmacological interventions in preventing the progression of impaired fasting glucose or impaired glucose tolerance. In older DPP participants, lifestyle intervention had an even greater impact than metformin. Among participants age 60 and older, lifestyle intervention reduced the risk of development of diabetes by 71 %. Participants in the 60- to 85-year-old age group were the most likely to achieve weight loss (5–7 % loss in body weight was achieved with dietary change and activity) and physical activity goals [68].

Hypoglycemia in Older Adults

Hypoglycemia is a major limiting factor in the management of diabetes. The incidence of hypoglycemia is relatively high in older compared to younger adults, with a variety of factors playing a role in this increased risk. These include poor nutritional status, cognitive dysfunction, polypharmacy, and

comorbid illnesses. Except in the severely malnourished, poor dietary intake by itself does not lead to hypoglycemia. The most common cause of hypoglycemia remains the use of blood glucose-lowering agents. Drugs that increase insulin secretion and insulin itself can cause hypoglycemia. A major finding of the DCCT, which was conducted with young, healthy adults, was that the major deleterious health consequence of tight blood glucose control in persons with type 1 diabetes is hypoglycemia [69]. Drugs that enhance insulin sensitivity (thiazolidenediones), decrease hepatic glucose production (metformin), or decrease carbohydrate absorption (alpha-glucosidase inhibitors) have very low risk of hypoglycemia, except when used in combination with insulin or an insulin secretagogue. When medication use creates problems of consistent hypoglycemia, patients must learn how to avoid and manage hypoglycemic episodes. Older adults taking insulin who have high variability in blood glucose levels, exhibit very low average blood glucose concentrations, have had diabetes for a long duration, have a low body mass index, or who have high levels of vigorous physical activity may be at particular risk of severe hypoglycemia [70].

Self-Monitoring and Dietary Treatment of Hypoglycemia

Frequent self-monitoring of blood glucose levels (SMBG) provides specific information to guide decisions about moment-to-moment treatment needs, thus helping individuals to anticipate or prevent severely low glucose levels. By increasing the frequency of blood glucose testing and making informed decisions about when to eat additional carbohydrate (e.g., eat 15 g of carbohydrate to raise blood glucose levels about 45 mg/dL) or to identify personal sources of vigorous physical activity contributing to low blood glucose levels, patients may learn to prevent severe hypoglycemia. Educating patients about the importance of always carrying glucose tabs, gel, or fast-acting carbohydrate snacks or placing them in various locations such as the car, or relative's homes may also aid in the treatment of mild to moderate hypoglycemic episodes. Recommendations for dietary management of hypoglycemia are below:

1. Check blood glucose level by glucose monitor.
2. If blood glucose less than 60 mg/dL or symptomatic—treat with 15 g of carbohydrate (e.g., four ounces of or regular soft drink [not diet], glucose tablets or gel tube, two tablespoons of raisins, one tablespoon of sugar, honey, or corn syrup, eight ounces of nonfat, or 1 % milk).
3. Repeat blood sugar reading in 15 min after treatment and again after 60 min.
4. Repeat step 2 until blood glucose is >60 mg/dL.
5. If meals are due within 60 min, eat meal now.
6. If meals are not due within 60 min, follow the glucose treatment with a snack containing carbohydrate and one protein (cheese and crackers, peanut butter and crackers, skim milk and crackers, or a small sandwich).
7. If blood glucose <40 mg/dL and/or subject is stuporous, confused, or unresponsive, give 1 amp of D50W as IV push and start D10W at 60 cc/h. Check blood glucose every 5 min and repeat till blood glucose >60 mg/dL or till awake. Give oral carbohydrate once awake.

Hypoglycemia Unawareness and Treatment of Hypoglycemia

As previously described, older adults with type 1 diabetes and those with type 2 diabetes who are on exogenous insulin regimens are at risk for hypoglycemia. Many individuals develop the syndrome of hypoglycemia unawareness, in which the warning symptoms that indicate that hypoglycemia is developing (e.g., tremulousness, tachycardia) are decreased or not detected. Without these warning symptoms, individuals are not able to take actions such as eating to prevent continued reductions in blood glucose levels and severe hypoglycemic episodes may result. Following episodes of hypoglycemia,

counterregulatory hormone stores may not be available, and thresholds for symptoms of hypoglycemia may shift to lower glucose concentrations. Thus, patients with recurrent hypoglycemia may be particularly at risk for unawareness and for severely low hypoglycemic episodes. Failure to test blood glucose levels regularly can contribute to the problem of hypoglycemia unawareness. This cycle is particularly problematic for older adults who are highly physically active or who skip meals, do not eat sufficient quantities of food to match their insulin doses, or consume a high-fat diet, which delays carbohydrate absorption and is not accounted for in the timing of insulin administration.

Alcohol consumption, while not typically problematic when consumed in moderation, can pose risks for hypoglycemia in older adults taking insulin. The disinhibiting effect of alcohol intoxication poses the risk of hypoglycemia unawareness due to inattention to internal cues, making blood glucose monitoring essential. The potential for a delayed risk of hypoglycemia the morning after evening alcohol intake should also be emphasized [71]. The problem of patient hypoglycemia unawareness should be considered if the patient's HbA1c is low (e.g., <6.0), and if s/he describes inability to detect counterregulatory autonomic symptoms (e.g., tremulousness, pounding heart, anxiety, queasy stomach, sweating, flushed face) when blood glucose levels are low [72].

Structured psychoeducational intervention and print materials to promote reduce hypoglycemia unawareness have been developed and systematically evaluated and have been shown to improve accuracy of recognition of current blood glucose levels, improved judgment regarding when to treat, reduced occurrence of severe hypoglycemia and improved judgment about not driving while hypoglycemic [73].

Diabetes Lifestyle Change and Physical Limitations

Diabetes-related comorbidities such as diabetic retinopathy, cardiovascular disease, peripheral vascular disease, and congestive heart failure may result in decreased usual activity and limit activities of daily living (ADLs) and instrumental activities in daily living (IADLs), including limited transportation options, limited ability to shop for food or ability to read restaurant menus. SMBG may also be influenced by reduced visual acuity. Hearing impairment may influence understanding of provider recommendations. Analyses from NHANES participants found twice the prevalence of hearing impairment in people with diabetes relative to those without, after controlling for age [74]. Comorbid health conditions may heighten the risk of these sensory difficulties, as the presence of heart disease, peripheral neuropathy, and having poor health were associated with hearing impairment in participants with diabetes [74]. Sensory limitations should be considered when providing education and instructions for older adults with diabetes. Diminished fine motor skills may also impact ability to functionally conduct a finger stick, conduct the steps necessary for using the glucometer and reading the results. Patients may need assistance adapting the choice of meter or approach to SMBG [75]. Comorbid health conditions increase polypharmacy, so pill boxes and mediplanners may also be helpful in simplifying medication management. Comorbid medical conditions and complications such as peripheral neuropathy may also contribute to pain, gait, and balance difficulties, increasing risks for falls. Hypoglycemia may also pose fall risks [3]. Management of severe hyperglycemia and hypoglycemia, avoiding polypharmacy and incorporating regular strength/stability exercises or participation in physical therapy into lifestyle approaches may also help to reduce the risks of falling in older adults with diabetes [3].

Self-Management Behaviors

Few studies of diabetes self-management education and training (DSME/T) have focused on older adults. Intervention guidelines have been predominantly based on expert consensus. As such, it is unclear if strategies for DSME that are effective with younger patients are optimal for older adults [76].

Older age may be associated with reduced readiness to make lifestyle changes such as increasing physical activity and diet modifications [77]. Many of the oldest of older adults may have limited knowledge or understanding of diabetes care. As previously described, sensory limitations may impact instruction and patient education delivery. Older individual's abilities and skills to effectively plan meals and make adjustments to food and insulin intake to accommodate blood glucose levels may be influenced by their cognitive functioning, health and numeracy literacy, functional status, and personal resources. Spreading information delivery over multiple contacts and use of memory cues such as large-print handouts and cues to use at home may facilitate learning and retention. Simplified self-care regimens that consider day-to-day quality of life are optimal [76].

Dietary Habits of Older Adults with Diabetes

Both the type of food consumed and the pattern of eating behaviors are important influences on nutritional status in older adults [78]. Adherence to a healthy diet has been found to be greater in older adults that viewed diabetes as a stable, long-term health condition relative to those who viewed diabetes symptoms as an intermittent problem, particularly for men [79].

Unhealthful snacking may threaten optimal diabetes diet adherence in older adults with diabetes, influencing the balance and timing of meals, medication use, and physical activity. A random telephone survey of older U.S. adults found that the 98 % reported snacking at least once each day, with evening the most common time and nearly all snacking occurring at home [80]. Taste outranked nutrition as selection criteria. Concrete suggestions for replacing highly processed, high-fat snack foods with fruits and vegetables and other nutritious snacks may assist older adults in selection of healthier snacks. Planning snack supplements as part of a meal plan may also be helpful, as demonstrated by a study of mid-life and older adults with diabetes found that low-glycemic, moderately high-protein snacks throughout the day promoted body weight and fat-mass loss, while not changing glycemic control, lipids, or inflammatory markers [81]. Patients may be encouraged to incorporate specific items into their shopping lists and keep them in the home as replacements for preferred but unhealthy ones. Evening activities that are alternatives to snacking (e.g., walking, crafts) may also be encouraged.

An additional influence on eating behavior in older adults with diabetes may be the social structure of mealtimes. Older adults who eat alone have been found to be more likely to be depressed and have less diversity in foods eaten relative to those who share mealtimes with others [82]. Homebound older adults may have particular difficulties with undernutrition. A study of homebound older adults found that 70 % were under-eating, with the highest risks in men, those receiving either infrequent care or receiving intensive caregiver aid, and those with hospitalization preceding home care. Under-eating was not limited to underweight individuals, but was also problematic for those with a higher BMI [83].

Psychosocial and Behavioral Issues Related to Self-Care and Dietary Intake in Older Adults with Diabetes

Depression

Estimates of the prevalence of depression in the general adult population with diabetes indicate a rate of 2–3 times that of the general population [84]. Adults with diabetes who are depressed have average HbA1c levels 0.5–1.0 % higher relative to those who are nondepressed. Depression in diabetes is also associated with additional functional impairment, lower levels of diabetes self-care, increased risk of macrovascular and microvascular complications, higher medical costs, and greater mortality [85].

In older adults with type 2 diabetes, depression was associated with increased risk of dementia [86]. In the Hispanic Established Population for the Epidemiologic Study of the Elderly (EPESE), death rates were substantially higher when elevated depressive symptomology was comorbid with diabetes, cardiovascular disease, hypertension, stroke, and cancer. Odds of death among individuals with diabetes with high levels of depressive symptoms are three times that of those without elevated depressive symptomology [87]. For both those newly diagnosed and those with ongoing diabetes, the demands of the regimen, particularly the often complicated dietary issues, may be perceived as "one more thing" to do in what may be seen as an already stressful existence [88]. Given the high rates of depression in this population, assessment of depressive symptomology and its impact on dietary intake, related aspects of diabetes self-care and health outcomes are critical.

Social Support

Level of social support, reflected by connections with individuals as well as community support, including social events, church and senior centers, has been linked to mortality rates in older adults with diabetes, with highest levels of social support having the highest survival rate. Having higher levels of social support is associated with lower rates of depressed mood, less difficulty with stress, fewer limitations in activities of daily living, better health ratings, lower likelihood of heart disease and shorter diabetes duration [89].

Social integration and network size also predict involvement in HbA1c provider monitoring and foot examinations, highlighting the potential role of social support in adherence to self-care recommendations [90]. Of note, substantial gender differences have been observed in diabetes health care behaviors, with higher levels of social support associated with improved glycemic control in women with type 2 diabetes and less control in men, perhaps reflecting differing social influences on patterns of eating, drinking, and physical activity level [91]. DSME/T programs that include the older adult's spouse may help to promote optimal diabetes knowledge, psychosocial functioning, and metabolic control. Spousal support can also promote adherence to diabetes self-care behaviors and may ultimately reduce diabetes-related distress [92]. In older adults who live with a spouse, the husband's food preference is often the best predictor of family meal nutrition [93]. Furthermore, negative spousal perceptions of diabetes patient's diet adherence and setbacks can increase their own diabetes-related distress and depressive symptomology in the long run [94]. This indicates that social isolation is an important influence on dietary intake, but also that day-to-day social support from family and friends may both positively and negatively impact dietary intake in older persons with diabetes and their spouses. As such, it is imperative to evaluate the social context of patients' dietary behaviors. Additionally, instrumental assistance with issues such as transportation, finances, and food preparation should be considered. Social support resources could also include community based options such as religious groups [95]. Adult day centers, health department wellness programs, and home-based nursing can also help to provide support. Examples of useful resource options have been compiled in a resource guide [96].

Cognitive Dysfunction

Systematic and meta-analytic review of population-based, prospective cohort studies of older adults and diabetes-related outcomes indicate that diabetes is associated with a faster decline in cognitive function among older adults. Prevalence rates of both Alzheimer's type and vascular dementia were twice that in persons with diabetes relative to those without [97]. Blood glucose control is associated with cognitive impairment. Hyperglycemia in nondiabetic individuals and higher average glucose

levels in individuals with diabetes are related to increased risk of dementia [98]. Multiple cross-sectional studies linking hypoglycemia to cognitive dysfunction [99, 100] and research indicating a bidirectional relationship of hypoglycemia and cognitive dysfunction [101]. A greater occurrence of hypoglycemic incidents is found in individuals with cognitive impairment [3], and a higher incidence of dementia is observed in individuals with a history of severe hypoglycemic episodes [102].

If frequent self-monitoring and adherence to specific dietary guidelines is within the cognitive abilities of the older patient with diabetes, then attainment of tight blood glucose control may be a reasonable goal. However, intensive self-management may not always be realistic for many cognitively impaired older adults. Unfortunately, despite the potential physical benefits, intensive management and tight control may require so many day-to-day demands, that this may be difficult to practically achieve. Cognitive dysfunction can make adherence to dietary recommendations particularly difficult. A large study of adults over age 75 with type 2 diabetes found that over one fifth had impaired cognitive status and that understanding of diabetes management (knowing how to adjust medication when ill) and self-care (blood glucose testing) was worse in those with impairment [103]. Older adults who are cognitively impaired may have difficulty remembering structured mealtimes that are coordinated with their insulin regimen or with following a complicated meal plan, such as carbohydrate counting or using a sliding scale to match insulin units to intake, making such treatment regimens too overwhelming to be practical. For some older individuals, a concrete, structured meal plan can help minimize ambiguity regarding their diabetes diet. Helpful strategies include using cues such as regular meals, setting alarms, providing written information with large print and pictures, and assessing comprehension and skill by asking for demonstrations. In addition, provision of home-based caretakers or meal services may also assist the older person with cognitive impairment or significant physical disability or other barriers to obtain access to optimal nutrition that is consistent with diabetes goals.

Attitudes and Dietary Intake in Older Adults with Diabetes

Older patients' personal views of diabetes may impact their diabetes self-care. A study of adults over age 60 with type 2 diabetes found that perceptions regarding the cause of diabetes, treatment effectiveness, and seriousness of one's diabetes were all significantly associated with quality of life and negative affect. Beliefs regarding treatment effectiveness were particularly predictive of dietary intake and physical activity [104]. An interview study of older adults with diabetes found that friends, family, and media were influential and critical in shaping expectations and diabetes care goals. Personal diabetes care goals predominantly centered on activities of daily living, maintaining independence, and avoiding becoming a burden to family. Diet and exercise were underemphasized relative to medication management [105]. Effective interactions with older patients should consider their experiences and influences, and focus on quality of life and patient definitions of their health care goals. Clearly communicating priorities in self-care tasks may facilitate adherence to medical goals and optimal care. Collaborative provider-patient discussions regarding self-care, and personal preferences and goals, and awareness of personal risk factors, may enhance patient motivation and treatment engagement. Integrating patient values and beliefs about health and quality of life, considering available resources, may best promote long-term regimen adherence [106].

Ethnic/Cultural Issues Influencing Self-Care and Dietary Intake

Research also suggests that ethnic minority, older adults, and traditionally "hard to reach" persons may have culturally unique health-related perspectives that are not effectively targeted by traditionally delivered health promotion interventions [107]. For example, focus group studies with

underserved ethnic minorities found that a prevailing belief was that better health behaviors could build resistance to acute illnesses and keep them healthy, but that chronic diseases such as diabetes were due to fate and heredity and beyond their individual control [105]. Most participants expressed an interest in "doing better" but were not able to specify how such healthful changes might be made. Qualitative evaluations of cultural influences on diabetes reveal the complexity of psychosocial influences on diabetes lifestyle change and why traditional health provider perspective based dietary interventions may fail. An interview-based study of Mexican American women with type 2 diabetes found that personal understanding and interpretation of their diabetes was most heavily based on their family's experiences and on community influences [108]. From the participants' perspectives, the severity of their diabetes was indicated by being treated with insulin injections and the provider being vigilant, while treatment with oral medications and the perception that providers had a lax attitude was taken to mean that the diabetes was not severe. Participant comments revealed that many found that provider comments were predominantly focused on negative aspects of their behavior, were confrontational, and at times demeaning. Provider focus on positive gains from behavior change, reinforcement for accomplishments and avoiding pejorative terms (e.g., obese) may go a long way in engaging many patients and enhancing a more collaborative relationship. Health provider cultural sensitivity, empathy, responsiveness, and continuity in care are also related to patient satisfaction with care in samples of older, underserved adults with diabetes [109]. Cultural beliefs and traditions may also directly impact use of nontraditional approaches to diabetes self-care. In-depth, structured interviews with older adults with type 2 diabetes divided into multiethnic groups (African Americans, Mexican Americans, Native Americans, and rural white Americans) found that one-fourth had used complementary approaches for their diabetes care (50 % of Mexican American participants, 20 % of African Americans, 15 % of Native Americans, and 15 % of rural whites). Many used herbal (15 %) or dietary (9 %) remedies, and teas, spiritual interventions, and other approaches (5 % each) [109].

The strong influence of family and culture on adherence to a diabetes diet and lifestyle change is also evident in focus group based qualitative research with predominantly older Southern, rural-dwelling African American women with type 2 diabetes [95]. The psychological impact of diabetes was characterized as stronger than the physical impact. Participants reported considerable life stress other than diabetes, particularly having a multi-caregiver role. Family members complaining about and being resistant towards healthy food preparation methods was common. Spirituality and religiosity were prominent and viewed as a primary source of emotional support, a positive influence on diabetes and a contributor to quality of life, with church described as an important source of social and emotional support. Findings demonstrate why consideration of the social and cultural context of older adult's lives is critical for the development of interventions to promote diet and lifestyle change.

Quality of Life and Diabetes Diet in Older Adults

For individuals with limited cognitive function or multiple comorbidities, the primary goal of care may be achieving a satisfactory quality of life rather than aggressive treatment regimens. In other cases, for those who are robust, goals and care may be similar to those for younger persons with diabetes. ADA and American Geriatrics Society Consensus Report guidelines for improving care of older persons with diabetes addresses quality of life issues that are more common in this population, including depression, pain, falls with injury, and declining functional status. These guidelines suggest that goals be developed based on functional status and personal desires [3]. See Table 11.1 for additional Consensus Report guidelines.

Table 11.1 Additional consensus recommendations for care of older adults with diabetes[a]

Screening for and prevention of diabetes
Screen older adults for prediabetes and diabetes according to ADA recommendations, if the patient will be likely to benefit from identification of the condition/disease and subsequent intervention
Implement lifestyle intervention for older adults with prediabetes who are able to participate and are likely to benefit from the prevention of type 2 diabetes
Management of diabetes
Encourage physical activity, even if not to optimal levels, and implement MNT using simple teaching strategies and community resources while considering patient safety and preferences
DSME/T in older adults should take into account sensory deficits, cognitive impairment, and different learning styles and teaching strategies and should include caregivers
In order to develop and update an individualized treatment plan, screen older adults periodically for cognitive dysfunction, functional status, and fall risk, using simple tools such as those at http://www.hospitalmedicine.org/geriresource/toolbox/determine.htm
Pharmacotherapy
Carefully choose antihyperglycemic therapies, considering polypharmacy. Avoid glyburide in older adult patients. Metformin can be used safely and is the preferred initial therapy in many older adults with type 2 diabetes, but at reduced dose in those with stage III chronic kidney disease, and avoid in those with stage IV or worse. Assess renal function using eGFR, not serum creatinine alone
Assess patients for hypoglycemia regularly by asking the patient and caregiver about symptoms or signs and reviewing blood glucose logs. In type 2 diabetic patients, hypoglycemia risk is linked more to treatment strategies than to achieved lower A1c (e.g., a patient with a low A1c on metformin alone may be at considerably lower risk of hypoglycemia than a patient with a high A1c on insulin)
If recurrent or severe hypoglycemia occurs, strongly consider changing therapy and/or targets
Assess the burden of treatment on older adult patients [caregivers], consider patient/caregiver preferences, and attempt to reduce treatment complexity
Management of older adults with diabetes in settings outside the home
The glycemic goals for hospitalized older adults with diabetes are usually similar to those for the general population. The use of SSI alone for chronic glycemic management is discouraged in inpatient settings as well as in LTC facilities
Transitions of older adults with diabetes (e.g., from home or LTC facility to hospital to post-discharge setting) are periods of high risk. Careful medication reconciliation and written information regarding medication dosing and timing help to minimize risk for hyper- and hypoglycemia. Early transition of diabetes care to an outpatient provider is important to modify drug therapy according to changes in clinical status

[a]Reproduced from Kirkman SM, Briscoe VJ, Clark N, Florez H, Haas LB, Halter JB, et al. Diabetes in older adults: a consensus report. J Am Geriatr Soc. 2012 Oct 25: 2342–56, with permission from John Wiley & Sons

Weight Loss and Quality of Life in Older Adults with Diabetes

Weight loss issues that must be considered for older adults with diabetes include the impact of restrictions on quality of life and potential loss of lean muscle mass from decreased protein intake. In research undertaken with younger adults with diabetes, weight loss programs that combine diet, physical activity, and theoretically guided behavior change techniques have been shown to be the most effective over the short term and can decrease insulin resistance to improve glycemic control [110, 111]. Hypocaloric diets, independent of weight loss, can also improve glucose tolerance and lipid levels and may also be appropriate for older, obese persons with diabetes. Physical activity was successfully incorporated into intensive weight loss support and education intervention with older adults with type 2 diabetes in the Look AHEAD (Action for Health in Diabetes) study. Mean participant age was 58 years, restriction of caloric intake was the primary approach with a goal of limiting total fat calories to 30 %, with a maximum of 10 % saturated fat and minimum of 15 % from protein.

At 1 year follow-up, intervention participants had lost an average of 8.6 % body weight, with greater weight loss and improved cardiovascular risk factors relative to participants in the control condition [112]. Four-year follow-up showed that at all annual assessments, the study's oldest participants (age 65–76 years at baseline) lost significantly more weight than the next oldest group (age 55–64), who, in turn, lost significantly more weight than participants in a younger age group (age 45–54 years) [113].

Recommendations for Imparting Dietary Information

When imparting diabetes diet information for behavior changes, it is critical to consider the psychosocial and cultural influences for each individual patient. Simple and concrete statements such as "eat less fat" or "get more walking in each day" may promote learning and minimize failure. Nutrition information is best presented in sequenced manageable steps that can then be individualized to the patient's setting. The National Diabetes Education Program has prepared materials adapted from those used in the DPP for use by primary care providers for middle age and older adults. Materials address motivational approaches that consider readiness for change, behavioral relapse, and the development of walking programs. This toolkit, the NDEP GAMEPLAN [114] is copyright-free and contains health care provider information with background information and patient handouts that may be copied. It is also important to be mindful of the range of functioning in older adults. Older adults of the World War II generation have tended to be characterized as somewhat reverential toward physicians and the health care system. However, baby boomers tend to have high expectations of their health providers, seeking a convenient yet collaborative relationship with access to additional resources such as self-help publications and internet-based supplements [115]. In order to meet the needs of the range of older adults with diabetes, it is clear that a "one size fits all" approach will not be effective. Rather issues related to culture and ethnicity and generational cohort must be considered.

Technological Advances in Diet Education Distribution

Advances in the delivery of diet and lifestyle change education to older adults in their homes have been made with the use of Internet, telephone, and remote telehealth monitoring approaches. A systematic review indicated that Internet-mediated interventions aimed at promoting a healthy lifestyle in adults over age 50 have yielded improvements in physical activity and weight loss. It is noteworthy that the majority of studies reviewed had developed social network forums as part of their website; however, all reported that they were rarely used by participants [116]. A health department–led individual counseling program, delivered predominantly over the telephone to low-income, ethnic minority adults with diabetes risk factors and an average age over 50, resulted in consumption of more fruits and vegetables and less fat, weight loss and triglyceride improvement relative to a wait list control group at a 6-month follow-up. Phone sessions had substantially higher completion rates relative to in-person group meetings and were rated as the most useful aspect of the program [117]. Systematic review of controlled studies also indicates benefits of telemedicine in home-based care interventions for individuals with chronic health conditions who are over age 60, including older adults with diabetes [118]. The most frequently studied telemedicine intervention involves monitoring of vital signs combined with personal interaction between health care provider and patient, followed by only personal interaction via telephone or videoconferencing. Randomized studies indicate predominantly positive results, particularly for behavioral endpoints such as adherence to medication or diet, and self-efficacy relative to medical endpoints such as blood pressure. In the review, the majority of

studies with older adults with diabetes reported positive outcomes for endpoints of glycemic control, blood pressure, lipids, and quality of life and behavioral outcomes. Across chronic conditions, studies including personal contact between the patients and the health care provider show superior outcomes compared to those without. The generalizability of studies of telemedicine in older adults, however, is limited by the exclusion of participants with cognitive, hearing visual impairments, or barriers to communication in many trials.

Conclusion: Clinical Recommendations

1. Establish the type of diabetes and medication regimen in order to appropriately integrate dietary goals.
2. Consider the importance of cardiovascular risk, including obesity and lipids, in developing diabetes dietary goals and routine assessment.
3. Work with the individual to set a goal of achieving and maintaining reasonable body weight. For obese older adults, moderate weight loss may achieve dramatic results and exercise may greatly enhance dietary intervention. Maintenance of behavior change and weight loss is critical. For underweight adults, focus on promotion of optimal nutritional intake and functional status.
4. Educate older adults with diabetes about the rationale for diet and lifestyle change and link to health outcomes; promote self-efficacy for change.
5. Consider the risk of hypoglycemia for older adults taking insulin—particularly those with poor nutritional status, cognitive dysfunction, poly-pharmacy, and comorbid illness. Encourage frequent self-monitoring and dietary self-treatment and preventive strategies.
6. Assess older adults' specific dietary patterns such as food choices, quantity eaten, and unplanned snacking and the lifestyle contexts in which they occur.
7. Address psychosocial issues that may influence dietary intake, including depression, social support, cognitive status, attitudes and perceptions, and the impact of the diabetes regimen on quality of life.
8. Address and intervene within individuals' cultural context, including family influences and church, when appropriate.
9. Provide a collaborative relationship with each patient, offer resources and provide concrete, behavioral strategies to promote behavior change.
10. When appropriate, provide self-help materials, including Internet resources.

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Chapter 12
Preventive Cardiology: Counseling Older At-Risk Adults on Nutrition

William E. Kraus and Julie D. Pruitt

Key Points

- Preventive cardiology is a discipline that focuses on the prevention of future cardiovascular disease in all populations, by reducing the burden of known cardiovascular risk factors such as hypertension, dyslipidemia, glucose intolerance, and obesity [1]. Preventive cardiology focuses on heart health by preventing the development of risk factors (health promotion or primordial prevention), the first clinical coronary heart disease, or stroke event (primary prevention) and recurrent events (secondary prevention) [2].
- Special concerns that can affect implementation of cardiac prevention strategies in older at-risk adults include complicated comorbidities; functional limitations, alterations in taste, smell, and appetite; difficulties with medication use/effectiveness; and limited financial, social, and/or caregiver resources.
- Preventive cardiology nutrition recommendations stress increasing the intake of fruits, vegetables, whole grains, and omega-3 and omega-6 fatty acids while substituting nonhydrogenated unsaturated fats for saturated and *trans*-fats. It further recommends minimizing the intake of beverages and foods with added sugar.
- While the basic tenets of these recommendations work well for older at-risk adults, clinical supervision becomes critical in successfully implementing healthy eating in this age group.

Keywords Cardiac event • Hypertension • Dyslipidemia • Lipid-modified diet • Sodium • Sugars

Core Components of Preventive Cardiology

Preventive cardiology brings a detailed understanding of the interplay between known and emerging risk factors to the long-term treatment of cardiac patients particularly targeting cardiometabolic risk factors. In essence, it translates a growing scientific knowledge base into clinical practice. The discipline of preventive cardiology applies research in vascular biology, clinical genetics, cardiovascular

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epidemiology, clinical pharmacology, and clinical trials to practical prevention strategies for patients. A key concept is the integration of multidisciplinary components such as smoking cessation, exercise therapy, nutritional counseling, and the best in pharmacologic medical therapy [1]. In this chapter, we will present a practical description of the nutrition component of preventive cardiology with an emphasis on the dietary recommendations available to older at-risk adults.

Nutrition and Cardiovascular Risk

Even with the advances in drug therapy for preventing coronary heart disease, diet, and lifestyle therapies remain the foundation of preventive clinical intervention. This is especially so for older adults. The American Heart Association AHA Diet and Lifestyle Recommendations note that with advancing age, the risk of developing coronary heart disease increases dramatically [2]. A number of longitudinal trials have shown that, as a group, older adults stand to benefit significantly from nutritional and lifestyle interventions that lower their risk or slow the advance of heart disease and cardiovascular events [3].

Research shows that older adults are open and interested in making and sustaining lifestyle changes. It also demonstrates that even relatively small improvements in risk factors (such as small reductions in BP and LDL cholesterol through diet and lifestyle changes) may be of substantial benefit. Improved dietary behaviors can also have a major impact on hypertension, type 2 diabetes mellitus, and dyslipidemias of many varieties [2].

In general, the goals and recommendations that apply to all populations covered by the AHA Diet and Lifestyle Recommendations are appropriate for older at-risk adults. However, with decreased energy needs and potentially higher vitamin and mineral requirements, older adults are well served by individual counseling that emphasizes nutrient-dense food choices [2].

Bette Davis, the iconic actor is famously attributed with the expression, “Old age is no place for sissies” [4]. She was, of course, commenting on the inevitable toll that aging has on the body and mind. With aging, every system, physiological and mental, experiences a decline and often a breakdown in function. This decline, wherever it occurs, cannot be treated in isolation. An approach that integrates all of the older at-risk adult’s comorbidities in a pragmatic whole is the one that works the best for each individual.

Special Issues of Concern for Older at-Risk Patients

As persons age, multiple changes occur throughout their bodies and in their lifestyle. Physical changes that affect metabolism, digestion, and caloric intake requirements have a direct and significant impact on cardiovascular risk. Socio-economic change in financial status, mobility, and ability to live independently also impact the person’s ability to manage cardiovascular risk. For each person the interplay of physical and socio-economic status is unique and diverse. It is therefore essential that a nutritional approach for preventing or managing coronary heart disease be tailored to the reality of each person [5].

For a health care provider, practicing preventive cardiology in older populations means making a thorough assessment of the person’s physical and environmental factors and using them to set up a personalized health plan. In addition to nutritional recommendations, the clinician should identify ongoing nutritional counseling that is both convenient and appropriate to the individual.

With this in mind, there are several issues that present special concerns for cardiac event prevention in older at-risk adults. In fact comorbidities, such as arthritis, chronic obstructive coronary artery disease, and dementia can prevent patients from being referred to nutritional counseling and interfere with heart-healthy eating plans for persons who are referred. In the likely presence of comorbid

disease states and associated treatments and altered physiologic response to food, according to Podrabsky and Remig, an average 75-year-old person has three chronic disease conditions and takes five prescription medications [6]. It is highly likely that each disease state and its treatments have their own dietary concerns and restrictions.

One hallmark of the aging process is a progressive decline in physical activity, which is itself a significant cardiovascular risk factor [7]. Although some may view frailty as an indication that lifestyle behavioral counseling, including nutrition, is far beyond the point of having an impact on cardiovascular risk, persons with limited functional capacity may actually derive the greatest benefit in the form of proportional improvements with minimal risk and improved quality of life [8]. In fact, the AHA Diet and Lifestyle Recommendations finds that older patients can successfully follow and sustain healthy behavior change [2]. However, at present, it must be noted that the benefits of nutritional counseling for older at-risk adults remain more conceptual than proven.

Some cardiovascular risk factors present particular challenges in older at-risk adults that can interact with nutritional factors. For hypertension, salt sensitivity increases in the already stiff vasculature of older persons and makes the use of diuretics as a first-line medication more justifiable. However, fragile volume status might make overtreatment and positional hypotensive episodes more likely. At the same time, a decrease in taste sensation may increase a person's desire to use more salt. Dietary sodium content may interact and complicate the process of finding a stable medical regimen for treatment of blood pressure, especially if the dietary sodium content is not stable. Counseling might include alternatives for salt and salt-free food enhancers to ensure the inclusion of foods that are nutritionally dense but uninspiring in taste. For dyslipidemia, accumulating evidence suggests that treating elevated low-density lipoprotein cholesterol levels is beneficial even in older individuals, and that physicians should not shy away from aggressive treatment of lipids, irrespective of the age of the patient [9]. For example, in the PROSPER study, designed to study the efficacy of cholesterol modification with pravastatin in older adults aged 70–82 years, at 3.2 years the active therapy reduced the risk of a primary cardiovascular endpoint by 15 % [9].

Given the well-known difficulty in compliance with statin therapy even in younger cardiovascular patients, nutritional therapy can be particularly valuable for the older at-risk adult in encouraging compliance and reinforcing dietary approaches to cardiovascular risk factors such as hypertension and dyslipidemias. For example, in the course of nutritional assessment the clinician might uncover a symptom that on the surface may not seem nutrition-related, such as lack of concentration or fatigue. This symptom might contribute to patient noncompliance with cardiac medication. By addressing the nutrition issue, the person's level of concentration or fatigue may improve enough for him or her to remember to take the prescribed cardiac medication.

Providing nutrition counseling to an older at-risk adult population elicits the need to discuss population-specific challenges and issues that must be considered in a comprehensive strategy. Implementation of the clinical recommendations that follow may be particularly difficult for this group. Many older at-risk adults have a limited or restricted ability to meet their nutritional needs. As a whole older adults often have limited financial resources for healthy food choices, be they inexpensive canned or frozen vegetables or a loaf of whole-grain bread, much less omega-3 fatty acid-rich fish or fresh fruit. They may also be faced with restricted access to markets and grocery stores or may be physically less able to take trips out of the house.

Dietary Intake and the Management of Heart Disease

Extensive research has been conducted on many different individual nutritional components and the impact they have on coronary heart disease and associated risk factors. Mente and de Koning completed an extensive review of prospective cohort studies or randomized trials investigating dietary

exposures in relation to coronary heart disease. They identified increased intake of fruits, vegetables, and whole grains, substitution of nonhydrogenated unsaturated fats for saturated and trans-fats, and increased intake of omega-3 fatty acids as effective dietary strategies for preventing coronary heart disease [10]. Additionally, incorporation of low-fat dairy products on a daily basis helps to control blood pressure and may, possibly, assist in weight management, if needed [11, 12]. Structuring heart-healthy nutrition education around these principles will support the goals of preventive cardiology.

Fruits and Vegetables

Numerous studies have demonstrated that diets rich in fruits and vegetables are correlated with prevention of coronary heart disease and associated risk factors [10]. In a large epidemiologic study, a significant inverse correlation between risk of coronary heart disease and intake of fruits and vegetables was noted. Every single serving/day increase in intake was correlated with a 4 % decrease in risk. Persons in the highest quintile of intake (9.15–10.15 servings/day) had a 20 % lower relative risk of developing coronary heart disease than persons in the lowest quintile of intake (2.5–2.9 servings/day). Especially beneficial were leafy green vegetables and vitamin C-rich fruits and vegetables [13]. In the landmark DASH trials, increased consumption of fruits and vegetables in the setting of additional healthy food behaviors, led to markedly decreased blood pressure levels [11]. The beneficial effects of including fruits and vegetables in the diet are thought to come, in part, from the provision of potassium, fiber, phytochemicals, and the displacement of unhealthier food choices.

Counseling persons to include additional fruits and vegetables in their diets should take into account several key elements. First, while respecting the person's dignity, discussion of ability to procure fruits and vegetables is important. Exploration of viable options for increasing fruit and vegetable intake, such as selecting inexpensive preparations (canned or frozen), selection of in-season varieties, home-delivered farm shares, and the like is important. Second, emphasis on the importance of serving the fruits and vegetables in a healthy and appealing manner is essential. People often offset the benefit gained from the inclusion of fruits and vegetables in their diet by adding copious amounts of fats, sugars, and salt during food preparation. Third, starchy vegetables such as corn, potatoes, peas, and beans should be considered part of the *starches* food group and not the *vegetable* food group. Nonstarchy vegetables are very low in calories and can be consumed liberally, even in the setting of weight management. Last, at-risk people should be encouraged to eat whole fruits and vegetables whether they are fresh, frozen, or canned in their own juice or light syrup over drinking fruit and vegetable juices is important. Whole fruits and vegetables provide the extra benefit of fiber and increased satiety. In general, over consumption of calories from fruit rarely occurs and only when a person consumes more than the recommended amount of juice or dried fruit—less satisfying foods. Increasing the consumption of healthy fruits and vegetables is often a new experience for many at-risk older adults. Increasing their self-efficacy through education and counseling to establish these new habits is critical in their eventual success.

Dietary Fats

There is undeniable evidence that diets high in saturated and *trans*-fats are significant contributors to the risk of coronary heart disease, while replacing saturated fats and *trans*-fats with healthy monounsaturated and polyunsaturated fats reduce risk. Differences in total fat intake do not significantly

Table 12.1 Benefits vs. risks of eating fish[a]

Some types of fish may contain high levels of mercury, PCBs (polychlorinated biphenyls), dioxins, and other environmental contaminants. Levels of these substances are generally highest in older, larger predatory fish and marine mammals.
The benefits and risks of eating fish vary depending on a person's stage of life.
• Children and pregnant women are advised by the U.S. Food and Drug Administration (FDA) to avoid eating those fish with the potential for the highest level of mercury contamination (e.g., shark, swordfish, king mackerel, or tilefish); to eat up to 12 oz (two average meals) per week of a variety of fish and shellfish that are lower in mercury (e.g., canned light tuna, salmon, pollock, catfish); and to check local advisories about the safety of fish caught by family and friends in local lakes, rivers, and coastal areas.
• For middle-aged and older men and postmenopausal women, the benefits of eating fish far outweigh the potential risks when the amount of fish eaten is within the recommendations established by the FDA and Environmental Protection Agency.
• Eating a variety of fish will help minimize any potentially adverse effects due to environmental pollutants.
Potential exposure to some contaminants can be reduced by removing the skin and surface fat from these fish before cooking. Consumers should also check with local and state authorities about types of fish and watersheds that may be contaminated and visit the FDA Web site for the most up-to-date information on recommendations for specific subgroups of the U.S. population (e.g., children, pregnant women).

[a]American Heart Association. (2013). Fish 101. Retrieved from http://www.heart.org/HEARTORG/GettingHealthy/NutritionCenter/Fish-101_UCM_305986_Article.jsp

influence disease risk; only substitution of saturated and *trans*-fats with monounsaturated and polyunsaturated fats significantly impact risk [14, 15]. This is an extremely important concept to grasp. In the Women's Health Initiative Study, an 8.2 % reduction in total fat intake (2.9 % from saturated fat, 0.6 % trans-fats, 3.3 % monounsaturated fats, 1.5 % polyunsaturated fats) did not result in significant impact on coronary heart disease risk [14]. However, replacement of 5 % of energy from saturated fat and 2 % of energy from trans-fat with monounsaturated and polyunsaturated fats was associated with a 42 % and 53 % lower risk of coronary heart disease, respectively, in the Nurses' Health Study [15]. Targeted reductions and substitutions of fat subtypes are critical to improving a person's cardiac risk profile.

In addition to replacing unhealthy fats in the diet with healthy fats, inclusion of omega-3 and omega-6 fats can provide substantial benefits. The 2010 Dietary Guidelines for Americans' recommends including 8 oz of fatty fish in the diet each week as moderate evidence has shown that this level of consumption is associated with reduced cardiac deaths among individuals with and without preexisting cardiovascular disease [16]. Plant-based sources of omega-3 fatty acids have also been indicated in the secondary prevention of coronary heart disease [17]. It is important to encourage older at-risk adults to increase omega-3 fatty acids in their diet by including eight ounces of low-contaminate (Table 12.1) fatty fish each week and plant-based sources such as flaxseed, English walnuts, and canola oil, within the context of recent safety advisories. Higher amounts of omega-6 may improve insulin resistance, reduce diabetes risk, and lower blood pressure. The AHA recommends a daily intake of at least five to ten percent of daily energy as omega-6 fatty acids. Replacing saturated fats with polyunsaturated fats is a good solution as they are a natural source of omega-6 fatty acids [18].

Managing the balance of fat in the diet through the replacement of unhealthy saturated and *trans-fats* with healthy omega-3, omega-6, monounsaturated, and polyunsaturated fats can represent a significant lifestyle change for many older at-risk adults. This will likely be a shift away from many of the comfort foods that are ingrained in their home environment. Acknowledging the difficulty of these changes can be helpful as the person begins to set goals. Smaller, more attainable goals lead to early success and increased self-efficacy.

Dairy Products

Dairy products may play a role in managing blood pressure and weight. Adding low-fat dairy products such as milk and yogurt to a diet rich in fruits and vegetables strengthens the diet's ability to reduce cardiac risk. In the setting of weight maintenance, the DASH feeding studies noted that addition of two to three servings of low-fat dairy products to the basic diet more than doubled the reduction in blood pressure achieved by subjects using this dietary approach [11]. While these positive effects on blood pressure have been well documented, research also suggests that dairy products may be a useful addition to weight loss programs. A meta-analysis of 29 randomized controlled trials concluded that dairy products may have a modest impact on facilitating weight loss in short-term or energy-restricted programs [19].

Studies also support the role of calcium and low-fat dairy products in weight and body fat mass management. Recent meta-analyses found that including dairy in the setting of energy restriction significantly improves loss of weight, fat mass, and waist circumference [19, 20]. A randomized controlled trial compared increased calcium through supplementation and inclusion of dairy products. While individuals taking calcium supplements experienced improvement over the control group in weight, total body fat, and trunk fat loss, individuals in the dairy group had substantially greater losses [12].

These smaller trials indicate that adding dairy products to the diet is beneficial in the management of weight and body fat. However, more extensive research is needed. Virtually all older at-risk adults can benefit from the inclusion of two to three servings of dairy products in their daily diet. Primarily, these servings should come from low-fat milk and yogurt. Owing to their higher fat content and lower calcium content, cheese and butter, should be considered as daily fat servings, rather than as dairy servings.

Whole Grains and Starches

In the past several years, starches have received a lot of negative press. Some fad diet creators even suggest virtually eliminating starches from the diet. However, starches are essential components of a healthy diet, as they provide certain essential nutrients and serve as a vital energy source. Starches also serve an important function in satiation. A distinction to be made during nutritional counseling is in the *type* of starch to include. While refined grains are stripped of their nutrients, whole grains provide a bounty of nutrients, phytochemicals, and fiber.

Inclusion of whole grains and cereal fiber in the diet decreases risk of disease. In the Iowa Women's Health study, Jacobs et al. found a clear inverse relation between intake of whole grains and risk of heart disease [21]. Persons in the highest quintile of intake (3.2 servings/day) had a 30 % lower relative risk of heart disease than persons in the lowest quintile of intake (0.2 servings/day) [21]. Similarly, the Nurse's Health Study also demonstrated a 34 % lower risk of heart disease in women in the highest quintile of intake of fiber. The decreased risk was only significant for dietary fiber from cereal grains, and not for fiber from fruits and vegetables [22].

Introducing or increasing whole grain products in the diet can be structured in a stepwise manner with the goal of at least half of all starch servings in the diet provided by whole grain products. It is productive to have the person begin to examine the starch products he or she currently consumes and identify areas for change. Initial increases may come from mixing whole grain breakfast cereals in with favorite refined grain cereals or purchasing whole grain pastas. Eventually, the person can continue to transition to additional whole grain products as the palate and gastrointestinal tract adjusts.

Added Sugars

As the American diet has become increasingly reliant on processed food and beverages, the general intake of added sugars has risen dramatically. It is estimated that the mean intake of sugars by all persons lies between 22.2 teaspoons (355 cal) and 34.3 teaspoons (549 cal) per day [23]. Dietary sugars can be divided into two types. The first type includes sugars that occur naturally in fruits and vegetables and are consumed as an integral part of the food. The second type includes sugars that are added to processed food or added manually just before they are consumed. For the purposes of cardiac prevention, nutrition counseling should emphasize natural sugar intake and set strict limits for any foods with added sugars.

Added sugars come in many varieties including sucrose, maltose, glucose, cane sugar, fructose, and high-fructose corn syrup, to name only a few. Research indicates that a heavy intake of added sugars, especially fructose consumption in the form of sugared soft drinks is driving the epidemics of insulin resistance, obesity, hypertension, dyslipidemia, and type 2 diabetes, all major risk factors for coronary heart disease [23]. For this reason the American Heart Association recommends limiting consumption of products with added sugar to no more than 6 teaspoons (100 cal) for women and 9 teaspoons (150 cal) for men per day [23]. Beverages sweetened with sugars may not be readily identified by at-risk people as problematic. In teaching about sources of hidden sugars, clinicians should remind their clients that sugary beverages count and encourage older at-risk adults to reach for plain water when they are thirsty rather than a sugared drink containing empty calories.

Teaching older adults about controlling their sugar consumption can be a very difficult issue and might take a two-pronged approach. In the first instance, the clinician can teach the difference between the natural sugars found in fruits and vegetables and the added sugars used in processed foods and beverages or by the spoonful to sweeten coffee, tea, or breakfast cereal. In the second instance the clinician can provide motivation to the person to satisfy the urge for something sweet with a piece of fruit rather than a piece of candy or a sweet drink. To help older at-risk adults manage their added sugar intake, clinicians might teach how to read and interpret the nutrition labeling on the food items. Not only will this skill come in handy for making better choices at the grocery store, it may help in exerting portion control at the table.

Additional Relevant Dietary Components

Stanols and Sterols

Plant stanols and sterols are organic compounds found naturally in vegetable oils, cereals, fruits, and vegetables. Additionally, they are now added to products such as margarines and orange juice. Due to their cholesterol-like structure, these compounds interfere with the absorption of cholesterol and cholesterol building blocks in the digestive tract. The net effect of this lowered absorption is a 6–15 % reduction in LDL cholesterol [24]. The Third Report of the National Cholesterol Education Program Expert Panel of Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) recommends consuming two grams of plant stanol and sterol esters per day as a therapeutic option for managing LDL cholesterol [24]. To achieve an optimal intake level, inclusion of fortified products is necessary as the amount of stanols and sterols occurring naturally in foods is minimal.

Alcohol

While alcohol intake and a reduction in cardiac events has been widely publicized in the popular media and supported by several research studies, most guidelines do not recommend encouraging the addition of alcohol in the heart-healthy diet. The addictive nature and adverse consequences of overconsuming alcohol may outweigh the potential benefits. In fact, as noted, excessive alcohol intake can be especially problematic in the older at-risk adult population. Also, it is becoming clear that many of the studies that found a potential benefit of moderate alcohol consumption perhaps overestimated the benefits by incorrectly including reformed high-volume alcoholic consumers in the abstinence group. While the proper role of alcohol in the diet and for risk reduction are still being investigated, if a participant currently consumes alcohol, the American Heart Association recommends limiting intake to not more than one drink per day for women and two drinks per day for men [2].

Sodium

Numerous studies have shown that reducing intake of dietary sodium can have a significant effect on lowering blood pressure, a key risk factor for heart disease. In the DASH-Sodium trial, subjects were maintained on sodium intakes of 3,300, 2,400, and 1,500 mg/day in a cross-over design. Blood pressure was significantly reduced with each incremental drop in sodium intake [25]. While sodium intake at the lowest level showed the greatest overall lowering effect, maintaining this level of intake is difficult at best. Therefore, the American Heart Association recommends consuming no more than 1,500 mg of sodium per day [2].

To remain under the recommended level of sodium intake, counsel older at-risk adults to steer clear of high sodium seasonings, canned meats, soups and vegetables, and salty snacks and to avoid adding salt when cooking or at the table. Encouraging persons to experiment with low-sodium flavor agents to maintain or add flavor to their foods is a viable strategy [25].

Alternative Dietary Patterns

One of the most significant ways that cardiac risk can be reduced is through achieving and maintaining a healthy body weight. As a result, older at-risk adults who are overweight or obese often solicit advice about initiating one of the numerous popular diets for weight loss. For this reason health professionals need to be aware of two key points emerging from research in this field. Several studies have noted that weight loss is not significantly different after 12 months in subjects following any one of several popular diets [26–28]. In a randomized clinical trial comparing a low-carbohydrate, high-protein, high-fat diet to a low-calorie, high-carbohydrate, low-fat diet, greater improvement of HDL cholesterol was experienced on the low-carbohydrate diet [27]. Changes in other risk factors (LDL, blood pressure, insulin sensitivity), however, were not significantly different between the groups or, as demonstrated by meta-analysis, were found to be unfavorable on a low-carbohydrate diet [27, 28]. When discussing alternative popular diets with persons, examine the restrictions set forth by the ones that limit the consumption of proven beneficial foods (fruits, vegetables, low-fat dairy products, and whole grains) discussed previously. The long-term health ramifications and safety of excluding or limiting these foods is, as yet, unknown.

Recommendations for Appropriate Caloric Intakes and Dietary Patterns

Practical implementation of a healthy diet pattern begins with laying a foundation of appropriate caloric intake. For the older at-risk adult population achieving an appropriate caloric intake may mean either a decrease or an increase in current caloric intake. In this population less strict adherence to specific calorie levels and more emphasis on healthy eating patterns should be the emphasis. The tool presented in Table 12.2 was developed by dietitians at the Duke Center for Living and Duke Cardiac Rehabilitation program. Based on the Harris Benedict equation, it is a user-friendly tool requiring minimal calculations to approximate caloric intake (see Table 12.2). Once an appropriate calorie level is identified, one can determine the recommended contributions from each dietary component. A healthy cardiac diet allows for an estimated 25–30 % of total calories from fat—mainly from healthy monounsaturated and polyunsaturated fats by limiting unhealthy saturated fat to 7 % of total calories. A quick reference for total fat and saturated fat gram allowance for varying calorie levels is provided (Table 12.3). Selection of the calorie level closest to the older at-risk adult's calculated needs is facilitated.

Table 12.3 shows two suggested meal plans that take into account the calories from fat and the recommendations for following a diet pattern rich in fruits, vegetables, low-fat dairy products, and whole grains. The first plan (Table 12.4, Chart 1) includes provisions for persons who consume beef, poultry, seafood, eggs, and cheese, while the second (see Table 12.4, Chart 2) is specifically designed for lacto-ovo vegetarians (individuals who do not consume animal products with the exception of eggs, cheese, and dairy products). To advise a specific person, one begins by finding the caloric level that most closely matches the patient's recommended caloric intake on the appropriate chart.

Table 12.2 Determining your daily calorie allowance[a]

Step 1:	Write current weight _____ (lbs.) then multiply by 10=	_____
Step 2:	Choose one from Steps a–e below. (*It is important **not** to have a calorie level <1,200 without evaluation by nutritionist.*)	
	a. If you want to tone up body, *maintain weight or lose less than 10 lb*, then add 500	
	b. If you want to *lose 10–25 lb*, then add 0.	_____
	c. If you want to *lose greater than 25 lb*, subtract 500	
	d. If you *weigh 350 lb* or more, subtract 1,000.	
	e. If you want to *gain weight*, add 1,000.	
Step 3:	Add calories in right hand column from Steps 1 and 2. This is your estimated Calorie needs per day	_____ *Calories per day*

[a]Calorie levels are based on a person engaging in ~30 min of exercise 3–5 days/week

Table 12.3 Daily fat gram budget chart

Calorie needs	Maximum daily *total* fat gram budget	Maximum daily saturated fat gram budget
1,300	40	10
1,400	43	11
1,600	48	12
1,800	51	14
2,000	58	16
2,200	66	17
2,400	73	19
2,600	79	20
2,800	87	22
3,000	95	23

Table 12.4 Recommended number of servings by food group for varying levels of kilocalorie intake for vegetarians and nonvegetarians

Chart 1[a]	1,300	1,400	1,600	1,800	2,000	2,200	2,400	2,600	2,800	3,000
Fat Grams	≤43	≤45	≤52	≤58	≤64	≤70	≤78	≤84	≤90	≤98
Starch[c]	4	4	5	5	6	7	7	8	9	10
Fruit	2	3	4	4	5	5	5	6	7	7
Veg	3+	4+	4+	5+	5+	6+	6+	6+	7+	7+
Dairy	2	2	2	2	2	2	3	3	3	3
M&Pd	3	3	4	6	6	8	8	8	8	9
Chart 2[b]	1,300 VEG	1,400 VEG	1,600 VEG	1,800 VEG	2,000 VEG	2,200 VEG	2,400 VEG	2,600 VEG	2,800 VEG	3,000 VEG
Fat Grams	≤43	≤45	≤52	≤58	≤64	≤70	≤78	≤84	≤90	≤98
Starch[c]	5	5	6	6	7	8	9	10	11	12
Fruit	2	2	3	3	4	4	4	5	6	6
Veg	3+	3+	4+	5+	5+	5+	6+	6+	7+	7+
Dairy	3	3	3	3	3	3	3	3	3	3
M&P[d]	2	2	2	3	3	3	3	4	4	5

[a]Chart 1 is a plan for people who eat beef, poultry, seafood, eggs, and cheese

[b]Chart 2 is a plan for people who are lacto-ovo vegetarian (eat only eggs, cheese, and dairy animal products)

[c]Include at least half of all starch servings from whole grain products

[d]M&P: Meat (beef, poultry, seafood, pork, etc.) and other proteins such as eggs, cheese, nuts

Conclusion

The goal of nutrition therapy for older adults at-risk of coronary heart disease is the adaptation and maintenance of healthy behaviors in order to improve cardiovascular risk profile and prevent all cardiac events over his or her lifetime. Nutrition therapy begins with an assessment of current dietary practices and a review of potential barriers, followed by identification of targeted areas for change and creation of a practical and effective plan. Including the services of a registered dietitian in an overall heart-healthy strategy may be beneficial in managing the complexities of changing dietary behaviors and providing nutrition education. Involving individuals who are part of the at-risk adult's support network and providing support and encouragement for each step will foster continued positive changes and cardiac risk reduction.

Clinical Recommendations for a Heart-Healthy Diet in Older Individuals

1. Complete a thorough assessment of the nutrition status and home socioeconomic context of the person.
2. Provide education on a diet rich in fruits, vegetables, low-fat dairy products, and whole grains and low in saturated and trans-fats.
3. Assist the at-risk adult in identifying changes they can make to substitute nonhydrogenated unsaturated fats for saturated and trans-fats in their diets.
4. Encourage the at-risk adult to increase their intake of natural food sources of omega-3 and omega-6 fatty acids.
5. Approximate the at-risk adult's optimal caloric intake (see Table 12.2) for supporting healthy weight maintenance goals.
6. Develop a person-specific implementation plan that acknowledges areas needing improvement and solutions to potential barriers.

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Chapter 13
Chronic Heart Failure

Justin M. Vader, Christopher L. Holley, and Michael W. Rich

Key Points

- Heart failure is the leading cause of hospitalization in the Medicare age group. The prognosis for established heart failure in persons over age 65 is poor, with 5-year survival rates of less than 50 % in both men and women.
- The pharmacotherapy of heart failure with reduced ejection fraction (HFREF) is well established, with angiotensin-converting enzyme inhibitors, beta-blockers, and aldosterone antagonists having the most proven benefit.
- Treatment of heart failure with preserved ejection fraction (HFPEF) is an area of active research, but no therapies have been definitively shown to reduce mortality.
- Unintentional weight loss in heart failure is likely due to both increased energy utilization and decreased availability of fat, protein (amino acids), and carbohydrates despite "normal" caloric intake.
- Moderate dietary sodium restriction, such as a 2-g sodium diet, is appropriate for most patients with heart failure, and excess fluid intake should be avoided.
- Some patients will require supplementation with potassium, calcium, and/or magnesium if adequate amounts cannot be obtained from the diet. However, the importance of most vitamins and other micronutrients in the pathogenesis and treatment of chronic heart failure has not been well characterized.

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> Dropsy [heart failure] is usually produced when a patient remains for a long time with impurities of the body following a long illness. The flesh is consumed and becomes water. The abdomen fills with fluid; the feet and legs swell; the shoulders, clavicles, chest, and thighs melt away.
>
> Hippocrates [1]

Introduction

Age-related changes in the cardiovascular system coupled with the increasing prevalence of cardiovascular disorders with advancing age, especially hypertension, coronary artery disease, and valvular heart disease, lead to a progressive rise in the prevalence of heart failure with increasing age. Nutritional factors may contribute to the development of heart failure and, conversely, heart failure may lead to nutritional deficiencies. Dietary factors also play a key role in heart failure management. This chapter provides an overview of the clinical features of heart failure and reviews the interactions between heart failure, nutrition, and aging. The chapter concludes with a summary of nutritional recommendations for management of older patients with heart failure.

Overview of Heart Failure

Background

Heart failure is a condition in which one or more abnormalities in cardiac function lead to an inability of the heart to pump sufficient blood to meet the body's metabolic needs while maintaining normal or near-normal intra-cardiac pressures and blood volumes. As of 2010, 6.6 million American adults are estimated to have heart failure, and by 2030 prevalence is expected to increase by 25 % [2]. Both the incidence and prevalence of heart failure increase with advancing age [3], with over 70 % of hospital admissions for heart failure occurring in persons 65 years of age or older [4] and more than 50 % occurring in persons over the age of 75 [5]. As a result, heart failure is the leading cause of hospitalization in the Medicare age group, and it is currently the most costly cardiovascular illness in the United States [6]. Moreover, it is anticipated that the rapid growth in the older adult population will result in a marked increase in the number of older persons with heart failure during the next two to three decades [7].

Etiology

In the United States, chronic hypertension and coronary heart disease account for 70–80 % of heart failure cases [8, 9]. In older women, hypertension is the most common etiology of heart failure, accounting for almost 60 % of cases, while in older men coronary heart disease and hypertension each account for 30–40 % of heart failure cases [9]. Valvular heart disease (especially aortic stenosis and mitral regurgitation) and non-ischemic cardiomyopathies are also common causes of heart failure in

older adults. Less frequent causes include infective endocarditis, pericardial disease, thyroid disorders, and drug toxicity (e.g., alcohol or anthracyclines).

Pathophysiology

The cardiac cycle is divided into a filling phase (diastole) and a pumping phase (systole). Impaired cardiac filling due to increased "stiffness" of the heart (e.g., from left ventricular hypertrophy as a consequence of hypertension) results in increased intra-cardiac pressures and reduced cardiac output despite preserved contractile function, leading to the syndrome of heart failure with preserved ejection fraction (HFPEF, sometimes called "diastolic heart failure"). Conversely, damage to the heart muscle (e.g., from a myocardial infarction) that results in impaired pumping action is referred to as heart failure with reduced ejection fraction (HFREF) or "systolic heart failure." Of note, both systole and diastole require energy in the form of adenosine triphosphate (ATP), with diastole being more sensitive to ATP depletion [10]. This explains why diastolic dysfunction precedes systolic dysfunction in the setting of ischemia. Although most patients with heart failure have evidence for both systolic and diastolic dysfunction, those with a left ventricular ejection fraction of less than 40–45 % are usually classified as having predominantly HFREF, whereas those with an ejection fraction above this range are classified as having HFPEF.

Recent studies indicate that about half of heart failure cases are associated with impaired systolic function, while the remainder have normal or near-normal systolic function at rest (i.e., HFPEF) [8, 11]. HFPEF is more common in women than in men, and the proportion of patients with HFPEF increases markedly with age. In the Cardiovascular Health Study, two-thirds of women over age 65 with heart failure had preserved systolic function, as compared with only 41 % of men in this age group [12]. Although treatment of systolic and diastolic heart failure is similar in some respects, it is important to evaluate ventricular function by echocardiography, radionuclide angiography, magnetic resonance imaging, or cardiac catheterization in all patients with newly diagnosed heart failure because, as discussed below, there are important differences in pharmacotherapy depending on the degree of impairment in contractile function.

Clinical Features

The cardinal symptoms of heart failure include exertional shortness of breath and fatigue, reduced exercise tolerance, orthopnea, and lower extremity edema. Palpitations and orthostatic lightheadedness are also common, but chest discomfort in the absence of ischemia is not usually present. Physical findings may include tachycardia, tachypnea, elevated jugular venous pressure, moist pulmonary rales, an S_3 or S_4 gallop, hepatomegaly, and dependent pitting edema. In patients with advanced or long-standing heart failure, there is loss of lean body mass, particularly muscle mass, which in severe cases may progress to the syndrome of cardiac cachexia.

Prognosis

The prognosis for established heart failure in persons over age 65 is poor, with 5-year survival rates of less than 50 % in both men and women [13]. Mortality models, particularly the Seattle Heart Failure Model, can individualize this estimate based upon clinical and laboratory data [14], although

these estimates may be inaccurate in patients over age 80 [15]. In addition to poor survival, chronic heart failure is characterized by recurrent hospitalizations for acute exacerbations [16, 17], a marked increase in the risk of sudden death due to arrhythmia [18], and substantially impaired quality of life due to diminished activity tolerance. Although the short-term prognosis (i.e., 3–6 months) is somewhat more favorable in patients with HFPEF compared to HFREF, the long-term prognosis is similar [19, 20], as are hospitalization rates, symptom severity, and functional capacity [21]. Noncardiovascular death is more common in HFPEF than in HFREF, but arrhythmias and progressive heart failure are the most common causes of death in both groups [22].

Treatment

Optimal treatment of chronic heart failure combines both nonpharmacological, pharmacological, and device-based approaches [23]. Essential nonpharmacological measures include patient education, dietary counseling, sodium and in some cases fluid restriction, attention to psychosocial and financial concerns, and close follow-up. Older patients with multiple comorbid conditions or complex environmental issues often benefit from a multidisciplinary approach to care delivery, involving nurses, social workers, dietitians, therapists, pharmacists, and physicians [24, 25].

The pharmacotherapy of systolic heart failure has been studied extensively over the last 25 years. Angiotensin-converting enzyme (ACE) inhibitors are the cornerstone of treatment, and available evidence indicates that these agents are as effective in older as in younger heart failure patients [26]. Angiotensin II receptor blockers (ARBs) and the combination of hydralazine and isosorbide dinitrate are suitable alternatives in patients who are unable to tolerate ACE inhibitors [27–30]. The beta blockers carvediolol, metoprolol, and bisoprolol have also been shown to reduce mortality and improve left ventricular function in stable heart failure patients at least up to the age of 80 [31, 32]. A fourth agent, nebivolol, showed a nonsignificant reduction in mortality in a trial conducted exclusively in patients >70 years of age [33]. Metoprolol and carvedilol are the only beta blockers approved for systolic heart failure in the U.S. Digoxin improves symptoms and reduces hospitalizations for heart failure but has no effect on survival, with similar effects in older and younger patients [34, 35]. Diuretics are important for maintaining normal volume status and for managing acute heart failure exacerbations, but with the exception of the aldosterone antagonists spironolactone and eplerenone, diuretics have no discernible effect on the natural history of heart failure. Spironolactone reduces mortality in patients with advanced systolic heart failure and is indicated in patients who remain symptomatic despite the above therapeutic measures [36]. The recent findings of the EMPHASIS trial, in which eplerenone provided a mortality benefit in New York Heart Association (NYHA) Class II patients, have led to expanded indications for spironolactone and eplerenone in the most recent European Heart Failure guidelines (Class IA recommendation for patients with NYHA Class II–IV symptoms and EF $\leq$35 %) [37, 38]. Current pharmacotherapy of systolic heart failure is summarized in Fig. 13.1.

In contrast to systolic heart failure, no agents are specifically indicated for the treatment of HFPEF. Trials with ACE inhibitors and ARBs have shown no mortality benefit in this population [39–41]. Pharmacologic agents that have been shown to improve *symptoms* in selected patients with diastolic heart failure include nitrates, ACE-inhibitors, and beta blockers [21, 39]. Guidelines recommend that hypertension be treated aggressively and coronary artery disease be managed with medications and/or revascularization as indicated [42]. Diuretics are indicated for controlling volume overload, but over-diuresis should be avoided.

While pharmaceutical management of heart failure has proven successful, surgically implanted left ventricular assist devices (LVADs) have emerged as an option for patients with advanced heart failure, either as a bridge to heart transplantation (BTT) or as stand-alone "destination" therapy (DT). Pulsatile LVADs improve longevity and quality of life compared to medical therapy in NYHA class IV heart

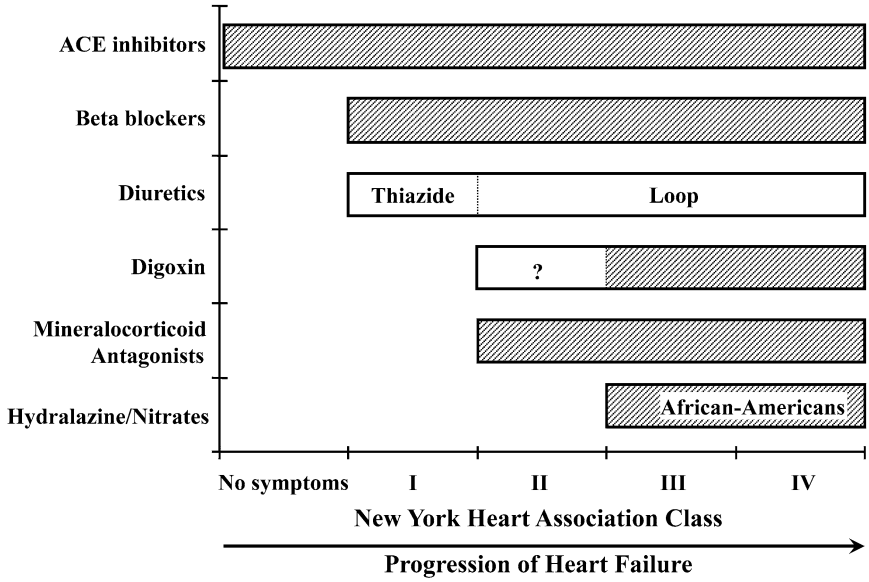

Fig. 13.1 Pharmacotherapy of left ventricular systolic dysfunction. Hatched regions denote conditions for which improved outcomes have been documented in prospective randomized clinical trials. *ACE* angiotensin-converting enzyme. *Angiotensin-receptor blockers (ARBs) and the combination of hydralazine/isosorbide dinitrate are acceptable alternatives or adjuncts to ACE inhibitors in selected patients

failure patients ineligible for heart transplant [43]. Second-generation continuous-flow devices now offer benefit beyond older pulsatile devices [44], and have supplanted pulsatile devices in clinical practice. Limited data suggest that carefully selected patients up to age 80 experience improved symptoms and quality of life with DT-LVAD, although the risk of gastrointestinal bleeding is higher than in younger patients [45].

General Nutritional Aspects of Heart Failure

Heart Failure as a Metabolic Syndrome

Heart failure is a chronic progressive disorder characterized by a host of neurohormonal, immunologic, and metabolic derangements (Table 13.1) [46]. In acute heart failure, activation of the sympathetic nervous system and renin-angiotensin-aldosterone axis serve to maintain cardiac output and preserve tissue perfusion. However, chronic activation of these systems is deleterious and perpetuates progression of the heart failure syndrome. Indeed, current therapy for heart failure focuses on antagonizing the harmful effects of these two neurohormonal pathways through the use of beta blockers, ACE inhibitors, angiotensin receptor blockers, and aldosterone antagonists.

In addition to activation of neurohormonal systems, chronic heart failure is associated with immunological dysregulation, as evidenced by increased levels of circulating tumor necrosis factor-alpha (TNF-α), interleukins 1 and 6, soluble adhesion molecules, and certain leucocyte chemokines [47, 48]. Activation of these cytokines likely plays a pivotal role in the apoptosis (programmed cell death) and anorexia that are features of chronic heart failure. In addition, some cytokines may exert direct cardiotoxic effects (e.g., through increased oxygen free radical activity), thereby contributing to heart failure progression.

Table 13.1 Neurohormonal and metabolic abnormalities in chronic heart failure

Activation/up-regulation/high levels	Reduction/resistance/down-regulation
Sympathetic nervous system	Vagal tone
• Increased circulating norepinephrine and epinephrine	
Activation of renin-angiotensin-aldosterone system	
• Increased angiotensin II levels	
• Increased aldosterone levels	
Atrial and B-type natriuretic peptide levels	
TNF-α and IL-1/IL-6	
Endothelin-1 and vasopressin (anti-diuretic hormone)	Peripheral blood flow (decreased nutrient delivery)
Cortisol levels	Dehydroepiandrosterone (DHEA)[a]
Insulin levels (in noncachectic patients)	Insulin sensitivity (manifest as insulin resistance[a])
Growth hormone	Normal or reduced insulin-like growth factor-1 (IGF-1)
Leptin	Ghrelin
Basal metabolic rate (BMR)	Thyroid function

[a]Denotes anti-anabolic effect

Many of the neurohormonal and immunologic abnormalities in chronic heart failure are also associated with important effects on metabolism. While the mechanisms underlying these effects are complex and not fully understood, the net effect is an imbalance between catabolic (tissue-wasting) and anabolic (tissue-building) factors [49]. Cardinal features of advanced heart failure include an increase in basal metabolic rate (BMR) [50], altered protein and fat metabolism, and impaired peripheral blood flow with reduced nutrient delivery to bodily tissues. In chronic advanced heart failure, these effects lead to tissue wasting and loss of lean body mass [51].

Cardiac Cachexia

Hippocrates's early description of "dropsy" (i.e., heart failure) cited at the beginning of this chapter provides a remarkably apt characterization of cardiac cachexia. While tissue wasting and loss of muscle mass occur early in chronic heart failure, marked tissue wasting and cachexia are hallmarks of advanced or end-stage heart failure.

Cardiac cachexia has been variously defined over the years, but a 2008 consensus statement defines adult cachexia as weight loss of 5 % or more within 12 months (or BMI <20) plus three of five clinical or laboratory criteria: decreased muscle strength, fatigue, anorexia, low fat-free mass index, and abnormal laboratory values (anemia, low serum albumin, or elevated markers of inflammation) [52]. Estimates of the prevalence of cachexia in patients with heart failure vary widely, but typically range from 10 to 20 %. Importantly, cachexia differs markedly from starvation (e.g., due to anorexia nervosa). Although patients with heart failure may exhibit signs of malnutrition, in cachexia there tends to be a greater loss of lean body mass, principally muscle mass but also bone mass, whereas in starvation there is preferential loss of adipose tissue in the early stages, with subsequent loss of muscle mass as malnutrition progresses [51]. In addition, prolonged starvation is almost invariably associated with a very low body mass index (BMI), whereas patients with cardiac cachexia may experience only modest reductions or even increased body weight, in part due to increased extracellular fluid accumulation (edema) and replacement of muscle mass by fat mass.

As noted above, the complex cascade of metabolic disturbances leading to cardiac cachexia is incompletely understood. However, circulating levels of TNF-α are invariably elevated in patients with cardiac cachexia; indeed, the TNF-α level is the strongest predictor of weight loss in heart failure patients [53]. It is currently unknown whether TNF-α plays a direct pathophysiological role in the

development of cardiac cachexia or if it merely serves as a marker for the cachectic state (and the severity of heart failure), but circulating TNF-α levels are a strong independent predictor of mortality in heart failure patients. Unfortunately, clinical trials of TNF-α blocking agents have been disappointing (see below).

Other circulating factors that may play a role in cardiac cachexia include endotoxin, leptin, and ghrelin. Circulating endotoxin may arise when extensive fluid overload causes gut edema, allowing bacterial toxins to move from the bowel to the blood stream. This leads to increased inflammatory cytokines with systemic effects as noted above. Plasma leptin levels have recently been shown to correlate with prognosis in cases of non-ischemic heart failure, with high plasma leptin predicting disease progression [54]. In contrast to leptin, ghrelin is a centrally acting peptide produced in the stomach that *stimulates* food intake and can increase circulating levels of growth hormone. Heart failure patients appear to have some degree of ghrelin-resistance, which normalizes after heart transplantation [55]. Administration of ghrelin has shown promising results in both animal models of heart failure as well as in a small clinical trial, in which heart failure patients treated with ghrelin for 3 weeks had increased left ventricular function, exercise capacity, and lean body mass [56, 57]. B-type natriuretic peptide (BNP), which is expressed at high levels in patients with decompensated heart failure, has been shown to exert anorectic effects and to reduce ghrelin concentrations when administered to healthy men, underscoring the interrelatedness of heart failure and energy balance [58].

Caloric Intake, Fat, and Protein

The occurrence of weight loss in patients with advanced heart failure is somewhat paradoxical, since heart failure is often associated with reduced physical activity. Furthermore, excepting those heart failure patients who develop anorexia (due either to heart failure itself or as a result of medications), caloric intake is similar in heart failure patients (including those with cachexia) and persons without heart failure [59]. This combination of preserved caloric intake and apparently reduced activity would be expected to result in weight gain rather than weight loss. What, then, accounts for the net loss in non-edematous body mass encountered in end-stage heart failure patients?

First, as noted above, most studies have shown that despite reduced muscle mass, there is an increase in BMR in most patients with heart failure, most likely due to increased energy requirements for respiration and the generalized catabolic state arising from neurohormonal dysregulation (esp. increased circulating catecholamines) [60, 61]. Second, although caloric intake is maintained, there is evidence that fat absorption is impaired in patients with heart failure, perhaps due to bowel edema [62]. Although intestinal handling of protein is usually preserved [63], alterations in protein and carbohydrate metabolism result in impaired delivery of these nutrients to the body's tissues [51]. Excessive adrenergic tone resulting in vasoconstriction is an important and potentially reversible mechanism that limits insulin and glucose delivery to skeletal muscle [64]. Further, compared to matched controls with similar dietary protein and carbohydrate intake, nonobese heart failure patients have increased nitrogen excretion and consequently negative nitrogen balance [65]. In sum, weight loss in heart failure is likely due to increased energy utilization, decreased availability of fat, protein (amino acids), and carbohydrates, and increased nitrogen excretion—all despite "normal" caloric intake.

Management of cardiac cachexia is problematic, and the best approach is to focus on prevention. In this regard, preliminary data suggest that both ACE inhibitors and beta-blockers may exert favorable effects on weight loss in heart failure patients. In a post-hoc analysis of the Studies of Left Ventricular Dysfunction (SOLVD) trial, patients receiving the ACE inhibitor enalapril were 19 % less likely to experience weight loss of 6 % or more during a mean follow-up period of 35 months compared to patients receiving placebo ($p=0.05$) [66]. Although cachexia is an ominous sign associated with significant mortality, there is some evidence that pharmacologic treatment of heart failure can

lead to partial reversal of the cachectic state. In a small observational study involving 13 heart failure patients with cachexia, 6 months of treatment with either carvedilol or metoprolol was associated with significant weight gain accompanied by favorable effects on plasma norepinephrine and leptin levels [67]. In another study of eight patients with advanced heart failure and cardiac cachexia, treatment with the combination of digoxin, the ACE-inhibitor enalapril, and the loop diuretic furosemide was associated with significant clinical improvement, as well as increased muscle bulk, subcutaneous fat, and serum albumin and hematocrit levels [68]. In contrast to these studies, two large trials of etanercept, a tumor necrosis factor (TNF) blocking agent, failed to demonstrate significant benefit and were discontinued [69]. These findings were particularly disappointing since TNF-α may play a role in the development of cardiac cachexia.

Beyond pharmacologic approaches to prevent or treat cachexia, a few studies have examined the role of nutritional support in advanced heart failure patients. In one small randomized trial, a high caloric diet failed to result in significant changes in nutritional status or clinical outcomes of patients with advanced heart failure [70]. In another study of patients with moderate to severe heart failure and malnutrition receiving high-energy nasogastric tube feedings for 2 weeks, total body weight and extracellular fluid weight declined but lean body mass increased [71]. There was, however, no change in oxygen consumption or cardiac function [72]. A third study involving only six patients undergoing mitral valve surgery showed that perioperative nutritional support was associated with improved clinical status and stable cardiac function. Regarding amino acid supplementation, in a study of eight patients with cardiac cachexia, infusion of branched-chain amino acids had no discernible effect on protein metabolism [73]. Conversely, a specially formulated oral amino acid supplement, in conjunction with standard pharmacologic therapy, appeared to increase exercise capacity via improved circulatory function, muscle oxygen consumption, and aerobic energy production in a small randomized trial of outpatients aged 65–74 with heart failure [74]. Finally, the GISSI-HF trial randomized patients with chronic systolic heart failure to placebo or 1 g/day of n-3 polyunsaturated fatty acids (n-3 PUFA). There was a modest, but statistically significant decrease in cardiovascular hospitalization and overall mortality [75]. The applicability of this observation to dietary intake of n-3 PUFA is not known. In summary, there are limited data at present to assess the impact of various modes of nutritional support on metabolic parameters or clinical outcomes in patients with advanced heart failure. While the observations in amino acid and PUFA trials are intriguing, additional study is needed before these interventions can be recommended for routine heart failure care.

Heart Failure and Obesity

The epidemic of obesity in the United States and elsewhere has led to an increasing proportion of heart failure patients who are overweight or obese. Obesity is independently associated with the development of heart failure, as well as with hypertension, diabetes, obstructive sleep apnea, pulmonary hypertension, and other comorbidities that adversely affect the heart failure patient. Obesity may also result in misdiagnosis of heart failure, since exertional shortness of breath may be due to pulmonary hypertension or physical deconditioning, while lower extremity edema may be caused by venous insufficiency. Conversely, sedentary obese patients may not experience significant shortness of breath until heart failure is far advanced, and early diagnosis of heart failure, at a stage when treatment is more likely to be effective, can easily be missed. Finally, the excess weight carried by overweight heart failure patients results in increased cardiac work, straining the already weakened heart. Indeed, obesity is often associated with increased heart rate and vascular resistance, effects that not only increase cardiac work, but which are diametrically opposed to the actions of beta-blockers and ACE inhibitors.

The effect of intentional weight loss in patients with heart failure is an area of active investigation. An emerging body of literature involving obese subjects describes favorable cardiac morphologic [76, 77], metabolic [78], and functional changes after marked weight loss [79]. However, there is currently no evidence that weight loss is associated with improved clinical outcomes in older heart failure patients. Furthermore, several studies have shown that older patients with heart failure and increased body mass index (BMI) have better outcomes than those with normal body mass index (BMI 20–25 kg/m^2), and that those with lower BMI (<20 kg/m^2) or cardiac cachexia have the worst prognosis [80]. This has been termed the "obesity paradox" and may reflect the fact that those with a higher BMI have better nutritional status and lower NYHA functional class than those with a lower BMI [81]. Thus, the value of weight loss in obese older patients with heart failure is unknown, and additional study is needed before specific recommendations can be made. In the meantime, it seems reasonable to advise older patients who are morbidly obese (BMI ≥40 kg/m^2) to lose a modest amount of weight through a combination of increased physical activity (including strengthening exercises to maintain or increase muscle mass) and reduced caloric intake.

Specific Nutrients in Heart Failure

Water and Sodium

Activation of the renin-angiotensin-aldosterone system in patients with heart failure results in sodium and water retention. As a result, untreated heart failure is usually associated with increased total body water and total body sodium. Of note, total body sodium is generally increased even when serum sodium levels are reduced (i.e., hyponatremia). This situation occurs in patients with advanced heart failure because fluid retention is more pronounced than sodium retention, in part due to the action of vasopressin (anti-diuretic hormone). Indeed, hyponatremia in patients with heart failure is associated with more severe hemodynamic and neurohormonal disturbances, and is a marker for poor prognosis [82]. Antagonists of the vasopressin type-2 receptor promote free water excretion and are approved for treatment of hyponatremia. Though clinical trials in acute heart failure failed to show a mortality benefit [83], these agents may be used for refractory symptomatic hyponatremia.

Diuretics are the mainstay of therapy for fluid overload in heart failure patients. Ideally, diuretic dosages are adjusted to maintain a normal state of hydration (euvolemia). However, over- and under-diuresis are both common, so that at any given time, a patient may be volume-overloaded, euvolemic, or relatively dehydrated, and careful assessment of volume status is thus essential in managing heart failure patients. From a practical standpoint, the simplest way to do this is by monitoring daily weights. Patients should be instructed to weigh themselves every morning without clothing, after voiding, and before eating, and weights should be recorded on a daily weight chart. An optimal or "dry" weight should be established, and variances of more than 2–3 lb in either direction should lead to adjustments in diuretic dosage. The rationale behind this approach is that short-term variability in body weight primarily reflects changes in total body water. Note, however, that non-edematous weight may change over longer periods of time, usually decreasing but occasionally increasing if the overall nutritional status improves. Therefore, periodic reassessment of the patient's desirable weight is appropriate.

In addition to monitoring daily weights and adjusting diuretic dosages, dietary sodium restriction plays a pivotal role in maintaining normal volume status and avoiding acute heart failure exacerbations, as evidenced by the fact that several studies have shown that dietary sodium excess is a common precipitant of repetitive heart failure hospitalizations [84, 85]. Dietary sodium excess contributes to fluid retention, and an acute dietary sodium load (e.g., potato chips, canned soup, "fast food") may

result in a sudden increase in intravascular blood volume, triggering a rise in intra-cardiac pressures and precipitating acute heart failure. Older patients with diastolic heart failure are particularly sensitive to salt intake and changes in blood volume, and are therefore less tolerant of a salt load. While there are no clinical trial data demonstrating improved outcomes with sodium restriction, it is standard of care that heart failure patients, family members, and other caregivers should be educated about the importance of avoiding high sodium foods [23]. Although some patients may find it difficult to adhere to a sodium-restricted diet, careful instruction and guidance from a dietitian is often effective in overcoming this barrier. In contrast to sodium restriction, fluid restriction is not usually required for most patients with mild to moderate heart failure unless significant renal impairment is also present. However, patients should be advised to avoid *excess* fluid intake—the oft-quoted dictum to "drink 8–10 glasses of water every day" does not apply to patients with heart failure. In addition, patients with advanced heart failure accompanied by hyponatremia may benefit from more stringent fluid restriction, e.g., 1.5 L/day total fluid intake.

Other Electrolytes

Apart from their effect on body water, diuretics have important effects on key electrolytes, including sodium, potassium, chloride, magnesium, and calcium. Thiazide and "loop" diuretics (furosemide, bumetanide, torsemide), as well as metolazone, promote urinary loss of sodium, potassium, chloride, and magnesium. As a result, these diuretics may be associated with hyponatremia, hypokalemia, hypochloremia, and hypomagnesemia. In addition, loop diuretics increase calcium excretion and may contribute to a negative calcium balance, although hypocalcemia due to loop diuretics is uncommon. Conversely, the potassium-sparing diuretics spironolactone, eplerenone, triamterine, and amiloride, as well as ACE-inhibitors and angiotensin receptor blockers, are all associated with potassium retention and may occasionally induce significant hyperkalemia. For these reasons, serum electrolytes should be monitored periodically in patients receiving long-term diuretic therapy, especially during periods of dosage adjustment, whenever thiazide and loop diuretics are used together, and in patients with impaired renal function.

Diet and nutrition play an important role in managing electrolytes in heart failure patients. Unfortunately, many trials evaluating micronutrient supplementation in cardiac disease states have excluded patients with heart failure [86]. Despite this limitation, some general principles apply. Patients with heart failure and preserved renal function should consume a diet rich in potassium, magnesium, and calcium, but low in sodium. Most patients on chronic loop diuretic therapy will require potassium replacement, either through high-potassium foods (e.g., fresh fruits) or as potassium supplements (usually administered as potassium chloride, which also aids in chloride replacement). Diuretic-induced hyponatremia is potentially life-threatening and may require hospitalization (e.g., if the serum sodium concentration falls to <120–125 meq/L). Treatment includes fluid restriction, reduction in diuretic dosage, temporary liberalization of sodium intake, and occasionally the use of vasopressin receptor antagonists. Hypomagnesemia is relatively common during long-term diuretic therapy, but may be overlooked unless serum magnesium levels are assessed. Importantly, magnesium deficiency may contribute to muscle fatigue and risk for arrhythmia via prolongation of the QT interval. Treatment consists of dietary therapy and magnesium supplements. The combined potassium and magnesium depleting effects of loop and thiazide diuretics may be moderated by the addition of an aldosterone receptor antagonist, thereby reducing the risk of arrhythmias [87, 88]. Patients with chronic heart failure often suffer bone loss (osteopenia) due to low levels of vitamin D and secondary hyperparathyroidism [46]. However, the value of calcium supplements in heart failure patients, with or without vitamin D, is currently unknown.

Other Minerals

Zinc, manganese, copper, and selenium all have anti-oxidant effects, and deficiencies of these minerals may be associated with increased lipid peroxidation and oxidative stress [89]. In addition, severe copper and selenium deficiency have been associated with cardiomyopathies in humans [90, 91], while zinc and manganese deficiency have been associated with myocardial contractile dysfunction in laboratory animals [92, 93]. Diuretics appear to increase urinary zinc excretion, and clinically significant zinc deficiency is common in older heart failure patients on chronic diuretic therapy [94]. Conversely, serious deficiencies of manganese, copper, and selenium occur infrequently in older adults consuming a normal diet. Based on currently available data, daily intake of each of these minerals should be sufficient to meet Dietary Reference Intakes (DRIs). Although some patients with diuretic-associated zinc deficiency may benefit from zinc supplements, there are currently no data to support routine use of such supplements in older heart failure patients.

Iron is essential for the production of hemoglobin and iron deficiency is common in older adults. Chronic anemia leads to an increase in cardiac work in order to preserve tissue oxygen delivery, and in severe cases may lead to high-output cardiac failure. In a randomized controlled trial, intravenous iron was beneficial in the setting of heart failure and iron depletion, even in the absence of anemia, with respect to symptoms, functional capacity, and quality of life [95]. Conversely, iron overload due to multiple blood transfusions or hemochromatosis has been associated with restrictive cardiomyopathy [96]. Guidelines do not stipulate what constitutes adequate or inadequate stores of iron in the setting of heart failure and it should be noted that oral repletion of iron has not been investigated for benefit in this setting. Iron intake should therefore be sufficient to maintain tissue stores and prevent chronic iron-deficiency anemia, but excess iron intake should be avoided.

Vitamins

Vitamin B_1 (thiamine) deficiency impairs oxidative metabolism and has been unequivocally linked to high-output cardiac failure [89, 97]. In addition, thiamine deficiency may contribute to "diuretic-resistance" in patients receiving moderate to high doses of loop diuretics over a prolonged period of time [98, 99]. In the United States, clinically important thiamine deficiency is most commonly encountered in alcoholics and in older heart failure patients treated with loop diuretics. Of note, both digoxin and furosemide diminish uptake of thiamine by cardiac myocytes, and the effects of these drugs are additive [100]. Thiamine deficiency responds promptly to either oral or parenteral thiamine administration, and is usually associated with substantial improvement in cardiac function and symptoms. Although chronic thiamine supplementation may be considered in selected high risk populations (e.g., alcoholics and poorly nourished older adults treated with high-dose loop diuretics), in most cases maintaining a well-balanced diet will ensure adequate thiamine intake.

Vitamin C supplementation has been associated with improved endothelial function [101–103], and some epidemiologic studies have suggested that increased intake of vitamin C correlates with reduced risk for cardiovascular disease [104–106]. However, there is no convincing evidence that vitamin C deficiency contributes to the development of heart failure, or that vitamin C supplements are beneficial in heart failure patients [89]. Vitamin E has anti-oxidant properties and reduces platelet adhesion [107], and several epidemiologic studies have reported that diets high in vitamin E, alone or in combination with vitamin C, are associated with a lower incidence of coronary heart disease [29, 108–110]. Despite this, several large randomized trials of vitamin E therapy failed to show significant benefit, and one meta-analysis suggested that high-dose vitamin E intake may be associated with increased mortality [111, 112]. Moreover, follow-up analysis of the Heart Outcomes Prevention

Evaluation (HOPE) trial and its extension (HOPE-TOO), showed that vitamin E therapy was associated with increases in the incidence of heart failure and in the risk of hospitalization for heart failure [113]. Therefore, vitamin E is not recommended for prevention or treatment of HF.

Deficiencies of folic acid, vitamin B_6, and vitamin B_{12} are common in older adults and contribute to age-associated increases in homocysteine levels [114]. Elevated homocysteine is an established risk marker for coronary and cerebrovascular disease in both older and younger adults [115–117], and elevated homocysteine levels have been associated with more severe heart failure and worse prognosis [118]. Despite plausible mechanisms for an adverse effect of homocysteine on myocardial function, there is currently no convincing evidence that lowering homocysteine levels through the use of folic acid and B-vitamin supplements reduces the risk of coronary or cerebrovascular events, or improves myocardial function or outcomes in heart failure patients [118].

Vitamin D is essential for maintaining normal calcium homeostasis, and marked vitamin D deficiency has been associated with decreased myocardial contractility in laboratory animals [119]. Vitamin D deficiency is common in older adults with or without heart failure [120, 121], and is associated with diminished functional capacity [122]. Although vitamin D supplementation would seem appropriate in these individuals, there is no evidence that such treatment alters the clinical course of patients with heart failure. In fact, vitamin D supplementation did not improve 6 min walk distance or quality of life in a randomized trial conducted in older heart failure patients with low vitamin D levels [123]. There are several ongoing trials investigating higher dose vitamin D supplementation. Currently, the DRI for vitamin D is 800 IU in persons older than age 70 and 600 IU daily for those younger than age 70.

Although high-dose niacin is FDA approved for the treatment of dyslipidemia, there is no evidence that niacin deficiency contributes to the development of cardiovascular disease [89], and a niacin preparation failed to reduce cardiovascular events compared with placebo in patients already on statin therapy [124]. Low beta-carotene intake has been associated with increased risk for myocardial infarction [125], but there is no evidence that vitamin A levels correlate with heart failure risk or that vitamin A supplements are useful in the prevention of cardiovascular disease [89]. In the Physician's Health Study, a trial notable for demonstrating the benefit of aspirin in preventing cardiovascular disease, beta-carotene was ineffective [126]. Similarly, there are no established links between vitamins B_2 (riboflavin) and B_{17} (pantothenic acid) and either the development or treatment of cardiac disorders [89].

Other Nutritional Supplements

Despite continued interest in the antioxidant coenzyme Q_{10} (ubiquinone), its role in the pathophysiology and treatment of heart failure remains controversial. Myocardial coenzyme Q_{10} levels are reduced in patients with heart failure, and low plasma coenzyme Q_{10} levels are associated with increased mortality [89], although an analysis of the CORONA trial did not identify coenzyme Q_{10} levels as *independently* prognostic [127]. As the commonly-prescribed lipid-lowering HMG-CoA reductase inhibitors (statins) are associated with depletion of coenzyme Q_{10} [128], the issue of coenzyme Q_{10} repletion arises frequently. Observational studies and some (but not all) small randomized trials indicate that coenzyme Q_{10} supplementation may improve LV function, symptoms, and exercise tolerance [129–133], but there are no large outcomes trials of coenzyme Q_{10} in heart failure, and routine administration of coenzyme Q_{10} is not recommended by guidelines—even in patients on statin therapy [134].

Carnitine, propionyl L-carnitine, and creatine phosphate are nutritional supplements which may enhance skeletal muscle performance in some patients with heart failure [135–137], but there is little evidence that oral administration improves cardiac function. In addition, there is no evidence that these agents improve long-term clinical outcomes in heart failure patients, and there are also concerns about the safety of these agents during chronic use [89].

Multinutrient Therapy

Older heart failure patients often have multiple nutritional deficiencies, suggesting that therapeutic interventions may need to be broad-based, rather than focusing on a single or even a relatively small number of micronutrients. This is supported by the favorable results in a study reported by Witte et al., in which 30 heart failure patients over age 70 were randomized to receive high-dose micronutrient capsules or placebo in double-blind fashion [138]. The capsules contained calcium (0.3× RDI), magnesium (0.5× RDI), zinc (1× RDI), copper (1× RDI), selenium (0.75× RDI), vitamin A (1× RDI), thiamine (140× RDI), riboflavin (1× RDI), vitamin B_6 (100× RDI), folate (25× RDI), vitamin B_{12} (200× RDI), vitamin C (8× RDI), vitamin D (2× RDI), vitamin E (40× RDI), and coenzyme Q_{10} (10× RDI). During a 9-month follow-up period, patients receiving the micronutrient capsules demonstrated decreased left ventricular volumes, an increase in left ventricular ejection fraction (mean 5.3 %), and improved quality of life scores, whereas no changes occurred in the placebo group. These findings require large-scale replication and enthusiasm is tempered by the fact that to date no trials have demonstrated a benefit with regard to death or rehospitalization when one or more micronutrients were added to standard therapy for HF [139].

Impact of Heart Failure Interventions and Age on Nutritional Parameters

Medication Effects

As noted previously, many of the agents used in the treatment of chronic heart failure may have beneficial effects on nutritional status. Conversely, there is a risk for drug-related side-effects and a potentially negative impact on the nutritional status of these patients. Diuretics directly impact fluid and electrolyte homeostasis, and diuretic-induced electrolyte abnormalities are very common. In addition, loop diuretics have been associated with thiamine deficiency, and thiazide diuretics in particular may adversely affect carbohydrate and lipid metabolism. Digoxin may be associated with nausea and anorexia, and these symptoms may occur in older patients even at therapeutic dosages. The ACE-inhibitor captopril occasionally causes dysgeusia (altered taste), nausea, and anorexia, and other ACE-inhibitors may be associated with similar side effects, although less frequently. Beta blockers may also influence carbohydrate and lipid metabolism, and depressive symptoms, including reduced appetite, may occur in older patients treated with these agents. Finally, the calcium channel blockers diltiazem and especially verapamil are commonly associated with constipation in older individuals.

Age-Specific Nutritional Issues

Older age is associated with increased risk for a broad range of nutritional deficiencies, and this risk is potentiated by the presence of cardiovascular disease in general and by heart failure in particular (see Chap. 21). In addition, older adults are more susceptible to the adverse effects of pharmacological agents and dietary interventions on nutritional parameters, in part due to preexisting nutritional deficiencies coupled with an increased prevalence of comorbid conditions. The latter issue may be particularly problematic, since the presence of several common comorbidities, e.g., coronary artery disease, diabetes mellitus, and renal insufficiency, may lead to serial dietary restrictions (low fat, low carbohydrate, low protein, low salt) culminating in a diet that is unpalatable and severely deficient in both calories and essential nutrients. It is therefore critically important that an appropriately detailed

nutritional evaluation, including dietary history, body weight, selected laboratory tests (hemoglobin, albumin, cholesterol, electrolytes, creatinine, blood urea nitrogen), and in some cases anthropometric assessments, be incorporated into the routine management of older patients with chronic illnesses, including heart failure.

Device-Specific Nutritional Therapies

As described above, the emergence of LVADs in the care of older patients with heart failure has introduced a new level of complexity. In addition to standard preoperative and postoperative nutritional considerations such as ileus, LVAD therapy may pose unique side-effects including chronic intravascular hemolysis, gastrointestinal bleeding, and chronic soft tissue infection. Ensuring adequate iron stores is important in patients with gastrointestinal blood loss, while chronic intravascular hemolysis calls for supplementation with vitamin B_{12} and folate to ensure adequate erythropoiesis to match erythrocyte destruction. Chronic soft tissue infection is rarely severe enough to result in net catabolism, but one important consideration in patients on long term antibiotics is the effect of mineral supplements on gut absorption of antibiotics. The most notable of these are the interactions between calcium and both tetracyclines and ciprofloxacin, in which absorption of both calcium and the antibiotic is reduced. Guidelines for nutrition in the setting of LVADs are emerging, but contemporary practice is largely shaped by analogy with similar disease states [140].

Recommendations

Nutritional guidelines for managing chronic heart failure in older adults are summarized in Table 13.2. As noted previously, nutritional management of older patients begins with a nutritional assessment, ideally with the assistance of an experienced dietitian or nurse. As with other chronic illnesses, the guiding principle in making nutritional recommendations to older heart failure patients is, first and foremost, maintenance of a well-balanced diet with sufficient calories, nutrients, and fluids to meet daily requirements. In addition, the diet should be both palatable and within the patient's financial means and physical capabilities. Few older patients with heart failure require a therapeutic weight reduction diet, since body weight correlates inversely with mortality in heart failure patients [80]. Indeed, in most cases it is appropriate to prescribe a diet that will either maintain current nonedematous weight or promote a modest increase in lean body mass. Although it has been suggested that the proportion of calories derived from protein and fat should perhaps be increased in older heart failure patients [51], there is little evidence to support this contention, and current recommendations are that 15–20 % of total calories be derived from protein, 25–30 % from fat, and the remaining 50–60 % from complex carbohydrates [141].

Moderate dietary sodium restriction, such as a 2-g sodium diet, is appropriate for most patients with heart failure [23]. More stringent sodium restriction is of unproven benefit; indeed, a recent meta-analysis of randomized trial data demonstrated that sodium restricted patients (average 1.8 g/day) had a nearly twofold higher risk of death compared to patients with normal sodium intake (average 2.8 g/day). Thus, overzealous salt restriction may be harmful [142]. Patients should be instructed to avoid very high-sodium foods, such as canned soups and sauces, tomato juice, most prepared lunch meats and prepackaged frozen entrees, pickles, fast foods, and certain ethnic foods which are high in sodium (e.g., Asian cuisine). Dining out is potentially problematic, and patients should be advised to call ahead to see if low-sodium options are available. Patients should also be instructed about the widespread availability of alternative seasonings which contain little or no salt.

Table 13.2 Nutritional guidelines for older adults with chronic heart failure

Component	Recommendation
Nutritional assessment	
Basic (all patients)	Obtain detailed dietary history
	Assess body weight and habitus
	Laboratory: hemoglobin, serum albumin, cholesterol, serum electrolytes (sodium, potassium, calcium, phosphorus, magnesium), creatinine, blood urea nitrogen
Supplemental (selected patients)	Anthropometric measures (e.g. skinfold thickness)
	Determination of lean body mass
	Folate, B_{12} levels
	Bone mineral density
	Iron stores (ferritin, iron, iron-binding capacity)
General diet	Well-balanced, rich in fruits and vegetables, whole grains, dairy products, lean meats
Caloric intake	Sufficient to maintain lean body mass; 1,600–2,000 cal/day in most cases
Protein	15–20 % of total calories
Fat	25–30 % of total calories
Complex carbohydrates	50–60 % of total calories
Fluids	~2 L/day
	1.5 L/day in setting of hyponatremia, severe renal failure, diuretic-resistance
	Avoid excess fluid intake
Electrolytes	
Sodium	2 g Na^+/day. Avoid overzealous restriction
Potassium, calcium, magnesium	Sufficient to maintain body stores and serum levels; supplement as indicated
Minerals	
Zinc, copper, manganese, selenium	Sufficient intake to meet DRIs; zinc supplements in selected patients
Iron	Sufficient to maintain body stores; avoid iron overload
Vitamins	
Thiamine (Vit B_1)	Supplement in alcoholics, possibly patients on chronic high-dose loop diuretics
Folate, B_6, and B_{12}	Supplement if deficient (common)
Cholecalciferol (Vit D)	Supplement if deficient (esp. in osteoporosis) DRI 800 IU/day if >70 year old, otherwise 600 IU
Beta carotene (Vit A)	No known relation to heart failure; maintain DRI
Riboflavin (Vit B_2)	
Niacin (Vit B_3)	
Ascorbic acid (Vit C)	
Alpha-tocopherol (Vit E)	
Dietary supplements	
Ubiquinone (coenzyme Q_{10})	Unproven benefit, not recommended
Carnitine	Unproven benefit, not recommended
Creatine phosphate	Unproven benefit, not recommended

Source is Food and Nutrition Board, Institute of Medicine. Dietary Reference Intakes: The Essential Guide to Nutrient Requirements. Washington, DC: National Academies Press; 2006. Updated Dietary Reference Intakes for Calcium and Vitamin D (2010)
DRI dietary reference intake

Fluid intake should be adequate to maintain hydration while avoiding volume overload. In patients with preserved renal function, about 2 L of fluid per day is appropriate. Excess fluid intake ("8–10 glasses of water a day") should be avoided, but fluid restriction is unnecessary in the absence of hyponatremia, severe renal failure, or advanced heart failure with diuretic resistance. In such cases, fluid intake should be limited to about 1.5 L/day. Alcohol should be avoided in cases of alcohol-induced cardiomyopathy, but in the systolic heart failure population light-to-moderate drinkers (one to ten drinks/week) do not appear to be at increased risk for adverse outcomes compared to nondrinkers [143, 144].

Caffeinated beverage consumption does not appear to be associated with increased incidence of heart failure [145] and may have favorable effects with respect to exercise in heart failure patients [146]. However, there are few data on the safety of large amounts of caffeine in patients with heart failure, especially with respect to the risk of inducing supraventricular or ventricular arrhythmias—moderation is therefore advised.

Dietary potassium, calcium, and magnesium requirements vary considerably depending on medications, renal function, and comorbid conditions. As a general principle, a well-balanced diet rich in fresh fruits and vegetables, whole grain breads and cereals, and dairy products will provide sufficient amounts of potassium, calcium, and magnesium to meet normal needs. However, many older heart failure patients will require supplemental administration of one or more of these electrolytes to overcome losses through urinary excretion or as a result of other metabolic abnormalities. Since individual requirements cannot easily be predicted, periodic assessment of serum electrolyte levels is appropriate.

As discussed above, the importance of most vitamins and other micronutrients in the pathogenesis and treatment of chronic heart failure has not been well characterized, and it is difficult to make specific nutritional recommendations in most cases. Since older patients are at increased risk for multiple nutritional deficiencies, it is appropriate to maintain a high index of suspicion, particularly in frail, socially isolated, or institutionalized elders, as well as those with multiple comorbidities and those receiving multiple medications. In particular, deficiencies of folate, B_{12}, vitamin D, and zinc are common, and dietary or pharmacological supplementation is indicated when specific deficiencies are identified or suspected. Since long-term administration of loop diuretics may deplete thiamine stores, thiamine replacement should be considered in such cases, particularly in the setting of increasing diuretic-resistance. Finally, although evidence supporting high-dose multivitamin and mineral supplements in older heart failure patients is sparse, daily use of a nonprescription multivitamin and mineral supplement may ease concerns about multinutrient deficiencies and is unlikely to be harmful. Conversely, the use of other dietary supplements, such as coenzyme Q_{10}, carnitine, or creatine phosphate, is not currently recommended, and patients should be screened for the use of these and other neutraceuticals of uncertain safety.

Conclusion

Optimal management of older adults with heart failure requires careful attention to their overall diet and nutritional status, as well as to specific nutrients. Additional research is needed to better define the role of nutritional factors in the pathogenesis and treatment of heart failure in patients of all ages.

Recommendations for Clinicians

1. Nutritional management begins with a nutritional assessment. Obtain baseline body weight and monitor at regular intervals. Recognize that caloric needs may change as body weight changes, and provide increased nutritional support if rapid unintentional weight loss occurs.
2. Patients should be encouraged to choose a well-balanced diet high in fruits and vegetables as excellent sources of vitamins and electrolytes.
3. Sodium restriction to 2 g/day is sufficient. Dietary counseling may be required to assist patients in achieving this goal. Overzealous sodium restriction (<1.5 g/day) is not advised.
4. Fluid restriction is not usually necessary, except when hyponatremia, severe renal failure, or advanced heart failure is present. In these cases, fluid should be restricted to ~1.5 L/day. Excess fluid intake ("8–10 glasses of water per day") should be avoided.

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5. Magnesium, potassium, and calcium levels should be monitored and supplemented as needed. Other nutrients of concern in high-risk patients include thiamine, folate, vitamin B_{12}, vitamin D, and zinc. Routine daily use of an oral vitamin/mineral supplement may be helpful in alleviating any deficits.
6. Caution should be exercised in translating the results of small trials or trials of proprietary pharmaceutical agents to dietary modifications.

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Chapter 14
The Relationship of Nutrition and Pressure Ulcers

David R. Thomas

Key Points

- A strong epidemiological association exists between nutritional status and the incidence, progression, and severity of pressure sores.
- The results of trials of prevention and treatment of pressure ulcers with nutritional interventions to date have been disappointing. While nutrient deficiencies are linked with poor wound healing, providing supplements to patients who are not deficient has not been shown to be of benefit for pressure ulcers.
- This paradoxical finding could be explained by a mechanism of weight loss occurring in a cycle of anorexia and cachexia. Cytokine-induced cachexia is remarkably resistant to hypercaloric feeding.
- Acknowledging these ambivalent findings, it is still important that general nutritional support be provided to persons with pressure ulcers, consistent with medical goals and patient wishes.

Keywords Wound healing • Under-nutrition • Nutritional supplements • Cytokines • Pressure ulcers

Introduction and Background

Wound healing is intricately linked to nutrition. Severe protein-calorie undernutrition in humans alters tissue regeneration, the inflammatory reaction, and immune function [1]. After vascular surgery, hypoalbuminemia and low serum transferrin levels predict wound healing complications [2]. Undernourished patients are more likely to have post-operative complications than well-nourished patients [3]. Although these markers do predict outcome, they do not correlate well with nutritional status [4].

Experimental studies in animal models suggest a biologically plausible relationship between undernutrition and development of pressure ulcers. When pressure was applied for 4 h to the skin of well-nourished animals and malnourished animals, pressure ulcers occurred equally in both groups. However, the degree of ischemic skin destruction was more severe in the malnourished animals. Epithelialization of the pressure lesions occurred in normal animals at 3 days post-injury, while

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necrosis of the epidermis was still present in the malnourished animals [5]. These data suggest that while pressure damage may occur independently of nutritional status, malnourished animals may have impaired healing after a pressure injury.

Epidemiological Associations of Nutrition and Pressure Ulcers

A strong epidemiological association exists between nutritional status and the incidence, progression, and severity of pressure sores. In a prospective study of high-risk patients, undernutrition (defined by an index of biochemical and anthropometric variables) was present in 29 % of patients at hospital admission. At 4 weeks, 17 % of the undernourished patients had developed a pressure ulcer, compared to 9 % of the non-undernourished patients. Thus, patients who were undernourished at hospital admission were twice as likely to develop pressure ulcers as non-undernourished patients (RR 2.1, 95 % confidence intervals [CI] 1.1, 4.2) [6].

In a 2007 study of 4,067 patients from 22 hospitals in Germany, a positive relationship was shown between the presence of a pressure ulcer and each of the following variables: unintentional weight loss of 5–10 %, a body mass index less than 18.5 kg/m^2, poor nutritional intake (from the Braden Scale), and being bedfast. Being bedfast for hospitalized subjects was the most critical risk factor with an odds ratio of 23 (95 % CI 10, 52). In 2,393 patients from 29 German nursing homes, a positive association for the presence of a pressure ulcer was observed for each of the following variables: an unintentional weight loss of 5 to greater than 10 %, a body mass index less than 20 kg/m^2, poor nutritional intake (from the Braden Scale), and probable inadequate nutritional intake (from the Braden Scale) [7].

In a long-term-care setting, pressure ulcers developed in 65 % of residents who were diagnosed as severely undernourished upon admission [8]. In another long-term care setting, the estimated percent intake of dietary protein, but not total caloric intake, predicted development of pressure ulcers [9]. Impaired nutritional intake, defined as a persistently poor appetite, meals held due to gastrointestinal disease, or a prescribed diet less than 1,100 kcal or 50 g protein per day, predicted pressure ulcer development in another long-term care setting [10]. Table 14.1 demonstrates the association of serum albumin and other nutritional variables with the development of a pressure ulcer. Pressure ulcers appear to be associated with traditional markers of nutritional status in some, but not all, studies.

Nutrition in the Prevention of Pressure Ulcers

This strong association of undernutrition with the development of pressure ulcers led to the hypothesis that providing hypercaloric feeding to persons at risk for undernutrition might lead to the prevention of pressure ulcers. Several trials have examined this hypothesis (Table 14.2). However, the combined results of trials of nutritional intervention for the prevention of pressure ulcers have been disappointing [11, 12].

The effect of oral nutrition supplements was observed in a nonrandomized group of hospitalized, severely ill patients. Nutritional supplements were given to 33 % of subjects on one ward and to 87 % of subjects on another hospital ward. There was no difference between groups in pressure ulcer incidence (26.4 % vs. 20.2 %), pressure ulcer prevalence at discharge (14.7 % vs. 10.3 %), mortality (15.6 % vs. 14.2 %), length of stay (17.3 days vs. 17.4 days), or nosocomial infections (26.4 % vs. 19.0 %) [13].

A multi-center, cluster randomized trial in persons older than 65 years who were in the acute phase of a critical illness examined the effect of two oral supplements per day in addition to the normal hospital diet. At the end of 15 days, the supplemented group had a reduced incidence of all stages of pressure ulcers (40 % in the nutritional intervention group versus 48 % in the control group) (relative risk 0.83, 95 % confidence intervals 0.70–0.99) [14].

Table 14.1 Epidemiological association of nutritional markers with development of a pressure ulcer

First author	Setting	Associated with presence of PU	Not associated with presence of PU
Allman [89]	AC	Albumin	Weight, hemoglobin, TLC, nutritional assessment
Gorse [1]	AC	Albumin	Nutritional assessment score
Inman [2]	AC, ICU	Albumin (measured at 3 days)	Serum protein, hemoglobin, weight
Allman [3]	AC	BMI, TLC	Albumin, TSF, arm circumference, weight loss, hemoglobin, nitrogen balance
Hartgrink [18]	AC, orthopedic		Nocturnal enteral feeding
Anthony [4]	AC	Albumin <32 g/L	
Moolten [5]	LTC	Albumin <35 g/L	
Pinchcofsky-Devin [8]	LTC	Severe malnutrition	Mild-to-moderate malnutrition or normal nutrition
Berlowitz [10]	LTC	Impaired nutritional intake	Albumin, serum protein, hemoglobin, TLC, BMI/weight
Bennett [6]	LTC		Weight, BMI, weight gain
Brandeis [7]	LTC	Dependency in feeding	BMI/weight, TSF
Trumbore [8]	LTC	Albumin, cholesterol	
Breslow [9]	LTC	Albumin, hemoglobin	Serum protein, cholesterol, zinc, copper, transferrin, body weight, BMI, TLC
Bergstrom [9]	LTC	Dietary protein intake 93 % of RDA vs. 119 %, dietary iron	Serum protein, cholesterol, zinc, copper, transferrin, weight, BMI, TLC
Ferrell [10]	LTC		Albumin, serum protein, BMI, hematocrit,
Bourdel-Marchasson [14]	LTC		Oral nutritional supplement (26 % vs. 20 % incidence)
Guralnik [11]	Community		Albumin, BMI, impaired nutrition, hemoglobin

AC acute care, *LTC* long-term care, *BMI* body mass index, *TLC* total lymphocyte count, *TSF* triceps skinfold thickness, *ICU* intensive care unit, *RDA* Recommended Daily Allowance

Table 14.2 Nutritional interventions in the prevention of pressure ulcers

First author	Setting	Intervention	Outcome
Delmi 1990 [15]	Hospitalized with femoral neck fracture	One oral nutrition supplement per day in addition to hospital diet vs. standard hospital diet alone	All-stage pressure ulcers 9 % in the nutritional intervention group vs. 7 % in the control group RR 0.79 (0.14–4.39, $p=0.8$)
Hartgrink 1998 [18]	Hospitalized with hip fracture and increased pressure ulcer risk	Overnight nasogastric tube feeding vs. standard hospital diet	Stage 2 or greater pressure ulcers 52 % in the nutritional intervention group vs. 56 % in the control group RR = 0.92 (0.64–1.32, $p=0.6$)
Bourdel-M 2000 [13]	Acute phase of a critical illness	Two oral supplements per day in addition to normal diet vs. standard hospital diet alone	All-stage pressure ulcers 40 % in the nutritional intervention group vs. 48 % in the control group RR 0.83 (0.70–0.99)
Houwing 2003 [16]	Hip-fracture patients	One supplement daily in addition to the standard hospital diet vs. noncaloric water-based placebo and standard hospital diet	Stage 1 and 2 pressure ulcers 55 % in the nutritional intervention group vs. 59 % in the placebo group RR 0.92 (0.65–1.3)

RR relative risk (95 % confidence intervals)

In hospitalized persons with femoral neck fracture, one group was randomized to receive one oral nutrition supplement in addition to the hospital diet or the standard hospital diet alone. There was no difference in the incidence of pressure ulcers between the two groups in this study [15].

In another population of persons with hip fracture, subjects were randomized to receive either 400 ml daily of a nutritional supplement enriched with protein, arginine, zinc, and antioxidants in addition to the standard hospital diet or the standard hospital diet and a noncaloric water-based placebo. There was no difference in the incidence of stage 2 or greater pressure ulcers between groups after 28 days (55 % in the supplement group vs. 59 % in the placebo group) [16].

Of these four trials of oral nutritional supplements for the prevention of pressure ulcers, only one suggests that a nutritional intervention may reduce the incidence of pressure ulcers. Similar results were found when another trial that used a group randomization was included in a meta-analysis [17]. The calculated number needed to treat in this analysis suggested that 20 patients would need to receive oral nutritional supplements to prevent one pressure ulcer.

In a trial of overnight enteral feeding in patients with hip fracture, no difference in pressure ulcer incidence, total serum protein, serum albumin, or the severity of pressure sores after 1 and 2 weeks was observed. After 2 weeks, 52 % of subjects in the enterally fed group and 56 % of the control group developed stage 2 or greater pressure ulcers ($p=0.06$). Of the 62 patients randomized for enteral feeding, only 25 tolerated their tube for more than 1 week, and only 16 tolerated their tube for 2 weeks. Comparison of the actually tube-fed group ($n=25$ at 1 week, $n=16$ at 2 weeks) and the control group showed two to three times higher protein and energy intake ($p<0.0001$), and a significantly higher total serum protein and serum albumin after 1 and 2 weeks in the actually tube-fed group (all $p<0.001$). In an intention to treat analysis there was also no difference in the incidence of sores of grade 2 or above [18]. It is possible that the lack of effect on supplemental enteral feeding was due to poor tolerance of the feedings.

A study of enteral tube feedings in patients with a pressure ulcer in a long-term care setting, observed 49 patients for 3 months [19]. Patients received 1.6 times basal energy expenditure daily, 1.4 g of protein per kilogram per day, and 85 % or more of their total recommended daily allowance. At the end of 3 months, there was no difference in number or in healing of pressure ulcers.

All of these clinical trials suffer from methodological problems, including weaknesses in study design and statistical power. Large, prospective, randomized controlled trials will be required to define the effect of nutritional interventions in prevention of pressure ulcers.

Nutrition in the Healing of Pressure Ulcers

Although correction of poor nutrition is part of total patient care and should be addressed in each patient, controversy exists about the ability of nutritional support to reduce wound complications or improve wound healing [20, 21].

Randomized, controlled trials have evaluated the effect of increased protein, vitamin C, zinc, and oral supplements in the treatment of pressure ulcers. One trial randomized by group found no difference in pressure ulcer healing between the nutritionally supplemented and control groups [17]. With the exception of a single trial of higher protein intake, no trial has demonstrated improved healing with the intervention. Table 14.3 summarizes the interventional trials for pressure ulcers.

Table 14.3 Nutritional interventions in the treatment of pressure ulcers

First author	Setting	Intervention	Outcome
Breslow [27]	Long-term care	24 % protein vs. 14 % protein enteral feeding	−4.2 cm^2 vs. −2.1 cm^2 decrease in surface area
Chernoff [27]	Long-term care	1.8 g/kg protein vs. 1.2 g/kg protein enteral feeding	73 % vs. 43 % improvement in surface area
Henderson [19]	Long-term care	1.6 times basal energy expenditure, 1.4 g of protein per kilogram per day	65 % PU at onset; 61 % prevalence at 3 months

(continued)

Table 14.3 (continued)

First author	Setting	Intervention	Outcome
ter Riet [47]	Long-term care	Vitamin C 10 mg vs. 1,000 mg	No difference in healing rate
Taylor [48]	Acute surgical patients	Vitamin C large dose vs. none	84 % vs. 43 % (control) reduction surface area at 30 days
Norris [56]	Acute hip fracture	Zinc	No difference
Lee [29]	Long-term care	Concentrated, fortified, collagen protein hydrolysate supplement, 15 g vs. placebo	Pressure Ulcer Scale for Healing Score (mean 3.55 intervention vs. 3.22 control)
Cerrada [1]	Long-term care	Oral = Diet plus 500 kcal, 34 g protein, 6 g arginine, vit C 500 mg, 18 mg zinc; Tube = 1,000 kcal, 55 g protein (20 %), 8 g arginine, vit C 380 mg, 20 mg zinc vs. standard 16 % protein	Reaching target of 30 kcal/kg/day did not affect wound healing. Controls had a greater increase in caloric intake (4.6 vs. 3.1 kcal/kg/day). No benefit from increased protein intake No independent effect of arginine or zinc
Desneves [38]	Long-term care	Standard hospital diet vs. Standard diet plus two high-protein/energy supplements vs. Standard diet plus two high-protein/energy supplements containing additional arginine (9 g), vitamin C (500 mg) and zinc (30 mg)	Improved Pressure Ulcer Score Healing group 3 (9.4 ± 1.2 vs. 2.6 ± 0.6 at week 3). No significant changes in biochemical markers, oral dietary intake or weight in any group
Leigh [39]	Spinal cord injury	Standard hospital diet plus 4.5 vs. Standard diet plus 9 g arginine	No evidence of a difference in healing rate between the two arginine dosages
van Anholt [40]	Multisite, non-malnourished	200 mL three times daily of a high-energy supplement enriched with arginine, antioxidants, and other micronutrients (not specified) vs. a noncaloric placebo	Complete healing of 6 ulcers in the supplemented group vs. 5 ulcers in placebo group

RR relative risk (95 % confidence intervals)

General Nutritional Support for Persons with Pressure Ulcers

It is clear that nutritional deficiency in the form of starvation is associated with increased mortality and morbidity. Therefore, nutritional requirements must be addressed in every patient and corrected when possible, consistent with the wishes and plan of care for each individual (Table 14.4).

Energy

An important question relates to whether the measured resting energy expenditure (mREE) is higher in persons with pressure ulcers. A meta-analysis of five trials, the mREE was 23.7 ± 2.2 kcal/kg/day in persons with a pressure ulcer ($n = 92$) versus 20.7 ± 0.8 kcal/kg/day in the controls without a pressure ulcer ($n = 101$), suggesting a small but significant difference ($p = 0.0001$) [22]. However, 43 % of the subjects with a pressure ulcer had a spinal cord injury, perhaps accounting for the difference.

In another study of 29 older hospitalized persons with a pressure ulcer, the measured resting metabolic rate did not differ from controls, and did not vary by ulcer size or severity [23]. The data suggest that a pressure ulcer may be associated with an increase in energy requirement, but the magnitude is small. Both of these two trials confirmed an estimated daily caloric requirement of 25–30 kcal/kg using the Harris-Benedict equation.

Table 14.4 Nutritional therapy for pressure ulcers

Estimated caloric intake	30–35 kcal/kg/day
Estimated protein intake	1.2–1.5 g/kg/day
Specific amino acids	Slight, if any, benefit
Supertherapeutic vitamin C	No demonstrated benefit
Supertherapeutic zinc	No demonstrated benefit

The Harris-Benedict equation can be used to predict caloric requirements, but controversy exists over accuracy in obese or severely undernourished individuals [24]. Other formulas have been adjusted for severely stressed hospitalized subjects [25]. The use of prediction formulas achieve almost the same results for caloric requirements as bedside clinical estimates [26].

General estimates for daily caloric requirements range from 25 kcal/kg/day for sedentary adults to 40 kcal/kg/day for stressed adults. Stress generally includes persons with burns, pressure ulcers, cancer, infections, and other similar conditions. Therefore, caloric requirements can be met at 25–30 kcal/kg/day for elderly patients under moderate stress.

Protein

Greater healing of pressure ulcers has been reported with a higher protein intake irrespective of whether or not a positive nitrogen balance was observed. In 48 patients with stage 3 through 4 pressure ulcers who were being fed enterally, undernutrition was defined as a serum albumin below 35 g/L *or* a body weight more than 10 % below the midpoint of the age-specific weight range. Total truncal pressure ulcer surface area showed more decrease (−4.2 cm^2 vs. −2.1 cm^2) in surface area in patients fed the enteral formula containing 24 % protein compared to a formula containing 14 % protein. However, changes in body weight or in biochemical parameters of nutritional status did not differ between the two groups. The study was limited by a small sample size (only 28 patients completed the study), nonrandom assignment to treatment groups, confounding effects of air-fluidized beds, and the use of two different feeding routes [27].

In a small study of 12 enterally fed patients with pressure ulcers, the group who received 1.8 g/kg of protein had a 73 % improvement in pressure ulcer surface area compared to a 42 % improvement in surface area in the group receiving 1.2 g/kg of protein despite the fact that the group that received the higher protein level began the study with larger surface area pressure ulcers (22.6 cm^2 vs. 9.1 cm^2) [28].

A concentrated, fortified, collagen protein hydrolysate supplement was evaluated in 44 subjects with 75 pressure ulcers, who were compared with 27 subjects with 33 pressure ulcers who received a noncaloric control. At 8 weeks there was a small but statistically significant improvement in the Pressure Ulcer Scale for Healing score for the protein-treated group (3.55 intervention vs. 3.22 control) [29]. The randomization process did not produce equal group size, and the number and severity of the pressure ulcers at baseline was not balanced between groups, potentially biasing the study.

In a long-term care setting, 93 residents with a wound were compared to 57 residents without a wound. Persons with a wound were started on an enteral tube feeding formula containing 1.25 g/protein/day, and persons without a wound were started on an enteral tube feeding formula containing 1.0 g/protein/day [30]. At admission, only 12 % of persons with a wound, and 21 % of persons without a wound had normal prealbumin levels. Over 14 months, the amount of protein in the feeding formula was increased or maintained based on the serum prealbumin levels. The prealbumin normalized or increased by 8 points in 42 % of persons with a wound and in 46 % of persons without a wound. However, protein intake was not predictive for persons who improved their serum albumin versus those who did not. There was no correlation observed between the Pressure Ulcer Scale for

Healing (PUSH) score and improvement in serum prealbumin. These data suggest that increasing protein intake, in some cases to greater than 2 g/kg/day, is not associated with greater healing of pressure ulcers. It also indicates that serum prealbumin is a poor marker of nutritional status.

The optimum dietary protein intake in patients with pressure ulcers is unknown, but may be much higher than current adult recommendation of 0.8 g/kg/day. Current recommendations for dietary intake of protein in stressed elderly patients lies between 1.2 and 1.5 g/kg/day. Yet half of chronically ill elderly persons cannot maintain nitrogen balance at this level [31]. On the other hand, increasing protein intake beyond 1.5 g/kg/day may not increase protein synthesis and may cause dehydration [32]. Studies in critically ill adults have shown that a protein intake of 1.2 g/kg/day of normally hydrated weight or 1.0 g/kg/day of resuscitated weight was more effective than a lower protein intake in achieving complete protein sparing in persons with severe systemic inflammatory response. However, further protein sparing cannot be demonstrated at protein intakes greater than 1.5 g/kg/day [33, 34]. The optimum protein intake for these patients has not been defined, but may lie between 1.2 and 1.5 g/kg per day.

Amino Acids

The association of dietary protein intake with wound healing has led to investigation of the use of specific amino acids. Leucine seems to be important in severely ill patients. Glutamine is essential for the immune system function, but supplemental glutamine has not been shown to have noticeable effects on wound healing [35].

Arginine enhances wound collagen deposition in healthy volunteers [36]. However, no effect on healing of pressure ulcers has been observed with arginine supplementation [37]. Sixteen inpatients with a stage 2–4 pressure ulcer were randomized to a standard hospital diet compared to a standard diet plus two high-protein/energy supplements or a standard diet plus two high-protein/energy supplements containing 9 g of arginine, 500 mg of vitamin C, and 30 mg of zinc for 3 weeks. PUSH tool scores improved in both the control and arginine/vitamin C/zinc groups, but not in the protein/energy supplemented group. The major improvement in PUSH score was in the arginine/vitamin C/zinc group. The groups were not similar at baseline, and no changes in biochemical markers, oral dietary intake, or body weight was observed in any group [38].

In a study of 23 participants with 31 nonhealing wounds, 4.5 g supplemental arginine was compared to 9 g supplemental arginine and healing evaluated over 3 weeks. Most of the pressure ulcers were stage 2 (74 %), or stage 3 (19 %), with 7 % stage 4. No difference in healing rates between the two treatment groups was observed, suggesting no dose–response effect for arginine [39].

Forty-three non-malnourished subjects with stage 3 or 4 pressure ulcers were evaluated in a multisite, randomized, controlled, double-blind trial. Subjects were screened to exclude malnutrition, defined as a body mass index less than 18.5 kg/m^2 for those younger than 70 years or 21 kg/m^2 for those older than 70 years. Other exclusion criteria were severe medical conditions, life expectancy shorter than 6 months, receiving palliative care, use of corticosteroids, and/or dietary restrictions, such as a protein-restricted diet. Subjects were offered 200 mL of a high energy supplement enriched with arginine, antioxidants, and other micronutrients (not specified) three times daily for a maximum of 8 weeks, or a noncaloric placebo, similar in taste and appearance, over the same timeframe. In the supplemented group, the mean healing rate measured by wound size was 0.26 cm^2/day compared to 0.14 cm^2/day in the control group over the first 3 weeks. By 8 weeks, the mean healing rate in the supplemented group was similar to the control group (0.16 cm^2/day vs. 0.15 cm^2/day, respectively). In this population screened to exclude undernutrition, complete healing was observed in six ulcers in the supplemented group, compared to five ulcers in the control group by 8 weeks. No change was observed in body mass index [40].

Twenty-eight subjects older than 65 years with a stage 3–4 pressure ulcer that was present for less than 1 month were randomized to receive a standard hospital diet with no supplement ($n=15$), or a standard hospital diet plus a supplement containing 500 kcal with 34 g protein, 6 g arginine, 500 mg vitamin C, and 18 mg zinc ($n=13$). Nine subjects who were tube fed in the treatment group (69 %) received a formula containing 1,000 kcal, 55 g protein (20 %), 8 g arginine, 380 mg vitamin C, and 20 mg zinc. Nine subjects who were tube-fed in the control group (60 %) received an enteral formula containing 16 % protein. All subjects were adjusted to a target of 30 kcal/kg/day. After 12 weeks, complete pressure ulcer healing was documented for only one person in the treatment group. The PUSH score between groups was different only at week 12. There was no difference in ulcer area measured in square millimeters at any time point. The percentage of decrease in pressure ulcer area in the treatment group was greater compared to the control group at week 8 and week 12. No nutritional parameter was different between groups except for the treatment group having a higher zinc level. Surprisingly, reaching a target of 30 kcal/kg/day did not affect wound healing, and no benefit from increased protein intake or independent effect of arginine or zinc was observed. These findings call into question empirically derived recommendations. In addition, no effect on wound healing measured by change in PUSH score or change in ulcer area was observed despite an increase in energy intake and protein intake over a 12-week period (controls 4.6 kcal/kg/day vs. treatment 3.1 kcal/kg/day). These data suggest that a specific nutritional formula may produce small benefits in improving pressure ulcer size. However, no specific supplemental nutritional component could account for the variation [41]. Additionally, based on a single trial to date, no improvement in wound healing has been demonstrated in response to high supplements of branched-chain amino acid formulations [42].

Vitamins and Minerals

The deficiency of several vitamins has significant effects on wound healing. However, supplementation of vitamins to accelerate wound healing in the absence of a deficiency state is controversial. Vitamin C is essential for wound healing and impaired wound healing has been observed in clinical scurvy. However, in studies of clinically impaired wound healing, 6 months of an ascorbate-free diet is required to produce a deficient state [43]. In animals that are vitamin C–deficient, wound healing is abnormal at 7 days but completely normal at 14 days [44].

There is no evidence of acceleration of wound healing by vitamin C supplementation in patients who are not vitamin C–deficient [45]. Supertherapeutic doses of vitamin C have not been shown to accelerate wound healing [46]. Two clinical trials have evaluated the effect of supplemental vitamin C in the treatment of pressure ulcers. In a multicenter, blinded trial, 88 patients with pressure ulcers were randomized to either 10 or 500 mg twice daily of vitamin C. The wound closure rate, relative healing rate, and wound improvement score were not different between groups [47]. An earlier trial in acute surgical patients with pressure ulcers found a mean reduction in surface area at 1 month of 84 % in patients treated with large doses of vitamin C compared to a reduction in surface area of 43 % in the control group ($p<0.005$) [48]. The recommended daily allowance (RDA) of vitamin C is 60 mg. This RDA is easily achieved from dietary sources that include citrus fruits, green vegetables, peppers, tomatoes, and potatoes.

Vitamin A deficiency results in delayed wound healing and increased susceptibility to infection [49]. Vitamin A has been shown to be effective in counteracting delayed healing in patients on corticosteroids [50]. Vitamin E deficiency does not appear to play an active role in wound healing [51].

Zinc was first implicated in delayed wound healing in 1967 [52]. No study to date has shown improved wound healing in patients supplemented with zinc who were not zinc-deficient [53, 54]. Zinc levels have not been associated with development of pressure ulcers in patients with femoral neck fractures [55]. In a small study of patients with pressure ulcers, no effect on ulcer healing was

seen at 12 weeks in zinc-supplemented versus non–zinc-supplemented patients [56]. Indiscriminate or long-term zinc supplementation should be avoided since high serum zinc levels may inhibit healing, impair phagocytosis, and interfere with copper metabolism [11, 57]. The RDA for zinc is 12–15 mg. but most elderly persons intake 7–11 mg of zinc per day [58], chiefly from meats and cereal.

Mode of Delivery

Enteral tube feeding is often considered for persons with poor oral intake. An observational study of persons ($N=1{,}124$) referred to a hospital for insertion of a percutaneous endoscopic gastrostomy (PEG) tube, but who had no pressure ulcer, found that these nursing home residents were twice as likely to develop a new pressure ulcer (OR 2.27, 95 % CI, 1.95–2.65) compared to matched controls who had no PEG tube. Similarly, those persons ($N=461$) with a prevalent pressure ulcer who had a PEG feeding tube inserted were less likely to have the ulcer heal (OR 0.70, 95 % CI, 0.55–0.89) compared to matched controls [59].

Factors Contributing to the Nutritional Paradox

Traditionally, weight loss and undernutrition have been classified as due to either a relative lack of dietary protein (kwashiokor) or lack of both dietary protein and calories (marasmus) [60]. This classification system focused clinical attention on a lack of adequate food. Simply put, weight loss in older persons was attributed to starvation. Measures of serum proteins or anthropormorphological parameters were thought to detect early starvation. Remedial nutritional strategies were aimed at increasing voluntary food intake, prescribing hypercaloric supplements, or by instituting parenteral or enteral feeding [61]. In general, these interventions have had only a modest effect in reversing weight loss [62, 63].

Recent data suggest that the major cause of weight loss in older adults is the anorexia/cachexia syndrome [64]. This has resulted in a new paradigm for defining the mechanism of weight loss in older persons. Current understanding of undernutrition defines three categories: (1) pure chronic starvation without inflammation, (2) acute disease or major injury with inflammation, and (3) chronic diseases or conditions that impose sustained inflammation of a mild to moderate degree [65]. One of the chief distinguishing factors is that starvation without inflammation is amenable to hypercaloric feeding in all but the terminally undernourished patients, while acute and chronic inflammatory conditions are remarkably resistant to hypercaloric feeding [66, 67].

Cachexia is directly related to inflammatory states, such as cancer or acquired immunodeficiency syndrome, and also occurs in other common conditions such as rheumatoid arthritis, chronic renal insufficiency, chronic obstructive pulmonary disease, ischemic cardiomyopathy, and infectious diseases [68]. Interleukin (IL)-1 concentrations are elevated in elderly patients with severe undernutrition of unknown etiology, [69] and levels of IL-1β and IL-6 can be increased in elderly persons without evidence of infection or cancer [70]. Tumor necrosis factor-α (TNF) levels are elevated in patients with severe undernutrition and congestive heart failure, but not in patients with congestive heart failure who do not have severe undernutrition [71]. Severe undernutrition occurs in both chronic infections and neoplastic disorders, suggesting that severe undernutrition develops along a common pathway and is not dependent on a specific infection or a particular neoplasm.

Measures of serum proteins are increasingly seen as acute phase reactants reflecting underlying inflammation rather than measures of starvation. Physiological stress (such as surgical operations), cortisol excess, and hypermetabolic states reduce serum albumin even in the presence of adequate

protein intake. Decreases in serum albumin may reflect the presence of inflammatory cytokine production or comorbidity rather than nutritional status [72]. Soluble IL-2 receptors are negatively associated with albumin, prealbumin, cholesterol, transferrin, and hemoglobin. The use of albumin and cholesterol in these patients as nutritional markers could potentially lead to over diagnosis of malnutrition [73]. This may explain why serum albumin has not consistently been an independent predictor of pressure ulcers.

Several cytokines, particularly IL-1α, IL-1β, and IL-6, have been suggested to be elevated in subjects with pressure ulcers. Whether these levels change with healing, or are predictive of healing is not known. These cytokines are known to also increase in severe undernutrition.

Serum IL-1β is elevated in patients with pressure ulcers [74]. Levels of IL-1α are elevated in pressure ulcers but low in acute wound fluid [75]. In hospitalized elderly patients suffering from bacterial pneumonia, cerebrovascular disease, or femoral bone fracture, serum IL-1 beta (but not IL-6) was higher in subjects with pressure ulcers. Albumin, hemoglobin, C-reactive protein, fibrinogen, and white cell count were also lower in subjects with pressure ulcers, despite no significant differences in age, gender, Braden scale, or underlying diseases between the two groups [75].

Circulating serum levels of IL-6, IL-2, and IL-2R are higher in spinal cord injured patients compared to normal controls, and highest in subjects with pressure ulcers. The highest concentration of cytokines were in subjects with the slowest healing pressure ulcers [76]. In other studies, IL-6 serum levels were increased in patients with pressure ulcers but IL-1 and TNF were not elevated [77].

Existing studies are not clear as to whether the elevation of inflammatory cytokines is due to the presence of a pressure ulcer or due to underlying severe undernutrition. Alternatively, the elevation of cytokine levels may be a common pathway for both conditions. The hypotheses are demonstrated in Fig. 14.1. Cytokine-mediated anorexia and weight loss are common in the population that develops pressure ulcers. The interrelationship is outlined in Table 14.5.

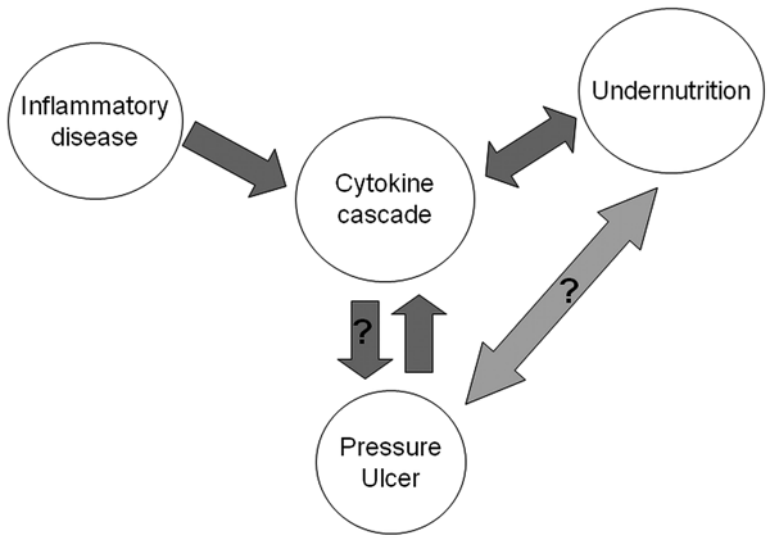

Fig. 14.1 Inflammatory disease may initiate the proinflammatory cytokine cascade, leading directly to development of a pressure ulcer. Alternatively, the development of a pressure ulcer may initiate the cytokine cascade, leading to undernutrition through suppression of appetite and cachexia. Undernutrition may lead to development of a pressure ulcer through either cachexia and loss of body mass or through the cytokine cascade

Table 14.5 Documented relations among cytokines, undernutrition, and chronic wounds

Undernutrition
Poor wound healing
Increased risk of infection
Increased incidence of pressure ulcers
Proinflammatory cytokines
Suppress appetite
Promote/interfere with wound healing
Chronic wounds
Source of cytokines
Increased association with undernutrition
Increased serum levels of cytokines

Interventions for Inflammatory-Mediated Cachexia

This new paradigm suggests that interventions targeting weight loss in older persons must address the anorexia/cachexia continuum. Assessment of appetite can suggest anorexia as a cause of decreased food intake [78]. A common cause may be loss of appetite, due to dysregulation of a variety of psychological, gastrointestinal, metabolic, and nutritional factors [79]. Loss of appetite may initiate a vicious cycle of weight loss and increasing undernutrition.

Cytokines may regulate appetite directly through the central feeding drive. Significant interaction between the central feeding drive, neuropeptide Y, and IL-1β has been demonstrated in rats [80, 81]. IL-1, IL-6, TNF, interferon-γ, leukemia inhibitory factor (D-factor), and prostaglandin E2 have all been implicated in cancer-induced severe undernutrition [82, 83]. Leptin, a central regulator of food intake and body fat mass, increases under the stress of hip operations [84] but is low in undernourished men [85].

The lack of effect of hypercaloric feeding in pressure ulcers may reflect that the underlying pathophysiology is cytokine-induced cachexia rather than simple starvation. Starvation is amenable to hypercaloric feeding in all but the terminally undernourished patients. Cytokine-induced cachexia is remarkably resistant to hypercaloric feeding [66, 67]. This may explain the modest results of clinical nutrition intervention trials in older persons [86].

Where possible, the underlying inflammatory condition should be sought. The importance of defining the distinction lies in developing a targeted therapeutic approach to weight loss in older persons [87]. Failure to distinguish among these causes of weight loss often results in frustration over the clinical response to therapeutic interventions.

Interventions to modulate cytokine activity are possible. Cytokine modulation has been postulated as a potential treatment for cachexia [88–94]. If a significant positive relationship exists between circulating cytokines and pressure ulcers, an opportunity for potential intervention to promote healing exists.

Conclusion

Wound nutrition is whole body nutrition. Unquestionably, providing nutritional support can prevent the effects of starvation. Death is an inevitable consequence of starvation. Whether or not nutrition can improve the outcome of pressure ulcers remains in dispute. Improvements in nutritional markers, such as serum protein concentrations, nitrogen balance, and weight gain, have not usually been accompanied by clinical benefits.

There is no doubt that undernutrition is not good for wound healing. However, there is no magic nutritional bullet that will accelerate wound healing. General nutritional support should be provided to persons with pressure ulcers, consistent with medical goals and patient wishes.

Clinical Recommendations

1. Provide optimum nutrition consistent with goals of care for each patient.
2. Optimize protein intake with a goal of 1.2–1.5 g/kg/day of protein.
3. A simple multivitamin supplement may be indicated for nutritionally compromised patients, but there is no data to support the routine use of vitamin C and zinc in patients with pressure ulcers.
4. Consider vitamin A supplements in patients on corticosteriods.
5. Consider whether a cytokine-associated inflammatory condition may be present and potentially treatable.

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Chapter 15
Nutrition Support in Solid Tumor Cancer Patients

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Key Points

- Nutrition support in the form of enteral or parenteral nutrition confers minimal benefit to patients with advanced, incurable cancer and sometimes leads to complications.
- Severely malnourished cancer patients who are being considered for curative surgery or highly effective cancer treatment gain modest benefits from nutrition support.
- A multidisciplinary approach is key for deciding how and when to start nutrition support for a cancer patient.

Keywords Nutrition support • Enteral • Parenteral • Preoperative • Immunonutrition • Dietary counseling

Introduction

Few situations in medicine evoke such controversy as nutrition support in patients with cancer. For purposes of this chapter, nutrition support is defined as the prescription and administration of enteral or parenteral nutrition, either of which are given in a manner that can potentially override volitional factors on the part of the patient. Despite the fact that many organizations, such as the American College of Physicians, the Working Group for Developing Guidelines for Parenteral Nutrition of the German Association for Nutritional Medicine, and the American Society of Parenteral Nutrition, have cautioned against the indiscriminate use of nutritional support and specifically against the use of parenteral nutritional support in patients with advanced cancer, a malignant diagnosis represents the most common primary diagnosis among patients receiving parenteral nutrition [1–3].

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Several factors might explain this controversy. First, although weight-losing, incurable cancer patients manifest a pathophysiology, which can be characterized by loss of appetite, a disproportionate loss of lean tissue, and possible hypermetabolism, these patients present with a clinical phenotype that is remarkably similar to that of a starving but otherwise disease-free individual [4]. In effect, these weight-losing cancer patients appear as if they are starving, thus providing a scenario that sometimes convinces health care providers to aggressively feed, when in fact many sources in the published medical literature, as alluded to below, indicate that feeding is perhaps not the most appropriate intervention. Second, for some health care providers, it seems almost to make intuitive sense to feed a weight-losing cancer patient. Weight loss suggests an energy deficit, and the easiest way to compensate for this deficit is to feed the patient aggressively, even in the setting of anorexia and even in the setting of an incurable malignancy. Although clinical trials do not support this approach, some health care providers develop a mindset that drives the mission of aggressively prescribing nutrition support to patients with advanced, incurable cancer. Finally, the emotional impact of watching an incurable cancer patient wither and die is difficult for the patient, for family members, and for health care providers [5]. The desire to do something, really anything—such as provision of nutrition support—sometimes becomes an emotionally driven, although less well scientifically justified, approach.

Nutrition Support in Patients with Advanced, Incurable Cancer

Some examples of patients with advanced, incurable cancer include the lung cancer patient who has liver metastases, has no chance of cure, and has no appetite and is losing weight. Another example is the patient with recurrent ovarian cancer, progressive weight loss, and a malignancy that is no longer responding to chemotherapy. Is nutrition support with either parenteral or enteral nutrition always the best choice for the advanced cancer patient with incurable disease? The answer is "no." For example, in 1981, Nixon and others described the findings of a controlled trial in 50 colorectal patients who were randomly assigned to receive either chemotherapy plus parenteral nutrition or chemotherapy alone [6]. Hypertonic glucose, amino acids, vitamin E, folic acid, and vitamin B_{12} comprised the parenteral nutrition. Of note, among the patients who had adverse events on the parenteral nutrition arm, one died of unclear reasons shortly after entering the trial, another developed sepsis with a staphylococcal infection, and yet another suffered from a cerebral vascular accident. More importantly, overall, parenteral nutrition-treated cancer patients died earlier than those who did not receive this intervention: 79 days versus 305 days ($P=0.03$). This prospective study represents one of many that indicate the detriments of parenteral nutrition in patients with incurable solid malignancies.

As further evidence of the detriments of parenteral nutrition in patients with advanced cancer, a series of prospective studies culminated in a series of meta-analyses, which substantiate this same conclusion of detrimental effects. In one of these meta-analyses, McGeer and others reported that parenteral nutrition is associated with inferior survival when administered to cancer patients receiving chemotherapy (relative risk 0.81; 95 % confidence interval 0.62, 1.0), and it was also associated with lower cancer response rates, (odds ratio 0.68; 95 % confidence interval 0.40, 1.1) [7]. Although these individual studies are often criticized for their smaller sample sizes and although these meta-analyses are often criticized for the heterogenous nature of their data, these observations continue to bear out the conclusion that parenteral nutrition should be prescribed to patients on chemotherapy and with advanced, incurable cancer at best with great caution.

Similarly, Baldwin and others reported a meta-analysis that consisted of studies that specifically focused on enteral nutrition [8]. This meta-analysis was spurred by the fact that some international guidelines fall short of recommending parenteral nutrition to cancer patients but allude to the use of enteral nutritional supplements. Thus, this meta-analysis sought randomized controlled trials that focused on oral nutrition supplements versus routine care among cancer patients with weight loss/

malnutrition or among cancer patients at risk for weight loss/malnutrition. Among the 13 identified studies that included 1,414 patients, the oral nutritional supplements were associated with greater improvements in weight and energy intake (mean difference in weight = 1.86 kg, 95 % CI = 0.25–3.47, $P = 0.02$; and mean difference in energy intake = 432 kcal/day, 95 % CI = 172–693, $P = 0.001$) but with no major improvements on mortality (relative risk = 1.06, 95 % CI = 0.92–1.22, $P = 0.43$). Of note, however, this meta-analysis also demonstrated notable heterogeneity among studies, and re-analysis after removal of these sources of heterogeneity showed that these statistically significant differences in clinical outcomes disappeared. Thus, although cancer patients appear to consume more calories with oral nutritional supplementation, this approach does not appear to lead to major improvements in survival, as hoped.

Alternative Palliative Strategies in Patients with Advanced Incurable Cancer

Admittedly, the aforementioned studies suggest that nutrition support does not, as a rule, prolong life in patients with advanced, incurable cancer, but might there be other goals—such as palliation of symptoms—to be achieved with nutrition support in patients with advanced, incurable cancer? To attempt to answer this question, McCann and others undertook a 32-patient study that monitored patient-reported outcomes over a 12-month period [9]. The study was small, but given the intensity of assessment, duration of assessment, and sensitive nature of studying and monitoring dying patients, this limited sample size seems most appropriate. Of note, not all these patients had cancer, and these patients were not receiving aggressive nutritional support. Importantly, 20 (63 %) had no symptoms of hunger and described that a sense of thirst was only fleeting. Following these patients over time, these investigators observed that symptoms such as loss of appetite and increased thirst were attenuated by allowing patients to eat small meals or snacks at will, by allowing them to drink fluids ad lib, by sucking on ice chips, and by applying lubrication to the lips. This study helps resolve the argument that aggressive nutrition support provides an important palliative strategy for patients at the end of life. In fact, many patients are not hungry or thirsty at the end of life, aggressive nutrition support does not appear necessary to palliate symptoms, and other relatively simple strategies, as alluded to above, can play a fundamental palliative role under these circumstances.

Along similar lines, Bruera and others randomly assigned 129 hospice-enrolled cancer patients to normal saline 1 L intravenously per day versus normal saline 100 mL intravenously per day (placebo) over 4 h [10]. The primary outcome was change in the sum of four dehydration symptoms (fatigue, myoclonus, sedation, and hallucinations, 0 = best and 40 = worst possible) between day 4 and baseline. Saline administration did not improve patient-reported dehydration symptoms, thus emphasizing further that the so-called "palliative effects" of parenteral hydration/nutritional interventions may be far more limited than we would hope and thus providing the impetus to further study or utilize simpler, less-invasive interventions.

Acknowledging Exceptional Circumstances Among Advanced, Incurable Cancer Patients

It should be noted that there are occasionally exceptions and that some patients with metastatic cancer appear to benefit from nutrition support, specifically from parenteral nutrition support. A single-institution, 20-year experience included 52 patients with a variety of diagnoses were included: carcinoid/islet cell tumor ($n = 10$), ovarian carcinoma ($n = 6$), amyloidosis/multiple

myeloma ($n=6$), colorectal carcinoma ($n=5$), sarcoma ($n=5$), pancreatic carcinoma ($n=4$), gastric carcinoma ($n=3$), lymphoma ($n=2$), pseudomyxoma peritonei ($n=2$), and other ($n=9$) [11]. The median interval from the initiation of parenteral nutrition to death was 5 months (range: 1–154 months), but 16 patients survived for 1 year or longer. Parenteral nutrition-related complications included catheter infections, thromboses, pneumothoraces, and liver disease, but none of these complications occurred at an especially high rate to raise alarm. Overall, it appears that parenteral nutrition may have contributed to the prolonged survival observed in some of these patients, but importantly it should be emphasized that this cohort represents a highly select group of patients and that the findings of this study should not be extrapolated to the majority of metastatic cancer who are losing weight.

Meeting the Nutritional Needs of Severely Malnourished Cancer Patients Who Have Highly Treatable Cancers

Are there any cancer patients—for example those without metastatic disease—who might truly benefit from nutrition support? It is important to emphasize that the sparing use of nutrition support applies primarily to patients with advanced, incurable cancer. Previous studies indicate that solid cancer patients with potentially curable or highly treatable cancers can, at times, benefit from nutrition support. Hence, the importance of making decisions on nutrition support in a highly collaborative, multidisciplinary manner cannot be overemphasized. In further support of expending the time to collaborate, a recent multicenter trial compared early versus late initiation of parenteral nutrition among 2,312 intensive care unit-treated adults, slightly under 20 % of whom had a cancer diagnosis [12]. If parenteral nutrition was not initiated before day 8, patients in fact manifested a faster recovery and fewer complications. Hence, taking the time to assess the status of the cancer, the goals of antineoplastic therapy, and the likelihood of cure, long-term survival, or durable tumor response should, can, and must go hand-in-hand with decisions on nutrition support, and the data above suggest that under some circumstances, there may be time to undertake such discussions. Three studies, as summarized below, are particularly instructive and provide guidance, as relevant to this point and as relevant to parenteral nutrition.

First, although the Veterans Affairs Cooperative Study did not exclusively focus on cancer patients, 65 % of the 395-patient cohort included cancer patients [13]. This study otherwise focused on preoperative malnourished patients, who were enrolled within a randomized trial that included either total parenteral nutrition for 7–15 days before surgery and 3 days postoperatively versus no intravenous nutritional supplementation. Major, 30-day postoperative complication rates were similar in both groups (25.5 % with total parenteral nutrition versus 24.6 %). Similarly, there were no major differences between groups with respect to 90-day mortality rates (13.4 % versus 10.5 %). Of note, in other analyses, patients who were assigned to the parenteral nutrition arm suffered a higher infection rate (14 % versus 6 %), but a planned subgroup analysis, which included only 24 patients who seemed to have severe malnutrition, also observed that parenteral-nutrition-treated patients also had fewer noninfectious complications (5 % versus 43 %). The conclusions from such subset analyses should be viewed with caution because they do not comprise the primary study analysis and because they provide conclusions that were drawn from a highly contracted subset of patients. However, such findings might suggest that parenteral nutrition in a small group of cancer patients, specifically those who are severely malnourished in a preoperative setting, might confer modest benefit.

Second, Fan and others studied 124 hepatocellular cancer patients; these patients, too, were studied in a preoperative setting where they were about to undergo a partial hepatectomy for their cancer [14].

Less than 20 % of this cohort reported losing greater than 10 % premorbid weight. Prior to this surgery, patients received parenteral nutrition versus placebo fluids. The latter had minimal nutritional or caloric content. Although mortality rates were not markedly different between treatment arms, those parenteral nutrition-treated patients manifested lower rates of morbidity after surgery; specifically they manifested less-problematic ascites and better liver function, as assessed biochemically. Assessing malnutrition in hepatocellular cancer patients can be challenging, particularly because ascites can mask weight loss, an often-used marker of malnutrition. This study is important because it suggests that parenteral nutrition can provide modest benefit to hepatocellular carcinoma patients, who are often malnourished, prior to surgery.

Finally, in a third preoperative study that examined the role of preoperative nutrition, Bozzetti and others focused on 90 gastric or colorectal cancer patients, all of whom had suffered loss of at least 10 % of their premorbid weight [15]. As was the case with the other two studies described above, this study examined these patients in a preoperative setting, providing half the cohort preoperative parenteral nutrition and the other half no nutrition support. Patients in the former group manifested lower postoperative complication rates (37 % versus 57 %) of both infectious and noninfectious etiology. A smaller trial, this study nonetheless adds further support to the premise that parenteral nutrition can reduce complication rates in preoperative cancer patients.

What is the role of nutrition support among head and neck cancer patients? This group of cancer patients offers somewhat of a unique situation that calls for the consideration of enteral nutrition support. The latter is perhaps the preferred consideration based on the old adage, "If the gut works, use it." Although the data are sparse to provide absolute justification for this enteral nutrition support, a confluence of factors, which includes eating impairment as a result of the tumor and that include mucositis from cancer treatment such as radiation, suggests that some type of enteral support makes sense under these circumstances. The data that support this claim include retrospective studies as well as some prospectively derived data.

For example, Daly and others conducted a randomized trial of 40 head and neck cancer patients who were receiving radiation and who were assigned to either oral nutrition versus nasogastric tube feedings, greater benefit appeared manifest in the latter group of patients [16]. These patients were observed to have higher caloric intake, less weight loss, and a more rapid resumption of the activities of daily living. Of note, tumor response rates with cancer treatment and overall survival were not statistically different between groups. However, this issue of reduced weight loss may not be minor. A recent prospective study among 533 head and neck cancer patients who were being treated with curative intent with radiation found that 30 % lost 0.1–5.0 % of their weight during cancer treatment, 26 % lost 5.1–10.0 %, and 24 % lost >10 % [17]. Importantly, these investigators observed a statistically significant association between weight loss and decline in global quality of life as well as physical functioning, social functioning, social eating, and social contact. Hence, weight loss under these circumstances represents more than a drop in numbers on a scale but rather a clinical change that is associated with major decrements in quality of life. Thus, the randomized trial alluded to earlier in this paragraph may have been too small to capture subtle improvements between treatment arms, but it nonetheless provides a hint of evidence that aggressive enteral feeding may provide an advantage over dietary counseling in head and neck cancer patients who are receiving radiation and that this advantage might also include improvements in quality of life. Other studies have suggested that the need to hold cancer treatment is reduced with the use of enteral nutritional support. To our knowledge, no studies have demonstrated that nutritional support clearly improves survival or treatment effect outcomes from radiation or combined modality therapy for head and neck cancer, but the fact that these patients suffer eating impairments and weight loss before and during cancer treatment leads many health care providers to readily adopt enteral feeding strategies as part of the cancer treatment plan.

Nasogastric Versus Percutaneous Endoscopic Gastrostomy Feeding in Head and Neck Cancer Patients?

The above raises the unresolved issue of how best to provide enteral nutrition support. Should these patients receive nasogastric or percutaneous endoscopic gastrostomy feeding? A recent Cochrane review attempted to provide further direction to answer this question and compiled the randomized trials that had focused on this issue [18]. This review raised important points, including the fact that the duration of percutaneous endoscopic feeding tended to be much longer and more expensive than enteral feeding, at least in one of the trials reviewed in this meta-analysis. Although the authors concluded that they were unable to provide clear direction on which method to use based on quality of life and cancer outcomes, the issues of duration of use and cost associated with percutaneous endoscopic feeding provide further details that might enter into the discussions as health care providers discuss options with cancer patients. Moreover, in our own experience, concerns over seeding tumor cells with insertion of a nasogastric tube, continued contact and erosion of tissue around the nares and further down from the tube itself, and the cosmetic challenges of interacting socially with a nasogastric tube in place appear to shift patients and health care providers towards considering percutaneous endoscopic feeding.

Should all cancer patients about to receive surgery or about to receive highly effective cancer therapy receive nutrition support in some manner? We do not think so. Although this question is controversial, justification for enteral or parenteral nutritional support can be found under the circumstances where a cancer patient faces the prospect of cure of their cancer or another major favorable outcome to be derived from cancer treatment. Importantly, it appears that cancer patients must also be showing clear signs of severe malnutrition and/or risk of malnutrition in order to derive benefit from nutrition support. Even under such circumstances, it should be noted that nutritional support does not appear to provide an improvement in survival but rather it provides a more modest set of benefits that center around reduced morbidity. Thus, it stands to reason that nutrition support can and should be prescribed under some circumstances to cancer patients but that a balanced discussion with the patient should precede this intervention.

A Word on Nutritional Counseling

As an aside, this chapter focuses on prescribing parenteral or enteral nutrition to cancer patients, the question often arises: What is the value of nutritional counseling in the absence of nutritional support to cancer patients? Although no final answer exists to this question, some studies, including those from Ravasco and others suggest benefit [19, 20]. A meta-analysis from Halfdanarson attempted to put these studies in context. These investigators accepted the fact that nutritional interventions have not yielded a survival advantage and instead focused on quality of life [21]. Quality of life had to have been measured by a validated questionnaire, and all randomized trials were sought that evaluated dietary counseling. These investigators identified five such trials that met this study's eligibility criteria. Quality of life scores among patients who received dietary counseling were only marginally improved compared to patients who did not receive this intervention ($P = 0.06$). However, this trend towards statistical significance suggests that human interactions and discussions about how to improve dietary intake definitely are exerting some positive influences on cancer patients. Thus, regardless of cancer status and regardless of the mixed findings reported in previous studies, it appears that dietary counseling can also be of value to weight-losing cancer patients.

Immunonutrition

Several formulas that are used for enteral nutrition include supplemental agents such as l-arginine and omega-3 fatty acids, and the term immunonutrition has been used to describe such feeding sources. Although it is outside the scope of this chapter to comment on all the available enteral formulations and methods for administering parenteral nutrition, some comments on immunonutrition seem appropriate. Several clinicians have started incorporating such formulations into their clinical practices, as a result of a growing number of clinical trials and meta-analyses. Cresci has offered guidance on the type of patient who may be best suited [22]: "Ideal candidates for these formulations… include the following: malnourished and non-malnourished elective surgery patients that may also have comorbid conditions such as diabetes, heart disease, lung disease, and obesity; critically ill ICU patients that have several comorbid conditions placing them at higher risk of infections; and critically ill trauma and surgical patients that are anticipated to remain in the ICU for >3 to 5 days."

In our opinion, however, the benefits of immunonutrition are compelling with a reduction in postoperative complications, but such results are not definitive. For example, one meta-analysis included 21 randomized controlled trials that in total included a robust sampling of 2,730 patients [23]. Although not all these patients were cancer patients, some were; and some were about to have surgery for either a gastrointestinal malignancy. Immunonutrition significantly reduced perioperative complication rates and even resulted in a reduced interval of hospitalization. Importantly, this meta-analysis represented clinical trial data that had been generated by only a limited number of authors, and notable heterogeneity existed among studies. Thus, although one can clearly justify the use of immunonutrition, in our opinion, the data in their totality do not seem compelling enough to enable us to consider this approach the clear standard of care. Of parenthetical note, the use of immunonutrition in patients with advanced cancer has yielded mostly negative neutral outcomes.

Conclusion

As described above, multiple negative, randomized controlled trials and subsequent meta-analyses underscore a limited role of nutrition support—particularly parenteral nutrition support—in patients with advanced cancer. These studies had prompted the American College of Physicians to issue a 1989 position statement that clearly advises against parental nutrition in cancer patients who are being prescribed chemotherapy with noncurative intent, and, over the span of more than two decades, this position statement has not been revised [1]. Moreover, even in patients with potentially curable malignancies, it appears that the benefits of nutrition support are restricted to only subgroups of patients with severe malnutrition. However, in reality, nutrition support—and, in particular, parenteral nutrition support—appears to be prescribed quite readily to cancer patients. In past years, 40 % of patients who are receiving home parenteral nutrition in the United States have a cancer diagnosis [24]. Similarly, in Sweden, the Netherlands, and France, these percentages are 80 %, 60 %, 27 %, respectively. Only in the United Kingdom is this percentage low at 5 %. It remains unclear whether all these patients have metastatic cancer or what sorts of circumstances resulted in these patients receiving such interventions. In view of these high rates of usage, factors other than evidence derived from clinical trials are likely driving these decisions. Understanding what motivates health care providers, patients, and their families to reach the point where they choose nutritional support will be key to making sure cancer patients are in fact receiving the most appropriate intervention at the right time in their disease course. Such an understanding will also provide assurance that patients' educational needs on this topic are being adequately met.

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Chapter 16
Nutrition and Chronic Kidney Disease

Xiaorui Chen and Srinivasan Beddhu

Key Points

- The development and progression of chronic kidney disease (CKD) is influenced by a number of dietary factors, including salt and protein intake and energy balance (obesity).
- While the benefits of a low protein intake in preventing the development of CKD are not firmly established, it is likely that a high-protein intake is detrimental to individuals with even mild impairment of renal function.
- Specific dietary recommendations regarding protein level and intakes of sodium, phosphorus, potassium, and fluids must be carefully individualized as appropriate for the level of renal function.
- Obesity is a risk factor for the development of CKD via a variety of mechanisms, including clinical or subclinical insulin resistance, hypertension, and possibly other metabolic derangements.
- However, obesity is associated with better survival in dialysis patients. This is likely because the deleterious metabolic effects of obesity are outweighed by its protective nutritional effects in Stage Five (V) CKD patients on dialysis.

Keywords Renal disease • Hemodialysis • Uremia • Metabolic acidosis

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Introduction

Based on the National Health and Nutrition Examination Survey (NHANES), it was estimated that 14 % of U.S. adults have chronic kidney disease (CKD) [1], and the prevalence of CKD in U.S. adults increased by 30 % between 1988–1994 and 1999–2004 [2]. Furthermore, CKD is a strong independent predictor of atherosclerotic events [3, 4]. The annual mortality on dialysis is approximately 20 %, and the total Medicare cost of end-stage renal disease in 2009 was estimated to be $29 billion [5]. Thus, CKD is extremely common, carrying a significant health and economic burden.

Nutritional status plays a major role in development and progression of CKD as well as strongly influences survival in established CKD. Thus, dietary interventions could potentially have a significant impact on decreasing the progression of CKD and improving the outcomes of those with established CKD. The data on (1) the impact of diet and obesity on the development and progression of CKD and (2) nutritional issues unique to advanced CKD (uremia) are reviewed in this chapter.

Role of Diet and Obesity on Development and Progression of CKD

Salt Intake, Hypertension, and the Risk of CKD

Hypertension is a very strong risk factor for CKD. In those with preexisting hypertension, lowering the dietary sodium intake to approximately 1 g/day is associated with better control of blood pressure [6, 7]. In those without preexisting hypertension, the beneficial effects of lowering salt intake have been controversial [8]. However, in the Dietary Approaches to Stop Hypertension (DASH) Sodium Study, 412 participants were randomly assigned to eat either a control diet (typical of intake in the United States) or the DASH diet (which is rich in vegetables, fruits, and low-fat dairy products). Within the assigned diet, participants ate foods with high, intermediate, and low levels of sodium for 30 consecutive days each, in random order. The effects of sodium were observed in participants with and in those without hypertension. The DASH diet was associated with a significantly lower systolic blood pressure at each sodium level. As compared to the control diet with a high sodium level, the DASH diet with a low sodium level led to a mean systolic blood pressure that was 7.1 mmHg lower in participants without hypertension, and 11.5 mmHg lower in participants with hypertension. Furthermore, high sodium intake [9] causes hyperfiltration patterns in healthy men with a BMI $\geq$25 kg/m^2. These studies suggest that lower sodium intake is not only beneficial for preventing the development of CKD, but also plays a role in slowing progression of kidney disease. Nonetheless, there are no randomized controlled trials that have examined whether reduction of dietary sodium in normotensive individuals will reduce the development of CKD.

Protein Intake and Kidney Function

The impact of protein intake on renal function likely differs based on the level of baseline renal function. Hence, these are discussed separately.

In Those with Normal Renal Function

A high-protein, low-carbohydrate diet has been shown to produce greater weight loss in obese subjects compared to a low-fat, high-carbohydrate diet [10]. However, there are concerns on whether a high-protein diet will cause nephrotoxicity. In a short-term study of 24 healthy young men,

high-protein diet has been found to significantly increase the glomerular filtration rate, as well as blood urea nitrogen, serum uric acid, glucagon, natriuresis, urinary albumin, and urea excretion [11]. In a 6-month randomized controlled trial of 65 healthy, overweight, and obese individuals, dietary protein intake changed from 91.1 g/day to a 6 months intervention average of 70.4 g/day ($P<0.05$) in the low-protein group and from 91.4 to 107.8 g/day ($P<0.05$) in the high-protein group [12]. These resulted in changes in glomerular filtration rate (GFR) of −7.1 mL/min in the low-protein group and +5.2 mL/min in the high-protein group (group effect: $P<0.05$). Kidney volume decreased by −6.2 cm^3 in the low-protein group and increased by +9.1 cm^3 in the high-protein group ($P<0.05$), whereas albuminuria remained unchanged in all groups. Thus, a high-protein diet led to increased renal mass and hyperfiltration. As hyperfiltration is a recognized risk factor for progressive kidney damage, theoretically a high-protein diet over the long term might result in kidney failure. On the other hand, as discussed below, obesity per se is a risk factor for kidney damage. Therefore, the risk-benefit ratio of long-term use of high-protein diet on kidney function remains unclear. Hence, based on the currently available data [10], short-term (6–12 months) use of high-protein diet in obese individuals for weight loss might be reasonable.

In Those with Chronic Kidney Disease

In animal studies, restricting protein intake delays the progression of renal disease. In smaller clinical trials of insulin-dependent diabetic nephropathy, low-protein intake resulted in slower decline of GFR [13, 14]. However, in the Modification of Diet in Renal Diseases (MDRD) Study [9], in 585 individuals with moderate CKD (GFR of 25–55 mL/min/1.73 m^2) compared to the usual-protein diet (1.3 g/kg/day), a low-protein diet (0.58 g/kg/day) did not result in slower decline of kidney function. A longer term follow-up using national registries of these patients after the study ended suggested that there might be an early benefit with low protein intake regarding the development of ESRD or the composite of ESRD or all-cause mortality [15].

In the same study, in 255 patients with more advanced CKD (GFR 13–24 mL/min/1.73 m^2), compared to a low-protein diet (0.58 g/kg/day), a very-low-protein diet (0.28 g/kg/day) with a keto acid-amino acid supplement did not result in significantly slower decline in GFR [10]. A recent longer term follow-up of these patients using the national registries after the study was completed, suggests that assignment to a very low-protein diet did not delay progression to kidney failure, but appeared to increase the risk of death [16]. More recently, 423 patients with stage 4–5 CKD were randomly assigned to low-protein diet (0.73 ± 0.04 g/kg/day) or a moderate protein diet (0.9 ± 0.06 g/kg/day). Over 48 months of follow-up, the mean monthly decline in the GFR did not significantly differ between the low protein diet and moderate protein diet (0.19 ± 0.48 mL/min/1.73 m^2 and 0.18 ± 0.46 mL/min/1.73 m^2) [17]. Thus, the role of protein restriction in slowing the progression of CKD remains controversial.

In summary, high-protein diet might be beneficial for weight loss in obese individuals with normal kidney function but should be avoided in those with even mild impairment of renal function. Therefore, kidney function should be estimated with a GFR estimating equation before high-protein diet could be prescribed particularly because mild kidney dysfunction is very common and is almost always asymptomatic.

Obesity, Insulin Resistance, and the Risk of CKD

While the impact of obesity on cardiovascular disease, hypertension, and diabetes are well established, only recently the data on the impact of obesity on kidney disease are emerging [18–22]. In an analysis of 320,252 adults, compared to those with normal BMI (18.5–24.9 kg/m^2), the risk of

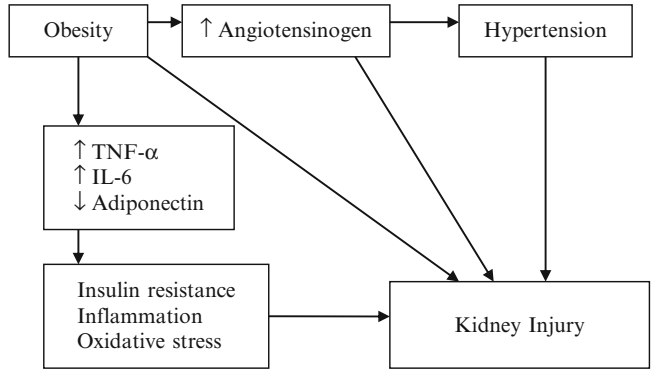

Fig. 16.1 Mechanisms of kidney damage in obesity

developing end-stage renal disease (ESRD) needing dialysis therapy was 1.87 (95 % CI, 1.64–2.14) for those who were overweight (BMI, 25.0–29.9 kg/m^2), 3.57 (CI, 3.05–4.18) for those with class I obesity (BMI, 30.0–34.9 kg/m^2), 6.12 (CI, 4.97–7.54) for those with class II obesity (BMI, 35.0–39.9 kg/m^2), and 7.07 (CI, 5.37–9.31) for those with extreme obesity (BMI ≥40 kg/m^2) [21]. Furthermore, in morbidly obese individuals who underwent bariatric surgery, loss of weight is accompanied by better control of blood pressure and reduction of glomerular hyperfiltration and proteinuria [22–24]. These data suggest that obesity is a risk factor for kidney disease.

In the above studies, higher baseline BMI remained an independent predictor for CKD/ESRD after additional adjustments for baseline blood pressure level and the presence or absence of diabetes mellitus [21]. However, diabetes is only one extreme of insulin resistance. It is possible that subclinical insulin resistance in nondiabetic individuals might reflect a poor metabolic milieu and might still lead to kidney injury. Indeed, in nondiabetic adults, insulin resistance is associated with development of CKD [25].

The potential molecular mechanisms for this phenomenon are depicted in Fig. 16.1. Adipose tissue is not a mere storage depot of fat. It is metabolically active and produces adipokines such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), plasminogen activator inhibitor, leptin, angiotensinogen, and adiponectin [26–40]. Alterations in production of these adipokines in obesity result in metabolic derangements that cause insulin resistance, dyslipidemia, hypertension, and inflammation [26–40]. In morbidly obese individuals who underwent bariatric surgery, loss of weight is accompanied by better control of blood pressure [41, 42] and reduction of glomerular hyperfiltration and proteinuria [22–24]. These data suggest that weight loss reduces kidney damage in obesity. A part of this effect might be mediated through hypertension and a part of this effect might be independent of hypertension. Insulin resistance, inflammation, and oxidative stress as consequences of altered production of adipokines in obesity might also result in kidney damage.

Nutritional Issues in Uremia

The previous section discussed the role of diet and obesity in the development and progression of CKD. In this section, nutritional issues that might be unique to uremia, i.e., the obesity paradox, the pathophysiology of wasting syndrome, and serum phosphorus in advanced CKD are discussed.

Obesity Paradox in Uremia

The annual mortality in dialysis patients is approximately 20 % a year. Better nutritional status as evidenced by higher body size, muscle mass, and serum albumin is associated with better survival in dialysis patients. In particular, in contrast to the associations of high body mass index (BMI) with increased mortality in the general population, high BMI is associated with better survival in dialysis patients [4, 43–51]. This phenomenon has been described as a risk factor paradox or reverse epidemiology of wasting disease [47, 52, 53]. Hence, it has been suggested that obesity is protective rather than harmful in dialysis patients [47].

Although high BMI is associated with better survival in dialysis patients, the associations of adiposity with traditional cardiovascular risk factors such as diabetes and nontraditional risk factors such as inflammation are not confined to the nondialysis population. Indeed, previous studies have shown that in dialysis patients, adiposity and/or high BMI is associated with insulin resistance [54], diabetes [55], inflammation [56], anemia [57], coronary calcification [58, 59], and carotid atherosclerosis [54]. It is perplexing: if adiposity is associated with these apparent cardiovascular risk factors, why is adiposity associated with better survival in dialysis patients?

These apparently perplexing associations might be explained if (1) adiposity has dual competing effects on survival; a protective nutritional effect and a deleterious metabolic effect resulting in insulin resistance, dyslipidemia, hypertension, and inflammation and (2) the level of kidney function modifies the relative importance of these effects [60]. In this paradigm, the deleterious metabolic effects of obesity outweigh its protective nutritional effects in the non-CKD population, the deleterious metabolic effects of obesity are neutralized by its protective nutritional effects in the moderate CKD population and the deleterious metabolic effects of obesity are outweighed by its protective nutritional effects in stage V CKD on dialysis. In other words, the overall effects of obesity on survival vary according to the level of kidney function, and there is an interaction of body size and presence or absence of CKD on survival, even though the metabolic effects of adiposity are not modified by the level of kidney function.

Pathophysiology of Malnutrition in Uremia

Figure 16.2 summarizes the likely causal pathways for sarcopenia (low muscle mass) in uremia. Muscle mass is the net result of muscle protein synthesis and breakdown. Decreased protein intake results in decreased muscle protein synthesis, whereas inflammation, oxidative stress, and metabolic acidosis promote muscle protein breakdown. Uremic toxins decrease muscle protein synthesis by decreasing protein intake as well as by directly inhibiting muscle protein synthetic machinery. Uremic toxins also increase muscle protein breakdown by inflammation, oxidative stress, and metabolic acidosis as well as by directly stimulating muscle protein catabolic pathways.

The relative importance of these pathways (decreased anabolism vs. increased catabolism) in causing uremic malnutrition remains controversial and the following discusses these issues.

Protein Intake and Nutritional Status

The current clinical guidelines recommend a dietary protein intake of 1.2 g/kg/day for hemodialysis patients [61]. These guidelines are based upon opinion and observational data. High-protein intake might result in increased serum phosphorus (discussed later) and metabolic acidosis which might be

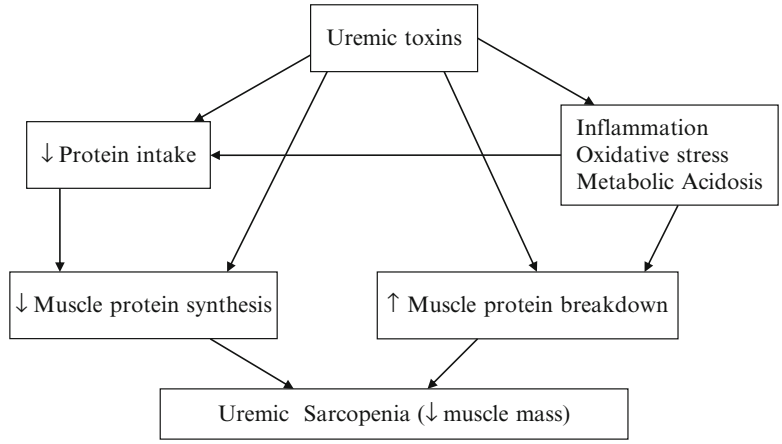

Fig. 16.2 Likely causal pathways for sarcopenia in uremia

detrimental in dialysis patients. Furthermore, as discussed below, there are controversies whether dietary interventions could have an impact on the nutritional status in dialysis patients.

It has been suggested that malnutrition in dialysis patients is a misnomer because uremic wasting (the state of low muscle mass, body weight, and serum proteins in dialysis patients) is caused by hypercatabolism and not decreased dietary intake [62]. In support of this theory, there are experimental data that suggest that acidosis [1, 5, 63] and TNF-α [64, 65] activate the ubiquitin-proteasome proteolytic system, the major pathway for protein catabolism [66]. Thus, it has been suggested that metabolic acidosis and inflammation may be the major determinants of the "state of loss of protein" in dialysis patients [67]. Further, in a small study of eight peritoneal dialysis patients, increase in dialysate lactate (which could buffer acids) was associated with decreased expression of skeletal muscle ubiquitin and improvement of nutritional indices in 1 month [68]. The other factors that are thought to contribute to this state of increased catabolism include resistance to anabolic activities of insulin and muscle breakdown induced by the hemodialysis procedure [62, 69, 70].

Nonetheless, while increased catabolism might play a causative role in the state of low muscle mass, body mass index, and serum proteins in dialysis patients, it remains unclear whether inflammation, oxidative stress, and metabolic acidosis are the key determinants of muscle mass in uremia. Dietary intake might still be the most important determinant of muscle mass and body size in dialysis patients. For instance, after starvation for a prolonged period, malnutrition is as likely in dialysis patients as in the general population. However, once malnutrition is established, it might be more difficult to reverse it in dialysis patients as compared to the general population. Thus, difficulties in reversing malnourished state with increased nutrition do not preclude that malnourished state is result of deficient dietary intake.

Metabolic Acidosis and Nutritional Status

As discussed above, metabolic acidosis [1, 5, 63] activates ubiquitin-proteasome proteolytic system, the major pathway for protein catabolism [66], and, hence, metabolic acidosis is proposed as the major cause of low muscle mass in dialysis patients. Thus, low serum creatinine levels, which reflect lower muscle mass in prevalent hemodialysis patients is expected in those with lower serum bicarbonate concentrations. However, in an analysis of the well-dialyzed participants of the HEMO Study, the

opposite association was present, i.e., those with higher serum creatinine concentrations (higher muscle mass) had lower serum bicarbonate concentrations [71], suggesting that acidosis was not a dominant determinant of low muscle mass.

Inflammation and Nutritional Status

TNF-α also activates the ubiquitin-proteasome proteolytic system [64, 65]. Thus, inflammation is thought to be a major determinant of muscle wasting in dialysis patients [62]. In an earlier analysis of the HEMO Study data, very high levels of CRP were associated with decreased serum creatinine levels [71]. In a separate study, mid-thigh muscle mass estimated by computed tomography was also negatively associated with CRP [72]. In addition to increased catabolism, inflammation may also suppress appetite resulting in malnutrition [52, 73–75]. Thus, it is biologically plausible that inflammation is associated with malnutrition in dialysis patients.

However, longitudinal associations between inflammation and low BMI have never been documented in dialysis patients. Furthermore, in the above longitudinal analysis of HEMO Study, each unit increase in natural logarithm of CRP was associated with a very modest 0.15 mg/dL decrease in serum creatinine [71]. Hence, a tenfold increase in natural logarithm of CRP will be associated with a drop in serum creatinine of 1.5 mg% in prevalent hemodialysis patients. Thus, the association of severe inflammation with loss of muscle mass in dialysis patients is plausible but might not be sufficient to explain the high prevalence of low muscle mass in dialysis patients.

In summary, as suggested in Fig. 16.2, the effects of deficient diet and increased catabolism need not be mutually exclusive and on the other hand, they might have synergistic effects. Interventional studies are warranted to determine the relative importance of anabolic vs. catabolic processes in uremic malnutrition.

Calcium-Phosphorus, Parathyroid Hormone, and Vascular Calcification

With decline in GFR, phosphorus excretion in the urine is reduced and phosphorus accumulates in the blood. This results in hypocalcemia as well as hyperparathyroidism.

Higher phosphorus, calcium phosphorus product, and parathyroid hormone levels are associated with increased vascular calcification [76] and mortality in dialysis patients [77]. Serum phosphorus could be reduced by decreasing dietary phosphorus intake. However, this is problematic because foods that are high in phosphorus are also high in protein. Therefore, in order to let the patient consume reasonable amounts of protein, phosphorus binders are used along with meals. These act by binding the phosphorus in the gut resulting in nonabsorbable compounds that are eliminated in stools.

Aluminum-containing phosphorus binders resulted in elevated serum aluminum levels with consequent osteomalacia [78, 79] and decreased mentation [80] (dialysis dementia). Therefore, aluminum-containing phosphorus binders have been largely abandoned. Currently, the two main classes of phosphorus binders are calcium-based or non-calcium-based. Randomized controlled trials showed that therapy with sevelamer (a non-calcium-containing phosphorus binder) as opposed to calcium-containing phosphorus binders were associated with decreased arterial calcification, particularly in those who are older and have preexisting calcification [81, 82]. In a follow-up analysis of one of these trials of 129 incident hemodialysis patients, in sevelamer-treated subjects, mortality, a prespecified secondary endpoint was lower. However, in a multicenter, randomized, open-label, parallel design trial ($n = 2{,}103$) of sevelamer and calcium-based binders, all-cause mortality rates and cause-specific mortality rates were not significantly different [83]. However, there was a significant age interaction on the treatment effect. Only in patients over 65 years of age was there a significant effect of sevelamer

Table 16.1 Summary of dietary recommendations based on the level of renal function

Condition	Appropriate diet
Obesity with normal kidney function (estimated MDRD GFR > 80 mL/min/1.73 m^2)	High-protein, low-carbohydrate diet (or other well-balanced, reduced-calorie diet)
	No fluid restriction
Impaired kidney function (MDRD GFR 30 to ≤80 mL/min/1.73 m^2)	Avoid high-protein diet
	Potential benefit of protein restriction (0.6 g/kg/day)
	Salt restriction (3–4 g/day)
	No fluid restriction if urine output is normal
Stage IV CKD (MDRD GFR 15–29 mL/min/1.73 m^2)	Avoid high-protein diet
	Potential benefit of protein restriction (0.6 g/kg/day)
	Salt restriction (3–4 g/day)
	Restrict potassium and phosphorus as needed
	No fluid restriction if urine output is normal
On dialysis	Potential benefit of high-protein diet (1.2 g/kg/day)
	Salt restriction (3–4 g/day)
	Restrict potassium and phosphorus
	Restrict fluid intake to 1–1.5 L/day

in lowering the mortality rate. There was a suggestion that sevelamer was associated with lower overall, but not cardiovascular-linked, mortality in older patients. Taken together with the above observational data, sevelamer might be beneficial in elderly who are likely to have arterial calcification but not in younger dialysis patients.

Conclusion: Dietary Recommendations Based on Level of Kidney Function

Table 16.1 provides a summary of diet recommendations individualized appropriately for the level of renal function. More extensive information about appropriate dieting modifications during various levels of CKD can be found at the National Kidney Foundation website (www.kidney.org).

In summary, diet and nutritional status exert a strong effect on both the development and the progression of CKD, and is a strong determinant of the outcomes in those with established CKD. Dietary and lifestyle interventions could reduce the burden of CKD in the United States.

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Chapter 17
Nutritional Concerns in Osteoporosis

Bess Dawson-Hughes

Key Points

- Adequate calcium intake, 1,000–1,200 mg per day, supports the preservation of bone mass in older adults.
- Higher calcium intake should be avoided because it adds no value and may increase risk of kidney stones and cardiovascular disease, although the evidence is inconsistent.
- Vitamin D lowers fracture risk by improving bone mass and lowering risk of falling. An intake of 800–1,000 IU per day is sufficient for most older adults.
- The magnitude of the risk reduction for falls and fractures with vitamin D supplementation is approximately 20 %.
- High, infrequent dosing with vitamin D should be avoided because it increases risk of falls and fractures.
- Lowering the acid load of the diet with alkaline salts of potassium has been shown to lower rates of bone resorption and, in some trials, to lower rates of bone loss, but the effect on fracture risk is unknown. There is some evidence that these salts improve muscle performance over the short term; long-term studies are needed to determine whether these favorable effects persist.

Keywords Calcium • Vitamin D • Acid–base balance • Potassium bicarbonate • Bone mass • Falls • Fractures • Nutrition

Introduction

Osteoporosis is defined as the state of reduced mass and architectural deterioration of bone that contribute to risk of fracture. The clinical outcome of ongoing bone loss is low-trauma fractures. The lifetime risk of a fracture is about 40 % [1] and one in four women will sustain a low-trauma fracture after age 50 [2]. There have been encouraging downward trends in risk of hip fracture over the last

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15–20 years in the United States [3, 4] and elsewhere [5], but not apparently at other skeletal sites [4]. Any small declines in fracture rates, however, would not result in fewer total fractures because of changing demographics. In the United States, the population at highest risk for fracture, men and women aged 65 years and older, is expected to increase from 40 to 89 million between 2010 and 2050 [6]. As a result of this demographic shift, the health care cost of fractures in the United States, estimated at $17 billion for the year 2005, is projected to be over $25 billion in 2025 [7].

Many factors contribute to age-related bone loss and increased fracture risk. Of central importance is genetics. In a recent study in 2,716 female twins who had at least two bone mineral density (BMD) assessments more than 4 years apart (mean follow-up 9.7 years), Moayyeri et al. [8] estimated heritability of bone loss at different ages from age 40 to 80 years. At age 40–45 years, heritability of the changes in BMD averaged 39.9 % for the total hip, 46.4 % for the femoral neck, and 69.5 % for the lumbar spine. Heritability of bone loss declined with increasing age and by age 65 years, there was no heritability of the rates of bone loss at any of these sites. The lack of heritability of bone loss in older subjects implies a greater role for life style in preserving bone mass in this vulnerable population. Exercise is an important determinant of bone health. Intense exercise programs in the elderly can improve bone mass modestly, by 1–2 % over the course of a year. The most important impact of exercise, particularly exercise that improves strength and balance, is to lower the risk of falling [9–11], a major risk factor for fracture.

Many nutrients affect bone development and preservation. The most extensively studied of these are calcium and vitamin D. Vitamin D also has an important role in muscle function. An emerging area of interest to the research and clinical communities is the role that the acid–base balance of the diet plays in preserving bone and muscle mass and function in older adults. This chapter is focused on the relationship of calcium intake, vitamin D status, and the acid–base balance of the diet to bone and muscle mass and strength and to the important clinical outcomes of falls and fractures in older men and women.

Calcium

Physiology

Calcium has many functions, including an important role in intracellular signaling and vascular and neuromuscular function. It is also critical for the development and preservation of the skeleton. About 99 % of the calcium in the human body is in bone. Calcium is part of hydroxyapatite, the crystalline component of bone that lends bone stiffness and strength. In addition to its structural role, calcium intake affects bone mass in adults through its impact on the remodeling rate. An inadequate intake of calcium results in less calcium absorbed, a lower circulating ionized calcium concentration, and an increased secretion of parathyroid hormone (PTH), a potent bone-resorbing agent. Typically about 5 nmol (200 mg) of calcium is removed from the adult skeleton and replaced each day. Dietary or supplemental calcium at sufficiently high levels, such as 1,000 mg per day or more, lowers the bone remodeling rate by 10–15 % in older men and women and the degree of suppression appears to be dose-related [12]. The reduction in remodeling rate accounts for the increase in BMD that occurs in the first 12–18 months of treatment with calcium. A high remodeling rate is generally associated with a greater rate of bone loss. The bone remodeling rate increases with aging; however, treatment with calcium will lower the rate in older women to rates commonly observed in premenopausal women [13]. It will also significantly lower circulating levels of PTH.

Calcium is absorbed by active transport across the mucosal cells, a process promoted by the active metabolite of vitamin D, 1,25-dihydroxyvitamin D [1,25$(OH)_2$D]. It is also absorbed by passive transport, a process that occurs in proportion to the luminal:serosal concentration gradient. Some calcium may be absorbed by solvent drag in the setting of large intakes of sugar. Active transport is the dominant mode of absorption at low calcium intakes, and passive transport dominates at high intakes. Calcium absorption has an hereditary component, linked to alleles of the vitamin D receptor (VDR); this component is apparent at low but not high calcium intakes [14]. Calcium is absorbed at the greatest rate in the duodenum; however, because of its greater length and absorptive surface, most calcium is actually absorbed more distally in the small intestine. Up to 10 % is absorbed in the colon. Calcium absorption efficiency declines with aging [15]. This is thought to be due in part to the age-related decline in intestinal VDRs [16]. Additionally, vitamin D levels tend to decline with aging, making vitamin D deficiency a contributing cause.

Basis for Setting Calcium Intake Requirements

The 2011 Institute of Medicine (IOM) recommendations for calcium intake are based primarily on short-term calcium balance studies. Randomized calcium intervention trials with changes in rates of bone loss and fractures were used as supporting rather than primary evidence because of limited quantities of trial data.

Hunt and Johnson analyzed calcium balance data in 155 young adults with calcium intakes ranging from 415 to 1,740 mg per day [17]. In this analysis, neutral balance was predicted at an intake of 741 mg per day. Several meta-analyses of randomized, placebo-controlled trials have addressed whether supplemental calcium lowers fracture risk. The Shea meta-analysis [18] of trials in postmenopausal women found that calcium supplementation increased BMD at every measured site by 1–2 %. It did not, however, significantly lower risk of vertebral (RR 0.77 [95 % CI 0.54–1.09]) or nonvertebral fractures (RR 0.86 [CI 0.43–1.72]). The 15 trials included in this analysis administered doses in the range of 500–2,000 mg per day over periods ranging from 18 months to 4 years. A subsequent meta-analysis found no significant effect of calcium on risk of nonvertebral (RR 0.92 [95 % CI: 0.81, 1.05]) and a significant *increase* in risk of hip fracture on calcium (RR 1.64 [95 % CI: 1.02, 2.64]) [19]. A subsequent and third meta-analysis confirmed the significant *increase* in hip fracture risk (RR 1.50 [95 % CI: 1.06, 2.12]) [20]. Thus, the weight of the evidence is that supplemental calcium alone will improve BMD modestly, but it is not effective in preventing fractures.

Based largely on the Hunt and Johnson data described above [17], the IOM identified 800 mg as the estimated average requirement (EAR) for adults. From the EAR, the IOM derived the Recommended Dietary Allowances (RDAs) shown in Table 17.1 [21]. The Tolerable Upper Limit for calcium was set at 2,000 mg per day.

Table 17.1 Recommended calcium and vitamin D intakes for older adults[a]

	Men	Women
Calcium, mg/day		
Age 51–70	1,000	1,200
Age 71+	1,200	1,200
Vitamin D, IU/day		
Age 51–70	600	600
Age 71+	800	800

[a]Table created with data from [21]

Safety

Calcium in amounts recommended has long been considered safe, but questions have been raised about the safety of high doses of calcium supplements. High intake from supplements has been associated with a 20 % increase in risk of kidney stones in women [22] but not in men [23]. In the Women's Health Initiative (WHI), treatment with 1,000 mg of calcium and 400 IU of vitamin D daily for 7 years was associated with an increased risk of kidney stones [24]. In contrast, high intakes of calcium from food sources may lower risk of kidney stones in men [23] and women [22].

Of more serious concern is the possibility that calcium supplementation may increase risk of cardiovascular disease. Surprisingly, in view of evidence that calcium lowers lipids levels [25], Bolland et al. reported in 2008 that healthy postmenopausal women treated with 1,000 mg of supplemental calcium, when compared with placebo, had significantly higher risk of myocardial infarction (RR 2.12 [95 % CI: 1.01, 4.47]) [26]. A subsequent meta-analysis by the same authors also identified an increased risk (OR 1.31 [95 % CI: 1.02, 1.67]) [27]. A recent large observational study found that calcium supplement use, particularly at higher doses, was associated with increased risk of cardiovascular disease mortality in men but not in women [28]. They found no association of dietary calcium intake with mortality in men or women. In the WHI, there was no increase in risk of cardiovascular disease with calcium and vitamin D [29]. Similarly, in 1,460 women, mean age 75 years, treatment with 1,200 mg per day of calcium, compared with placebo, for 4.5 years didn't increase risk of cardiovascular disease [30]. Thus, the question remains open.

Since there is no evidence that intake in excess of the RDA adds any benefit either in the general population or in patients being treated with pharmacotherapy for osteoporosis, and since the possibility for harm remains open, supplement use that takes total calcium intake substantially above the RDA should generally be avoided.

Calcium Recommendations

Calcium intake in older men and women in the U.S. averages about 750 mg per day [21], so the average gap between actual and recommended calcium intake is 250–450 mg per day. Increasing intake from foods sources is the first strategy. This can be achieved by adding 1–1.5 servings of a calcium-rich food such as dairy foods or fortified orange juice to the diet.

For those unable or unwilling to increase their calcium intake from food sources, a calcium supplement can be used to fill the gap. Few elders will need more than about 500 mg of supplemental calcium per day, and this can be taken in a single dose. For individuals who have unusually low calcium intakes from food, such as individuals who avoid dairy foods, higher supplement doses may be needed. When that dose exceeds 500 or 600 mg per day, the dose should be split for better absorption efficiency [31]. Several forms of calcium are available. The most commonly used supplement is calcium carbonate (40 % calcium by weight) and the second most common is calcium citrate (21 % by weight). Calcium from citrate is slightly better absorbed than calcium from carbonate; however, differences in absorbability are generally offset by differences in their calcium contents, so the amounts of calcium absorbed per gram of supplement are similar. With regard to timing of calcium supplements, calcium carbonate should be taken with a meal for better absorption [32], whereas citrate may be taken at any time.

Vitamin D

Physiology and Interactions with the Aging Process

Vitamin D is acquired mainly through synthesis in the skin after sun exposure. UVB rays stimulate the conversion of the precursor, 7-dehydrocholesterol, to vitamin D_3. Vitamin D_2 and vitamin D_3 are absorbed from vegetable and plant foods, respectively. Their absorption requires the presence of bile acids and occurs in the proximal jejunum and the distal ileum by passive diffusion [33]. Few foods contain significant amounts of vitamin D and in periods when sun exposure is lacking or ineffective, many people will need supplements. The effectiveness of sun exposure is related to latitude, altitude, time of day, degree of skin pigmentation, sunscreen use, and other factors. At higher latitudes such as 42° North (Boston), sun exposure in the winter does not promote skin synthesis because the needed UVB rays don't reach earth's surface. Vitamin D status, assessed clinically by measuring the serum 25-hydroxyvitamin D (25OHD) level, is commonly poor in the elderly for several reasons. Sun exposure produces less vitamin D in older adults than in young adults because the concentration of the precursor in the skin is lower [34]. Additionally, many elders avoid sun exposure because of concern about skin cancers. Absorption efficiency of ingested vitamin D does not appear to decline with aging [35].

Vitamin D affects fracture risk through its impact on muscle, balance, and risk of falling and through its effects on calcium homeostasis, bone mass, and strength. The means by which vitamin D insufficiency affects bone and muscle and influences fracture risk are illustrated in Fig. 17.1.

Muscle Performance, Balance, and Falls

The active form of vitamin D, $1,25(OH)_2D$, acts on muscle by binding to classical nuclear VDRs. Mice lacking the VDR have smaller muscle fibers throughout adult life [36]. VDRs in human muscle have been identified and been shown to decline as a function of aging [37]. However, it is not universally agreed that VDRs exist in human muscle [38]. In humans, severe vitamin D deficiency is characterized clinically by profound muscle weakness, particularly in proximal muscles, and by muscle pain and impaired gait [39, 40]. Even mild vitamin D insufficiency appears to influence muscle

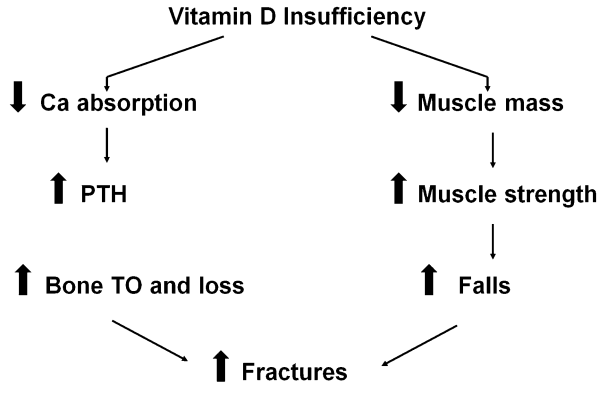

Fig. 17.1 The pathway by which vitamin D influences fracture risk

performance in the general older population. In 4,100 ambulatory adults aged 60 years and older participating in The Third National Health and Nutrition Examination Survey (NHANES III), lower extremity muscle performance, measured as the 8-foot walk test and the repeated sit-to-stand test, was poorest in subjects with the lowest 25OHD levels and was progressively better at increasing 25OHD levels throughout and even beyond the upper end of the reference range [41]. A similar association was observed in a prospective cohort of older Dutch men and women [42]. In this study, however, performance reached its maximum at a 25OHD level of about 50 nmol/L. Randomized, controlled vitamin D intervention trials with muscle performance outcomes have presented a mixed picture. In a meta-analysis of these studies, Stockton and colleagues concluded that vitamin D had no significant effect on lower extremity muscle strength except in individuals with low starting serum 25OHD levels (<25 nmol/L) [43].

Poor balance is a known contributor to risk of falling. Balance in clinical trials has been measured by quantifying the degree of sway in the anterior-posterior and medial-lateral directions in subjects standing on a force platform. Two trials have evaluated the effect of vitamin D on sway. Both trials compared the effect of 800 IU of vitamin D_3 plus 1,000 mg of calcium per day with calcium alone in elderly adults. The vitamin D groups had an up to 28 % improvement (reduction) in body sway [44, 45] over periods of 2 and 12 months, when compared with the calcium alone groups. These studies implicate a role for vitamin D supplementation in improving balance in elders. This may be an important means by which vitamin D affects risk of falling.

The impact of vitamin D on risk of falling has been examined in several randomized controlled trials and in as many meta-analyses. In one meta-analysis, risk of falling was significantly reduced, by 20 %, in the trials administering 700–1,000 IU per day of vitamin D, whereas doses of 400 IU per day were ineffective [46]. In a different meta-analysis, the risk reduction with vitamin D was 17 % when compared with placebo [47]. In acute hip fracture patients, 2,000 IU of vitamin D_3 per day was no more or less effective than 800 IU per day in affecting fall rates [10]. A recent evaluation of a 500,000 IU dose given orally once per year to elders actually increased their risk of falling when compared with placebo [48]. Thus while further evidence is needed, it appears that intake in the range of 700–1,000 IU per day is the amount needed for maximal protection against falling and that large single doses should be avoided.

Vitamin D: Bone Mass and Fractures

In several cross-sectional studies, serum 25OHD levels are inversely associated with serum PTH levels and positively associated with BMD [49–51]. Moreover, in randomized, controlled clinical trials, supplementation with vitamin D has lowered rates of bone loss in older adults [52, 53], with most of the benefit occurring in the wintertime [53]. The magnitude of the reduction in bone loss is on the order of 1–2 % over a 1- to 2-year period, or approximately one-half of the usual loss. These BMD changes are too small to account for the significant impact that vitamin D has on fracture risk (to be described below); most of the anti-fracture benefit from vitamin D is thought to result from its improving strength and balance and lowering risk of falling.

Many randomized controlled trials have examined the effect of vitamin D with and without calcium on fracture rates in older men and women. Several investigators have performed meta-analyses of the trials, each focusing on slightly different questions and therefore applying different trial inclusion criteria. It's not surprising that they have reached somewhat different conclusions. An individual subject-level meta-analysis, while not free of shortcomings, allows much more analytical flexibility and refinement than a study-level meta-analysis. A subject-level meta-analysis utilizing age, gender, living arrangement (institutionalized or free-living), treatment assignment, dose of vitamin D, calcium intake, and compliance with administered supplements (placebo or vitamin D with or without calcium) of each participant was performed in 31,022 persons, age 65 years and older [54].

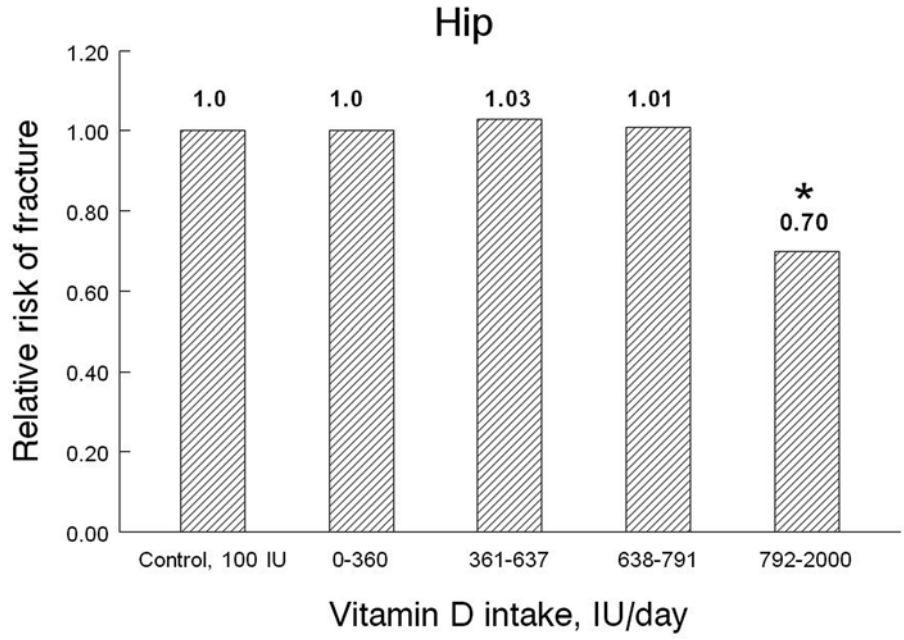

Fig. 17.2 Adapted from the individual subject-level meta-analysis of 11 randomized controlled trials to determine the impact of vitamin D on hip fracture risk [54]. The bars represent the relative risk of hip fracture by quartile of vitamin D intake in 31,022 participants, after adjustment for study, age group, sex, and type of dwelling

In the intent-to-treat analysis, participants assigned to treatment with vitamin D had a nonsignificant 10 % reduction in risk of hip fracture when compared with placebo (hazard ratio, 0.90; 95 % confidence interval [CI] 0.80–1.01) and a significant 7 % reduction in risk of nonvertebral fracture (hazard ratio 0.93 [CI] 0.76–0.96). The risk of hip fracture was also examined by quartile of total vitamin D intake, including intake from study supplements and outside supplements, as was allowed in several of the trials, including the WHI. There was a 30 % lower risk of hip fracture in the highest quartile of intake, 792–2,000 IU per day, median 800 IU per day, than in each of the other quartiles, after adjustment for study, age group, sex, and type of dwelling (Fig. 17.2). Hip fracture risk in the third quartile did not differ from the risk in the lower two quartiles. The highest quartile also had significantly lower risk of nonvertebral fracture (hazard ratio 0.86, [CI] 0.76–0.96). These results suggest that an intake of at least 800 IU per day is needed to lower fracture risk in men and women age 65 and older. This intake is in accord with the IOM recommended intake of 800 IU per day for men and women age 71 years and older, but higher than the intake of 600 IU recommended for persons age 50–70 years (see Table 17.1) [21]. Strengths of this subject-level meta-analysis are that it contains data from a large number of trials including the WHI; it takes account of compliance with study pills, which was as low as 50 % in one of the trials [55], and it accounts for vitamin D intake not only from study pills but also from personal supplement use during the trial, a practice that was allowed and widespread in the WHI and several other trials. Meta-analyses can be used to estimate the dose or 25OHD level needed to minimize fracture risk, but they can never be as precise as a single multiple-dose study with fracture as the primary outcome. A multiple-dose anti-fracture efficacy trial is not likely to be conducted, and we must therefore make the best possible interpretation of smaller, single-dose trials when seeking to define the optimal dose of vitamin D for musculoskeletal health. Another limitation of current trial data for defining the vitamin D requirement is that most of the higher dose vitamin D trials also administered calcium to the vitamin D group, so one cannot differentiate the effects of vitamin D alone from the combined effects of vitamin D and calcium.

Recommendations for Vitamin D Replacement

Based on available evidence, an intake of about 800 IU per day of vitamin D is sufficient to lower risk of falls and fractures in the general population of older men and women. Daily and weekly dosing give similar increases in serum 25OHD levels [56]. Monthly dosing, favored by some patients, is also effective, although the variability in increment in 25OHD is somewhat greater than it is with more frequent dosing [56]. Most now agree that vitamin D_3 is preferred over vitamin D_2, because it gives a larger 25OHD increment. This, of course, can be offset by giving a higher dose of vitamin D_2. With monthly administration of oral vitamin D_2, the circulating 25OHD level starts to decline about 2 weeks after each dose, a phenomenon not seen with monthly administration of vitamin D_3.

Acid–Base Balance of the Diet

The effects of the acid–base balance of the diet on bone and muscle, while less well studied than those of calcium and vitamin D, is of growing interest, and lowering the acid load of the diet may be a promising adjunct to more established nutritional preventive strategies. Aging is associated with a low-grade, progressive metabolic acidosis [57]. In young adults, the kidney responds to metabolic acidosis by increasing renal net acid excretion (NAE) to minimize perturbation in blood pH [58]. The gradual decline in renal function in older adults limits their capacity to excrete hydrogen ions [59]. The diet consumed by many people in the United States and elsewhere contributes to the acidosis. An acid-producing diet is one in which intake of alkali-producing fruits and vegetables is inadequate to neutralize the intake of acid-producing cereal grains and animal protein. Fruits and vegetables are metabolized to the alkaline bicarbonate and protein and cereal grains are metabolized to sulfuric, phytic, and other acids [60–62]. Figure 17.3 illustrates the distribution of NAE of values of 171 healthy older men and women enrolled in our recent bicarbonate trial (described below); 96 % of the subjects had positive NAE values, indicating that their usual diets were acid-producing.

There is extensive evidence that an acidic environment has negative effects on bone. It impairs osteoblast function [63–65] and increases bone resorption [66] through activation of a proton receptor on osteoclasts [67]. Acid also has a direct physicochemical effect on bone [68]. In several small metabolic studies, a single daily dose of alkali over a period of 1–3 weeks lowered biochemical markers of bone turnover [69, 70]. A meta-analysis of calcium balance studies found no evidence that the dietary acid load affected calcium balance [71]. In contrast, a recent randomized controlled trial found that 90 mmol per day of the alkaline salt, potassium citrate, significantly improved calcium balance over a 6-month period [72]. Several studies have described associations of diets rich in fruits and vegetables with higher BMD and/or lower rates of bone loss [73–77]. Three relatively small randomized controlled trials in older men and women have also been reported. In one, supplementation of postmenopausal women with 35 meq per day of an alkaline salt of potassium reduced rates of bone loss over 1 year [78]. In a 2-year trial with a larger dose of 60 meq per day in 201 older men and women, potassium citrate significantly lowered rates of bone loss, increased a biochemical marker of bone formation, and decreased a biochemical marker of bone resorption, when compared with placebo [79]. In a third trial, neither an alkaline salt of potassium nor fruit and vegetable intake significantly affected changes in BMD [80]. The reason why the latter trial had discordant results is not clear.

An acidic environment also has negative effects on muscle. Clinical states of chronic metabolic acidosis including starvation [81–83], trauma, sepsis and burns [84–87], and chronic renal failure are states of muscle wasting in humans [88]. In rats, acid loading promoted nitrogen excretion, an indicator of muscle wasting [89]. In a small metabolic study, daily treatment with an alkaline salt of potassium reduced nitrogen excretion in postmenopausal women on acid-producing high-protein diets, and discontinuation of the alkali was followed by an immediate increase in the urinary nitrogen excretion toward

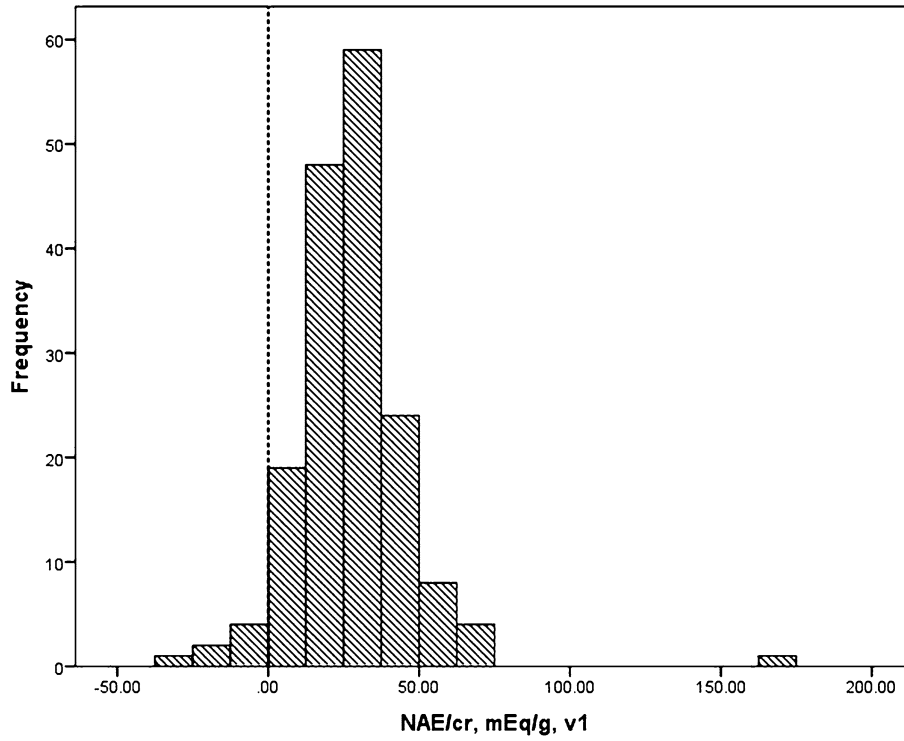

Fig. 17.3 The distribution of net acid excretion (NAE) values of 171 healthy men and women age 50 years and older with normal renal function. Ninety-six percent of the subjects had positive NAE values, indicating that they were consuming acid-producing diets. Vegetarians were excluded, but there were no other dietary restrictions in these subjects

its baseline level [62]. The authors calculated that the bicarbonate-induced decline in nitrogen wasting, if sustained, would be sufficient to offset the decline in muscle mass that occurs with aging (64 g of nitrogen or 1.0 kg of lean body mass per decade). In our recent 3-month trial, administration of 60 meq per day of potassium bicarbonate to healthy older men and women significantly lowered nitrogen excretion and, in the women, improved lower extremity muscle power. Longer-term studies are needed to determine whether these favorable effects persist and result in improved muscle mass and performance. Treatment with alkaline salts of potassium (or preferably increasing the intake of fruits and vegetables) warrants further evaluation as a potential risk modifier of age-related losses in both bone and muscle. Even small gains in prevention would have large consequences for the elderly population.

Conclusion

A calcium intake of 1,000–1,200 mg per day is needed to support the preservation of bone mass in older adults. Higher intakes offer no added benefit, may increase risk of kidney stones, and should be avoided. A vitamin D intake of 800–1,000 IU per day lowers risk of falls and fractures in older adults who are vitamin D insufficient. High, infrequent dosing with vitamin D should be avoided because it increases risk of falls and fractures. There is evidence that supplementation with alkaline salts of potassium (potassium citrate or bicarbonate) improves muscle performance and calcium balance over the short term. Long-term intervention studies are needed to determine whether these favorable effects persist.

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Chapter 18
Dementia-Related Mealtime Difficulties: Assessment and Management in the Long-Term Care Setting

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Key Points

- Mealtime difficulties in persons with dementia can lead to chronic under-nutrition, with profound effects on both physical health and quality of life.
- Mealtime difficulties related to dementia are best dealt with in the clinical setting by an interdisciplinary team approach, where clear communication among team members can promote effective care management.
- The Need-Driven Dementia Compromised Model provides a problem-solving framework that prompts caregivers to examine behaviors through the lens of background factors (e.g., lifetime habits and routines, physical health, physiological factors) and adaptable proximal factors (e.g., caregiver interactions, environmental factors) in order to look for modifiable factors.
- Careful hand feeding is a viable alternative to percutaneous gastrostomy feeding (PEG) and is often the preferable intervention to support oral intake of food and fluids in advanced dementia.

Keywords Mealtime difficulties • Dementia • Long-term care • Feeding

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Significance and Impact of the Problem

Background

By the year 2050, the number of persons with dementia aged 65 and older in the United States is expected to increase from 5.4 to 16 million persons [1]. While most persons with dementia (PWD) prefer to be cared for in their home environment, as the disease causes progressive functional and behavioral decline many will require institutional care. For these PWD, this means placement in assisted-living facilities or skilled nursing homes (NH). The number of PWD in the NH setting is expected to double to three million by the year 2050 [1]. While NHs attempt to address the multiple needs of their residents, the very basic need for adequate nutrition to promote health may be compromised by frailty, chronic illness, and cognitive decline. In fact, the ability to feed oneself is the last activity of daily living (ADL) to be lost; this is especially true in persons with Alzheimer's disease and related dementias. The adverse impact of chronic under-nutrition due to ongoing mealtime difficulties is profoundly felt on both physical health and quality of life for the PWD [2]. This chapter focuses on this frequently neglected topic, exploring both the assessment and management of mealtime difficulties in PWD and offering some innovative and practical strategies for managing such difficulties.

Impact of Mealtime Difficulties

In the institutional setting, complaints about mealtimes are common, ranging from noisy and cluttered meal environments and over-burdened staff, to restricted diets that appear and smell unappetizing and that may not be accepted by residents. Within this context, dining may be transformed into more of a task to be accomplished by the staff who assist, rather than a process to be facilitated and enjoyed. As a result, staff and resident may lose an opportunity for social interaction, which is often missing within institutional settings [3].

Adding to the concern regarding this high-risk mealtime scenario is the extreme vulnerability of PWD. They are often unable to express their needs due to a loss of language ability and have only their behaviors as a means to express their needs to caregivers. The behaviors, such as turning away of the head, clamping the mouth shut, and/or physically pushing away feeding assistance, are frequently thought of as "resistant" or "aversive" when, in fact, they may be the only means of communication available to the PWD. When these behaviors are interpreted as "resistive" or "aversive," feeding assistance attempts may stop, leading to malnutrition and dehydration, and potentially contribute to an earlier death if not acknowledged and appropriate interventions taken.

In NHs across the country, malnutrition, dehydration, and weight loss due to chronic poor oral intake remains one of the largest, silent epidemics [4]. A major risk factor for experiencing nutritional problems is cognitive impairment (dementia), and approximately 65 % of NH residents have documented moderate to severe dementia [5]. When a PWD loses the ability to self-feed adequately, mealtime support from NH staff becomes critical for their nutritional health. In 2013, the national average of the "percentage of long-stay residents who lose too much weight" was 7.5 %, a rate higher than falls (3.3 %) and pressure ulcers (6.4 %) [2]. Yet, under-nutrition due to mealtime difficulties is a largely preventable, reversible problem.

Seeking a Solution

While several members of the health care team may play important roles in dealing with feeding issues in PWD in other settings (see subsequent section), in the long-term care (LTC) setting it is the nursing staff that interacts most directly with patients during mealtimes and it is they who have the best opportunity to assess and address mealtime challenges. However, current training programs for direct care workers, certified nursing assistants and licensed nursing (cumulatively referred to as nursing staff), do not include content on dementia feeding skills [6, 7]. Certified nursing assistants (CNAs) typically provide about 90 % of feeding assistance to PWD, and interventions used are learned "on the job" and are typically non-evidence-based [7, 8]. Recent work provided evidence that when a group of nursing staff observe the identical mealtime experience, they frequently develop quite different interpretations of the meal and interaction: for example, believing a resident was refusing food halted one staff member's attempts, while another staff member who saw the same resident's repetitive behaviors as a misunderstanding of eating was able to alter the routine and achieve a successful interaction during which food was consumed [9]. In 2003, the first nursing clinical practice guidelines for dealing with mealtime difficulties were published, and they were updated in 2008 and 2012 [10, 11]. In 2010, the American Medical Directors Association (AMDA) published clinical practice guidelines for altered nutritional status in the LTC setting [12]. In subsequent sections, we will provide recommendations to foster clinical integration of various disciplinary approaches and offer mealtime interventions that are personalized to individual PWD and thus most likely to be effective.

Causes of Mealtime Difficulty in Persons with Dementia

Underlying causes of mealtime difficulties can be framed through the lens of problems with the place (environment), with the people (caregiver interactions), and with the person (with dementia) [13]. We will use this framework that is more easily taught to caregivers, illustrated in Table 18.1, to address

Table 18.1 Precipitators of mealtime difficulties for persons with dementia

Person	People	Place
Physiologic:	Poor continuity of care during transitions	Poor quality of diet offered
Appetite/food intake regulation	Outside staff unaware of usual needs/patterns	Unappetizing dining environment (odors, sounds)
Oral health problems	Inadequate oral care provided	Disruption of meal routines
Dysphagia or swallowing issues	Sensory equipment not provided or not functioning	Mismanagement of snack/med-pass selections
Sensory impairments	Nonfunctional positioning; left in bed for meals	Medication mismanagement
Altered absorption or digestion		Adaptive equipment not provided
Acute and chronic diseases, associated therapies		Inadequate lighting
Constipation		
Pain		
Difficulty with self-feeding (physical or neurological disability)		
Dependence on enteral or parenteral feeding		
Psychological:	Lack of family involvement	Social interaction at meals de-emphasized
History of poor nutrition habits	Burn-out and/or compassion fatigue of families and staff who are tired and burdened with lack of resources, support	Inadequate staffing
Depression		Lack of involvement of families or significant others at meals (could be not welcomed by agency)
Dementia		Distractions—noise, television
Other cognitive impairments		
Long-standing emotional or mental illness		

complex, yet common, mealtime challenges encountered, including broader environmental considerations and caregiver behaviors and how they may be interpreted by PWD. This multilayered approach has been supported in a model introduced in the mid-1990s that shifted the thinking of care for PWD from caregiver focused to providing person-centered care for this vulnerable population, the Need-Driven Dementia Compromised (NDB) Model [14]. When a dementia-related behavior is exhibited, the underlying premise is that the PWD is attempting to communicate an "unmet" need. The NDB Model provides a problem-solving framework by prompting caregivers to examine the behavior through the lens of more stable, background factors (e.g., lifetime habits and routines, physical health, physiological factors) and adaptable proximal factors (e.g., caregiver interactions, environmental factors). By carefully examining background (change the person) and proximal factors (change the place and/or people) that may contribute to or be antecedents to "problematic" behaviors, caregivers can look for a reversible or modifiable factor to alleviate dementia-related mealtime behaviors.

The Interdependent Roles of the Caregiving Team

The study of mealtime difficulties related to dementia has increased in prevalence over the past 30 years [15]. As this clinical condition is observed by many members of the interdisciplinary team, each discipline is able to focus on alleviating mealtime difficulties from different perspectives. When there is clear communication among team members, this creates the best possible condition for effective care management.

Physician/Nurse Practitioner/Physician Assistant

The key role of these health care providers in minimizing the impact of mealtime difficulties is to address modifiable issues that may be interfering with food and fluid intake. Examples include treatment of acute illness, addressing oral and/or swallowing problems, and adjustment of medications that might interfere with appetite or ability to optimally participate in a meal. These team members may also prescribe/provide oral high-density protein supplements or appetite stimulant agents; the former has been found effective in a systematic review while the latter have questionable efficacy in this population [16].

Dietitians and Dietary Managers

Patients with cognitive decline frequently have poor nutrient intake and weight loss associated with increased morbidity and mortality [17]. The Registered Dietitian (RD) plays an integral role in the nutritional care of elderly PWD in a variety of areas, including oversight of the overall nutritional adequacy of the meals and supplements being provided, whether orally or enterally [18]. The RD is responsible for menu planning that balances micro- and macronutrients, provides the appropriate amount of calories, and allows for appropriate modifications for therapeutically modified diet and texture prescriptions [19]. Often the RD acts as an advocate for the resident so as to tailor severe dietary restrictions to better match individual preferences, especially when life expectancy is not long [20]. Additionally, RDs are responsible for the evaluation of the nutritional status of all residents, including PWD, using anthropometric and clinical measures. Quick nutrition intervention when there are changes in these status indicators can lessen negative trajectories and improve quality

of life for these residents. The RD is thus a key contributor to the management of comorbidities, being responsible for the development of revised nutrition care plans related to new medical issues that may arise (e.g., pressure ulcers, recent weight loss) and for discussing end-of-life issues surrounding enteral nutrition with the family caregivers. It is common for PWD to be receiving enteral nutrition by tube feeding; the RD is responsible not only for the composition of these feedings but also may provide a careful discussion of these decisions with family members and the interdisciplinary care team [18].

Of utmost importance is the need for collaboration and coordination of care among all members of the care team. In some LTC settings, especially smaller institutions, RDs are not available on a full time basis but work as consultants, visiting the facilities on a part time basis. So it is especially important for RDs to work closely with all the other members of the team, especially those who have direct daily contact with the resident. The RD works with Certified Dietary Managers to plan and implement dietary interventions for residents that are tailored to their needs, as prescribed by the physician, and to plan/implement prescribed meals that are visually appealing and with appetizing aromas. Keller et al. [21] found that allocating additional RD time to residents with dementia, while further individualizing their meal plans, resulted in positive outcomes in relation to weight maintenance.

Nursing

Nursing's role on the team includes coordinating each team member's contribution for problem-solving, inclusive of Registered Nurses (RNs), and through other levels of professional nursing. Licensed Practical Nurses (LPNs) and CNAs monitor meal intake and changes in condition on a daily basis, monitor bowel and bladder contributing factors, provide the direct feeding assistance required for meals, and monitor environmental considerations that may impact meal intake. Additionally, they may have the greatest contact with family or friends who could be welcomed at mealtimes and their assistance of the PWD could be tailored through teaching them to use the Change the Person, People and Place model [12].

Consultant Therapists

Social Worker

This specialist is consulted when depression or other affective impediments to adequate dietary intake are a concern. As a liaison to friends and family, they can obtain critical information about past preferences, practices, and cultural issues that could be enacted at meals. In many NHs, they update information about end of life wishes, including use of artificial nutrition and hydration. The social worker may also assist when PWDs need assistance in getting access to food programs and related services when discharged.

Speech Language Pathologist

The speech language pathologist (SLP) conducts instrumental swallow assessments when dysphagia is suspected. Based on these evaluations the SLP may recommend changes in food/fluid viscosities and textures to improve oral intake while avoiding the risk of aspiration, and swallow exercises or technique changes for people with mild cognitive impairment or early-stage dementia.

Occupational Therapy

This specialty may be consulted for assistance with the external limitations to being able to self-feed. These specialists often approach the problem from the perspective of recommending adaptive equipment related to meals (e.g., built up plates and silverware), positioning devices and environmental adaptations.

Physical Therapy

Another determinant of meal intake is the physical ability to take in the meal. The physical therapists may offer strategies to improve upper extremity strength and reduce the development of hand/arm contractures through exercises that build strength and/or promote better range of motion.

Family Caregivers

Family caregivers play an important role by being able to provide a social and cultural history for PWD that may impact nutrition. Examples of information provided include food preferences, normal body weight, and daily eating patterns. Reviewing specific mealtime difficulties and associated factors with the family caregivers may provide contextual insight and assist with development of problem-solving strategies. The family caregiver may also be particularly effective in assisting with mealtimes by providing social support as well as feeding assistance.

Interdisciplinary Team Approach

All members of the interdisciplinary team should document results of care plan meetings and goals of care set in conjunction with legally authorized representatives in the medical record. Documentation should include the extent of the nutritional problems, a description of all identified or probable contributing etiologies, and the prognosis. Updates to the care plan should be ongoing, and indicative of appropriate palliative care measures, with progress notes maintained indicating effectiveness of the plan. In addition, Advance Directives should be documented (e.g., desires for Artificial Nutrition and Hydration, Do Not Resuscitate [DNR] and/or Do Not Hospitalize, and/or Medical Orders for Scope of Treatment [MOST] forms).

Assessment of Mealtime Difficulties in Persons with Dementia

In LTC settings, often times the first sign that a PWD is experiencing a mealtime difficulty is weight loss. Weight loss is defined by the Minimum Data Set (MDS) 3.0 as unplanned weight loss of 5 % in 1 month or 10 % in 3 months [22]. This is true even when the current body mass index (BMI) is normal or elevated since excess body fat can mask low levels of lean muscle mass. When weight loss occurs, careful investigation into potential reversible causes is the cornerstone of quality care.

Evaluation of Compromised Meal Behaviors Using the Need-Driven Dementia Compromised Model

Aversive feeding behaviors have been identified in the current literature as: clamping mouth shut, turning away of the head, pushing away assistance, holding food in the mouth, refusing to swallow, and/or allowing food to drop out of the mouth [23]. These behaviors were identified in the mid-1990s and subsequently tested by a tool known as the Edinburgh Feeding Evaluation in Dementia Scale (EdFED) [23–30]. More recent work has grouped these feeding difficulties according to their occurrence during the phases of the feeding cycle, which are initiating self-feeding, maintaining attention, getting food to the mouth, chewing food, and swallowing food [31].

When the EdFED was developed, much of clinical care provided to PWD was viewed from the perspective of the caregivers. Behaviors were interpreted as interfering with clinical care and the tasks needing to be completed. When viewed through the NDB Model, the behaviors are seen as meaningful and can be useful when providing and planning care [14].

When these behaviors are seen as meaningful forms of communication, it becomes more appropriate to refer to them as dementia-related mealtime behaviors, which carries less of a negative connotation. When caregivers interpret dementia-related mealtime behaviors as an attempt by the PWD to communicate preferences such as food or fluids desired at that moment in the meal, needing more time to chew/swallow, and/or an attempt to exert some control over the meal assistance process, caregivers tend to spend more time providing feeding assistance and the PWD consumes more food [32–34]. Conducting a meal observation to determine which dementia-related mealtime behaviors are being exhibited and at which point in the feeding cycle they occur provides the basis for beginning to solve mealtime difficulties.

Background Factors: Change the Person

Neurologic/Cognitive

The loss in ability to self-feed has been linked to disease progression, weight loss, and functional decline [35, 36]. As a person moves through the disease trajectory, caregivers should anticipate changes in functional, motor, and sensory abilities. As these changes occur, PWD will need more caregiver support at meal time. Assessment of cognitive ability can be achieved by routine Mini Mental State Examinations (MMSE) and comparing results over time, in addition to use of the MDS 3.0 Brief Inventory for Mental State (BIMS). Both instruments assess/screen attention, memory, visuospatial ability, and language skills.

As cognition declines, it impairs the ability of the person with dementia to initiate and maintain self-feeding. As a person becomes more dependent, behaviors may emerge that may often be interpreted as aversive or resistive. Use of the EdFED can provide insight into the types of behaviors observed and whether or not they are active (e.g., clamping mouth shut) or passive (e.g., allowing food to fall out of the mouth) [11].

Health Status

Changes in instrumental activities of daily living (IADLs) and ADLs may signal diminished functional ability and a requirement for more caregiver support. In early dementia, the loss of one or more IADLs, such as the ability to use the telephone or pay bills correctly is where family caregivers may

notice deterioration. In long-term care settings, changes in ADLs will likely be the indicator that PWD need more caregiver support.

In addition to cognitive assessment, assessment of affective state should be conducted. In situations where the PWD still has the ability to communicate feelings with words; use of the Geriatric Depression Scale (GDS) would be appropriate. In the later stages of dementia, observation of behavior may provide insight into whether or not a PWD is expressing sadness, anxiety, boredom, or loneliness. Caregivers may see an emergence of repetitive vocalizations, or increased agitation as attempts to communicate affective difficulties.

Review of Vital Signs/Lab Work and Weight Patterns

The examination of vital signs and weight patterns over the past 6–12 months is a critical factor when beginning to assess a PWD exhibiting weight loss. This information is critical for providing insight into a slow and insidious weight loss, versus a more acute change in condition. In the NH, body weights for residents have emerged as a principle monitoring and screening indicator [12]. Weights are reasonably accurate, noninvasive, acceptable to patients, and fairly inexpensive indicators to maintain [12]. Weights should be obtained at admission, weekly thereafter for 4 weeks to establish baseline, and then monthly thereafter if weight is stable [12].

Any change in vital signs must be investigated for an underlying cause, including differential diagnoses of an infectious process. Assessment of blood chemistries can provide insight into correct dosing of certain medications, elevation in white blood cell counts, and or other hematologic changes that could contribute to or be an indicator of an acute change in the physical condition. Serum albumin is the most frequently used biomarker for establishing protein malnutrition and can provide insight into nutritional status in the previous 3 weeks; however, this is a stress-related marker and the level may be indicative of chronic inflammatory states [12]. Serum pre-albumin has a shorter half-life and may be a better indicator for acute responses to nutritional interventions [12]. Assessment for hypermetabolic states is critical for adequately treating conditions such as hyperthyroidism or a malabsorption syndrome [12]. Baseline laboratory assessments should include a complete blood count, basic metabolic panel, drug levels as indicated, hemoccult, thyroid-stimulating hormone, urinalysis with culture and sensitivity as indicated, and testing for malabsorption syndromes [12].

Meal Intake and Bowel Movement Review

When a PWD begins to lose weight, caregivers must begin the process of assessing how and why the weight loss is occurring. In skilled nursing homes, all residents are monitored every shift for percentages of meal intake and the occurrence of bowel movements. Meal intake must be examined for patterns that can help identify the causes of weight loss. For example, if the PWD is indicated to be eating 100 % of every meal served and yet still losing weight, perhaps not enough food is being offered at each meal time. Another example would be a pattern of every breakfast intake being 0 %, and lunch and dinner patterns being 100 %; this would prompt investigation into reasons why the person isn't eating breakfast. Possible reasons might include being too sleepy at breakfast or not liking the types of foods offered at the breakfast meal. Meal patterns should be investigated with direct caregivers to determine the underlying problem, some of which might be easily modified (e.g., serve breakfast at a later time in the morning). Constipation is a common problem in older adults that can contribute to reduced food intake by causing bloating and abdominal discomfort. This is an easily modified, reversible condition that caregivers can identify for appropriate intervention. Absence of bowel movement documentation of 3 days or more is the "gold standard" for identifying and intervening for constipation.

Other assessments for determining potentially reversible causes for low meal intake include determination of stage of dementia, screening for depression, identifying any medications that might contribute to low intake, and dealing with underlying nausea, vomiting, or diarrhea, fluid retention and/or edema, or infection [12].

Psychosocial Factors

Knowing the personal life history of the PWD may help put mealtime difficulties into context. A PWD's age, gender, personality type, previous occupation, history of psychosocial stress, and general behavioral responses to stress are important factors in identifying potential triggers for behavioral problems [14, 37]. Adaptive strategies that were used as coping strategies by the PWD prior to cognitive impairment may not work when the PWD no longer has control over their environment. An example follows:

A PWD is exhibiting anxious behaviors that frequently interrupt the evening meal (e.g., wringing of the hands, repetitive smoothing of their hair). In a discussion with the family caregiver, the staff determines that this behavior is associated with fatigue and that the PWD was accustomed to an afternoon nap in her past routine. The staff institutes an afternoon rest period that helps to alleviate the anxious behavior, dinner intake is improved, and the addition of an anti-anxiety medication is avoided.

Proximal Factors: Change the People, Change the Place

Personal Factors

Emotional Fact-ors. Depression is a common culprit in weight loss in LTC settings, and is a treatable etiology [12]. Mealtimes are the greatest opportunity for social interaction, yet many direct care workers treat meals as simply a task to be completed [38]. Determination of the amount of support needed, and the amount of time needed to provide social interaction while increasing meal intake is vital. Family caregivers, when available, may be able to help either directly or indirectly when emotional factors interfere with meal intake.

Physiological Determinants of Intake. Potential physiologic etiologies for weight loss include frank anorexia. However, a milder but long-term disparity between energy expenditure and intake can also lead to weight loss [12]. Assessment of meal intake less than 75 % is often associated with weight loss, but if a person with dementia is eating 100 % of meals and weight loss is still occurring, assessment of energy expenditure is critical. Registered Dietitians can assist the team by estimating caloric needs, while nursing can provide information on repetitive movements, fidgeting, rocking, and/or wandering that can contribute to weight loss by elevating energy expenditure [12].

Other physiological factors that may contribute to poor food intake include dry mouth, oral, or dental pain. PWD should be evaluated by a dentist, preferably with a specialization in geriatrics, for poor fitting dentures, broken teeth or decay, or gingivitis [12]. CNAs should be instructed in proper methods to promote oral hygiene in dependent persons. Swallowing ability should be carefully observed and it may be necessary to discuss a swallowing evaluation with speech therapy [12]. The continuation of previously prescribed therapeutic diets (e.g., low sodium, low fat diets) needs to be carefully weighed in risk/benefit discussions with the interdisciplinary team and legally authorized representatives.

Table 18.2 Recommendations for improving the physical and social environment[a]

Physical
• Choose the dining environment best suited for the individual PWD (resident room, dining room, or other location). Some PWD may eat more food when less activity is going on around them, while others may benefit from increased social interaction
• If traffic of other staff or residents is distracting to the PWD, limit or eliminate these interruptions during the mealtime
• Adequate staffing to assist in all aspects of mealtime care including oral care after meals, provision of adaptive equipment and functional positioning for seating
• Food preparation close to eating environment may provide smells associated with mealtimes, another cue that it is nearing time to eat
• Music from the PWDs cohort that promotes a calm environment
• Adequate lighting, and contrasting table cloths/placemats. Be sure cups, plate, and silverware are on contrasting background. Reduce glare
• Adaptive equipment as needed and suited to PWD ability
Social
• Consistent seating if dining environment promotes meal intake
• Caregivers should talk with the PWD about the meal, explain what items are, and provide verbal and visual cueing as appropriate
• Position PWD so that eye contact can be made; may sit in front of PWD or to the side if providing hand-feeding assistance
• Family members should be welcomed into dining experience and share meals with PWD, if appropriate

[a]Adapted from [10]

Functional Performance. The ability of a person with dementia to feed themselves independently must be assessed with consideration given to the person's ability to initiate a meal and difficulties in using proper utensils, scooping the right amount of food, recognizing the amount of food provided, maintaining attention while eating, and/or maintaining alertness during a meal [36, 39, 40]. Upper extremity ability, positioning, fine-motor ability for holding utensils and/or finger foods, and any difficulty chewing or swallowing should be assessed and taken into account [12].

Physical and Social Environment

A list of recommendations for improving the physical and social environment is provided in Table 18.2 and more specific details are discussed in the following paragraphs. When possible, low-intake meals should be observed for potential problems. The nature of caregiver interactions (positive or negative) can strongly impact a PWD's meal intake [33]. For some, it may improve if a family member or friend is present; it has been shown that eating with a family member or caregiver increases calorie intake in homebound older adults [41].

Meal observations can provide insight as to whether or not a change has occurred in the level of support needed with feeding assistance, and/or if an environmental change might be necessary. Noise levels, dining area traffic, inability to maintain attention on the meal, and position in dining room can all contribute to distractibility at mealtime.

Light Level, Noise Level, and/or Temperature. The physical environment is touted as a vital component for dining. Where one eats can be as important as what one eats, and providers can ask themselves if they, too, would be willing to eat in the conditions under which LTC residents consume their meals [11, 12, 37]. Every effort should be made to make the dining setting comfortable and familiar (*not* in bed if at all possible). Cleanliness and lack of clutter, adequate lighting and contrasting colors to enhance visualization are basic considerations for supporting adequate meal intake [11, 12, 37, 42].

Dining Ambience. It has been suggested that the smells of freshly cooked foods can be used to stimulate appetite. The difficulty with this in LTC settings is that the kitchen is often in a location far from resident and dining rooms. If possible, some food items can still be prepared and cooked on the unit to provide the aroma, such as baked bread or vegetable soup. Some facilities have achieved the same effect by infusing essential oils of vanilla, cinnamon, or apple pie spice into the dining area.

Staff Stability and Staff Mix. The critical importance of staff training and stability factors for ensuring a well-trained and skilled workforce to care for persons with dementia cannot be over-emphasized. Consistent assignment of staff to work with PWD allows for staff to get to know the individual resident and respond to mealtime behaviors in ways that permit the meal to continue. By appropriately responding to the cues given by the PWD, meal intake is maximized. For example, a staff member working with the same PWD every day would know that the PWD holding food in their mouth will do so until a drink is offered. Rather than interpreting the behavior as negative and ceasing feeding attempts, a drink is offered and the meal continues.

Choosing the Best Course of Nutritional Care for the PWD

When determining which interventions are most appropriate for any given individual PWD, discussions with the interdisciplinary team and family members/legally authorized representatives are a vital part of goal-setting as the prognosis is discussed [12]. The most important and obvious goal is to promote self-feeding as much as possible, offering support only when functionally challenged or fatigued but still hungry to finish meal. Many recommendations for promoting this goal have been discussed in the preceding sections; they are also summarized at the end of the chapter. Depending upon where the PWD is in the disease process, goals of care should be established for maintenance or end-of-life management (end-stage dementia) [12]. Advance Directives should be reviewed for insight into wishes related to artificial nutrition and hydration through Living Wills. Plans of care should include interventions for each identified risk factor and/or potential etiology identified in the assessment. However, all caregivers, both professional and family/friends, need to realize that even the most individualized care strategies may not be successful in altering mealtime issues; the overall goal then becomes maintaining dignity and quality of life. Because of its critical importance in determining the best nutritional quality of life for the PWD, the closing sections of the chapter are devoted to a discussion of the benefits and risks of tube feeding versus careful hand feeding for those with advanced dementia.

Weighing the Risks/Benefits of Percutaneous Endoscopic Gastrostomy Tube (PEG) Feeding

As dementia progresses, loss of the ability to swallow and/or consume adequate food/fluids to sustain life are features of the disease and indicative of entering end-stage dementia. This stage in the disease process can create tremendous moral and ethical dilemmas for family members and/or legally authorized representatives regarding whether or not to maintain continued careful hand feeding or opt for tube feeding placement. The decision to place a feeding tube (or not) must be a well-informed decision based on current evidence and accurate information. At the point the decision needs to be made, families need support answering questions including but not limited to:

- Are there advance directives indicating a preference for life-sustaining artificial food/fluids?
- If the person with dementia could speak for themselves, would they want the current quality of life prolonged until death?

- Will the nutritional intervention have a significant positive impact on the person's overall condition or prognosis?
- What does the patient or family hope to achieve by placing the tube feeding—what is the desired outcome?

Families and residents need to be aware that placing a feeding tube does not decrease risk of aspiration or risk of pressure ulcer development, nor does it decrease a person's risk of suffering. In fact, quite often feeding tubes placed in persons with dementia cause agitation, discomfort, diarrhea, abdominal pain, and increased risk of local complications [12, 43, 44].

Careful Hand Feeding as an Alternative to PEG Feeding

Thoughtful consideration for engaging a person with dementia with actual food intake is an ethical and moral consideration that is often overlooked by harried staff who simply want to complete the task of providing food to residents. Careful hand feeding is a viable alternative to PEG feeding and we believe that in most cases it is the preferable intervention to support oral intake of food and fluids for PWD. This recommendation, that tube feeding should not be the approach for persons with late-stage dementia, was recently supported by two major professional medical groups – the American Geriatrics Society and the American Academy of Hospice and Palliative Medicine [45]. Our recommendation reflects the shift in thinking that moves the plan of care from curative to care focused. Careful hand feeding requires time and a highly skilled workforce to adequately and appropriately support a PWD during mealtimes [46, 47]. Unfortunately, careful hand feeding has not yet been recognized as a reimbursable nursing skill and therefore long-term care facilities only receive compensation for feeding tube management [48].

Three techniques for hand feeding are illustrated in Fig. 18.1. Current clinical practice guidelines for hand feeding present the first two techniques as evidence-based options for providing feeding assistance, namely direct hand and hand over hand feeding [37, 47, 49, 50]. *Direct hand feeding* is the most widespread hand feeding technique and is accepted in common practice for providing meal assistance to those who require it. *Hand over hand* is seen as a second option if a person still has fine motor ability to hold a utensil and simply need guidance in getting the utensil from the plate after acquiring a food item, to the mouth. The caregiver places their hand *over* the person's hand (holding the utensil), moving it towards the mouth. From the perspective of the PWD, this may inherently feel like the caregiver is forcing their hand towards their mouth; as such, it may elicit an aversive behavior of pushing the caregiver's hand away.

Evidence is emerging that a third hand feeding technique, *hand under hand*, exists and should be considered a third, viable careful hand-feeding technique [51, 52]. Hand under hand feeding assistance is beneficial for persons with dementia who have lost fine motor skills to hold the utensils, but still have gross motor skills. Hand-under-hand feeding assistance requires the caregiver to hold the utensil, and place their hand *under* the PWD's hand. From the perspective of the PWD, this feeding assistance elicits feelings of control over the movement, and feeling as though they initiated the movement. Evidence supports the benefit of providing persons with dementia verbal and auditory cues with meals, in agreement with the hand-under-hand technique, which provides a motor cue for a lifelong movement associated with intake [51, 52]. Further study is needed to determine under what conditions each hand-feeding technique would be most appropriate, and what intra-individual differences predict the best technique to use.

Fig. 18.1 Hand feeding (a) is the most commonly used hand-feeding technique, but should be reserved only for fully dependent persons. The hand-over-hand technique (**b**) is an option if a person still has sufficient fine motor ability to hold a utensil; it is used to guide a person's hand towards his/her face. A third technique is the hand-under-hand feeding approach (**c**). For persons with dementia, this approach may elicit more of a sense of control over the movement and allow them to feel as though they initiated the movement. Figures courtesy of Melissa Batchelor-Aselage

Clinical Recommendations

1. Individualized interventions are critically important to prevent chronic under-nutrition due to on-going mealtime difficulties in PWD.
2. An interdisciplinary approach is the best way to focus on alleviating mealtime issues; clear communication among team members creates the best possible condition for effective care management.
3. Based on the Need-Driven Dementia Compromised Model, caregivers are prompted to examine the background (change the person) and proximal factors (change the place and/or people) that may contribute to "problematic" behaviors and look for reversible or modifiable factors.
4. Self-feeding should be promoted for PWD whenever possible, offering support only when functionally challenged or fatigued but still hungry to finish the meal.
5. Careful hand feeding is a preferable alternative to PEG feeding to support oral intake of food and fluids for PWD with end-stage dementia.

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Chapter 19
Nutrition at the End of Life

Michi Yukawa and Christine Seel Ritchie

Key Points

- The majority of patients, patients' families, and friends consider nutrition and fluid intake as an essential part of life and not an aspect of medical treatment. As such, health care providers need to be sensitive to the complex psychosocial issues surrounding decisions regarding food and fluid intake in terminally ill patients.
- Case law in the United States considers artificial nutrition (enteral and parenteral) to be medical treatment and thus recognizes a patient's right to refuse artificial nutritional support.
- During discussion of feeding options, health care providers should keep in mind the overall goals of care for the patient and frame the conversation with patients, patient's families, and friends focused on their goals, whether it is for curative treatment, rehabilitative treatment, or comfort-focused treatment.

Keywords Nutrition support • Terminal illness • Palliative treatment

Introduction

Nutritional support during the final phase of life is an important and sensitive issue that must be addressed through careful discussion between patients, the patient's loved ones, and the health care team. Because food is an integral part of day-to-day life, the loss of interest in or the inability to partake in this activity often causes great distress for caregivers. Furthermore, caregivers view provision of food and hydration as basic care and not medical treatment, and as such they frequently struggle to determine which feeding options to choose for their loved ones. In the final weeks of an individual's

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life, the issues central to decisions about nutritional support shift to a cautious weighing of its burdens and benefits. Therefore, health care providers need to be well versed in the issues surrounding nutrition and hydration in terminal illness in order to assist patients and their families in treatment decisions. This chapter will focus on the benefits and limitations of nutritional support in the final *weeks to months* of life. The principles presented in this chapter may not be generalizable to populations with a longer life expectancy, even if the underlying disease process is similar.

Definitions

Comfort feeding only/recreational feeding is assisted oral feeding provided by a caregiver to provide food or fluid as requested or desired by the patient [1]. Feeding of this kind may not provide adequate nutrition or hydration for patients; the goal is enjoyment for the patients. *Non-oral feeding* means giving nutritional support through a nasogastric tube, gastrostomy tube, or gastrojejunostomy tube. Providing water or electrolyte solution via non-oral route is *artificial hydration. Artificial nutrition* includes enteral nutrition by nasogastric tube, percutaneous endoscopic gastrostomy tube, percutaneous jejunostomy tube, gastrostomy tube or gastrojejunostomy tube, and parenteral nutrition.

Legal, Religious, and Ethical Precedents for Decision-Making

Multiple legal decisions are available to provide guidance to physicians concerning the nutritional treatment of terminal patients. In the Karen Ann Quinlan Case of 1976, the court upheld the right of individuals to forgo life-sustaining care and enabled her parents as surrogate to make treatment plans on behalf of Ms. Quinlan [2]. The Barber Case in 1983 involved a patient in a deep coma after cardiopulmonary arrest following surgery to close an ileostomy. A California lower court initially indicted two physicians who stopped intravenous fluids and feeding tubes for murder [3]. However, the spouse testified that the patient had stated "no Karen Quinlan" and thus the appellate court dismissed the murder charges because the charge of murder requires proof of an act of commission. The distinction between acts of omission and acts of commission is central to discussions of the ethics of terminal nutrition and hydration. Acts of omission may be unlawful if there is a known duty to act. There was no duty to act in the Barber Case because of the patient's known prior wishes for no treatment [3].

In 1986, the appellate court in the Bouvia Case ruled that refusal of medical support by a competent patient is a fundamental right. The patient was a 29-year-old female with severe cerebral palsy who was bedridden, immobile, in constant pain, and competent to make her own medical decisions. A feeding tube was placed against the patient's wishes. The patient then petitioned to remove the feeding tube. The lower court refused the petition, stating it was a form of suicide. An appeals court later ruled in favor of the patient [4]. In the 1990 Nancy Cruzan case, the parent of Nancy Cruzan, a woman in a persistent vegetative state, requested cessation of nutritional support. The US Supreme Court stated that patients have a right to die and that competent patients can refuse therapy. They also made it clear that artificial nutrition/hydration was no different than any other medical treatment. However, they also concluded that the state (in this case, Missouri) can set its own evidentiary standards regarding what is considered clear and convincing evidence of the patient's wishes to withdraw life support [2].

Although the courts see artificial nutrition/hydration (ANH) as medical treatment, many patients and caregivers do not share this opinion; they see ANH as basic treatment that cannot be withdrawn. This tension around ANH is demonstrated by the fact that many states have separate additional statutory requirements for ANH, beyond that required for other forms of medical treatment [5, 6]. This tension was also made manifest in the Terry Schiavo case, a case where there was substantial

public disagreement regarding the ethics of discontinuing tube feeding in a woman in a persistent vegetative state [7].

Religious, cultural, and personal views often influence and take precedence over prevailing legal/ethical positions on ANH. Prior to Terry Schiavo's case, the National Conference of Catholic Bishops stated that "Catholics are not obligated to use extraordinary or disproportionate means where there is no hope"; nevertheless, they also recommended a "presumption in favor of providing nutrition and hydration to all patients, including patients who require medically assisted nutrition and hydration, as long as this is of sufficient benefit to outweigh burdens involved to the patients" [8, 9]. However, since the Schiavo case, the Catholic position on ANH has become less clear [10]. According to the most recent two Popes, providing nutrition and hydration is considered "ordinary care" and not an extraordinary life preserving measure. The US Conference of Catholic Bishops in November of 2009 stated that Catholic health care facilities should offer food and water and even ANH to all patients regardless of their irreversible condition [10]. However, the Bishops' list of exceptions include use of ANH in cases where it will fail to prolong life or is "excessively burdensome or causes marked physical discomfort" [10].

Other religions such as Orthodox Judaism promote the continuation of ANH once it has been started [11]. Buddhists believe that a person who dies of hunger will become a hungry and restless soul and thus some Buddhists may also prefer ANH at the end of life [12]. However, in Hindu culture, decreased oral intake is often considered an indication of imminent death and not a cause of death. They view voluntary reduction of nutrition and fluid as a terminally ill person's preparation for an expected death in a self-controlled and dignified manner [12]. Therefore, they may be less likely to choose ANH at the end of life.

The lack of public consensus surrounding ANH requires that health care providers pay close attention to the burden and benefit of ANH and make sure patients and their proxies understand as fully as possible the benefits, burdens, and uncertainties associated with these therapies. Only then can patients or their caregivers truly determine what is consistent with their values and priorities.

In summary, case law in the United States confirms that enteral nutrition is medical treatment and not basic care. Patients have the right to refuse this form of medical treatment. Withdrawal of artificial nutritional support to allow a patient to die is not equivalent to euthanasia. In the former instance, the goal of discontinuing therapy is to remove burdensome interventions in the setting of a life-threatening or terminal condition; in the latter, the intended result is the death of the patient.

Nutrition and Hydration in Advanced Illness

The scientific literature provides sparse guidance regarding the benefits and burdens of nutrition and hydration at the end of life, with most studies conducted in cancer or advanced dementia patients. A few studies have begun to address patients' perspective on ANH at end of life and quality of life for those terminally ill patients.

Artificial Nutrition and Hydration in Terminal Cancer

Malnutrition and unintentional weight loss are cardinal symptoms in advanced cancer, and are poor prognostic indicators. Prevalence of malnutrition and weight loss can range from 46 to 85 % depending on types of cancer [13]. In addition, cancer cachexia, which is associated with metabolic abnormalities, anorexia, early satiety, decreased food intake, and loss of lean body mass, occurs in 80 % of patients in the advanced stages of cancer [14–16]. The underlying pathophysiology of cancer cachexia

is unknown, but it probably is due to combination of tumor burden, effects of cytokines, and adverse effects of cancer treatments [13, 14, 17]. The benefit of nutritional support in cancer cachexia remains questionable. Two systematic reviews of literatures failed to show improvement in survival tumor response, decreased toxicity, or decreased surgical complications in cancer patients receiving enteral nutrition [13, 14, 18]. The only exception may be in GI, head and neck, and esophageal cancer patients who are malnourished [19, 20]. A recent study in esophageal cancer patients demonstrated decreased frequency of hematological toxicities (neutropenia, leukopenia, and thrombocytopenia) in patients receiving enteral nutrition during neoadjuvant chemotherapy [21]. These findings are somewhat equivocal, however, and balanced by studies that question benefit. In a secondary analysis of the Radiation Therapy Oncology Group 90-03 Study, a trial primarily aimed at evaluating four different radiation fractionation schedules in head and neck cancer, findings did not suggest benefit of prophylactic nutrition support (PNS). Whereas patients receiving PNS had less weight loss by the end of treatment and less grade 3–4 mucositis, by 5 years, patients receiving PNS had poorer locoregional control and poorer survival [20].

Artificial Nutrition and Hydration in Terminal Dementia

Dementia is a progressive terminal condition with an average life expectancy of 4–9 years after an initial diagnosis of dementia [22, 23]. The Functional Assessment Staging System (FAST) is one system used to follow the course of Alzheimer's disease thereby helping to decide how far the disease has progressed [24]. There are seven stages in the FAST system, with the first stage comprising essentially no symptoms and the last stage describing advanced, end-stage dementia. At stage six, the patient needs supervision in dressing, bathing, toileting, and eating and becomes dependent on the caregiver. Patients typically either die or are institutionalized after 3 years in this stage. This is the stage when Alzheimer's disease patients may stop eating spontaneously, but can be encouraged to eat. At stage seven, Alzheimer's patients lose the ability to speak, ambulate, eat, and control their muscles and smile. When patients reach this stage it is very difficult to maintain nutrition because encouragement to eat becomes less successful. Patients at stage 7 typically die within a year, and difficulty eating is a marker for the terminal phase of Alzheimer's dementia.

Addressing the Costs and Benefits of Artificial Nutrition and Hydration in Advanced Dementia

Physicians and families have difficulty discussing nutrition support for patients with advanced dementia. Decisions around nutritional support may elicit more emotion from families than ventilator support or cardiac resuscitation. Families may articulate a concern that they are "starving" their loved one. They fear the ill person will not survive as a direct result of not eating. These issues are so difficult that sometimes physicians and families do not initiate discussions around nutrition.

Finucane attempted to address these difficult questions based on the limited clinical data available [25]. He reviewed primary concerns commonly cited as rationale for enteral nutrition, and included aspiration pneumonia, skin breakdown, quality of life, and survival as outcomes. His review of the literature did not indicate that enteral nutrition improved any of these outcomes. However, many of the studies reviewed were not solely of patients with dementia and many had methodological limitations. Multiple other controlled observational studies showed that tube feeding in dementia patients do not improve their survival rate, decrease aspiration risk, or improve wound healing [26–28]. A recent Cochrane review of tube feeding in advanced dementia patients also failed to provide sufficient evidence to suggest benefit in these patients [29]. Enteral tube feeding did not increase survival or prevent pressure ulcers in these patients.

Gillick addressed quality of life issues in nutritional support and found that advanced dementia patients who were tube fed were often deprived of taste, touch, and social interaction [30]. Sanders also evaluated survival with tube feeding [31]. He found that in a nursing home, the patients who were fed by a gastrostomy tube and those fed by hand had the same survival rates. He found that among gastrostomy patients, patients with dementia had a much worse prognosis (54 % 1-month mortality) compared to those without dementia (28 % 1-month mortality).

Despite the results of these studies, nursing home residents with advanced cognitive impairment often receive tube feeding. According to one study, the incidence of PEG tube placement among 97,241 nursing home residents with dementia in the United States was 53.9/1,000 patients with 48.3 % of them dying within a year after PEG tube placement [32]. Furthermore, one survey of primary care physicians in Hawaii showed that decisions to insert tube feedings were associated with internal medicine specialty, family preference, and fear of liability [33]. Another study explored the expected benefit of tube feeding held by physicians [34]. Physicians endorsed more benefit of tube feeding for patients after stroke or for those without ability to eat orally. Even for patients with neurodegenerative diseases, physicians felt that tube feeding would improve nutrition (93 %), hydration (69 %), and prolong life (49 %) [34]. One group of investigators performed an interdisciplinary team education study to teach attending physicians about the evidence suggesting lack of benefit of PEG tubes in advanced dementia [35]. Their intervention trended toward fewer PEG tube placements in patients with advanced dementia [35]. Further education of medicine and surgical subspecialists about lack of benefit of PEG tubes in advanced dementia patients may facilitate more informed decisions about feeding options by patient's family and surrogate decision maker.

Alternative Approaches to Artificial Nutrition and Hydration in Advanced Dementia

In Alzheimer's dementia patients, skillful feeding approaches may provide an effective alternative to artificial nutrition. These include the appropriate selection of food consistencies, and minimization of distractions. Additionally, adequate time for feeding and verbal cuing to chew the food and swallow must occur. The mid-day meal is when food intake is often greatest, and presents an opportunity to effectively focus feeding efforts [36]. "Comfort feeding only" is an alternative method to provide nutrition and fluids to advanced dementia patients. Patients are offered sustenance if they would like to eat or drink and they are not forced. "Comfort feeding only" focuses on patient's individual comfort. This approach allows family members and surrogate decision maker a way to continue nutrition and hydration for patients without the added burden of tube feeding [1].

Artificial Nutrition at Terminal Stages of Other Neurological Diseases

Amyotrophic lateral sclerosis (ALS) is a progressive motor neuron disease which is characterized by progressive paralysis and respiratory failure. The prevalence of malnutrition varies from 16 to 53 % in ALS patients and the mortality rate is 7.7-fold higher for ALS patients who are malnourished [37, 38]. A recent Cochrane review stated that there was insufficient evidence to show survival advantage or improvement in nutrition after PEG tube placement [39]. Since there were no randomized controlled trials, they reviewed prospective nonrandomized and retrospective studies. Some studies showed increased survival rates and improved nutritional status with tube feeding while others did not [39]. Two studies revealed no enrichment in quality of life after instituting enteral nutrition [39]. Another study compared survival rates of bulbar and spinal onset ALS patients after PEG placement, which showed no difference in survival rates [40]. Having low forced vital capacity (FVC < 50 %) and old age were associated with poor prognosis after PEG placement [38, 40]. Therefore, enteral nutrition may be more beneficial for younger patients with bulbar-onset ALS at early stage of the disease.

Parkinson's disease is another neurodegenerative disease, which, at its terminal stage is associated with dysphagia and malnutrition. One small study showed lack of weight gain in patients after PEG placement [41]. In fact, male patients continued to lose weight after starting enteral nutrition. No information was collected on quality of life [41].

Patient's Perspective on Food and Hydration at End of Life

In an often-quoted study, the authors completed a prospective study of patients in a comfort care unit, the majority of whom had cancer or stroke as their terminal diagnosis. The patients were alert and competent. Food was offered and feeding was assisted but not forced. The patients were followed for thirst, hunger, and dry mouth and to see if food or fluid relieved the symptoms [42]. Sixty-three percent of the patients studied did not experience hunger; and additional thirty-four percent reported hunger initially that subsequently resolved. Similarly, 62 % had no thirst or thirst only initially. Most of the patient's symptoms were easily controlled with a small amount of food or water. The authors concluded by stating that hunger and thirst were uncommon in the terminal phase despite food and water intake inadequate to sustain basal energy requirements. Furthermore, a recent qualitative study of patients in Palliative Care Units revealed that patients did not want to be forced to eat and they did not want their weights monitored [43]. Some patients ate to please their caregiver rather than to satisfy themselves [44]. Caregivers who push food on the patient with anorexia may inadvertently contribute to the patient's distress instead of comforting the patient [42]. Less is known about how dementia patients perceive symptoms related to feeding. It is hard to know if patients with dementia experience discomfort from not eating or burdens related to assisted eating because they are noncommunicative at this stage.

Addressing Treatment Goals and Decision-Making for Terminal Patients

When treatment goals are discussed early following the diagnosis of a terminal condition, the patient often can decide for himself or herself what their wishes are regarding ANH at the end-of-life. In this way, the goals will reflect the preferences and values of the patient. Unfortunately, patient's wishes are often not known regarding tube feeding.

When a patient becomes terminal and is nondecisional, there are established guidelines as to how decisions are to be made. The advanced directive, if one exists, is the document that should be consulted first to know the patient's prior expressed wishes. If the advanced directive does not answer the specific question that needs to be addressed, then the legal guardian or the agent of the advanced directive makes the decision based on what they think the patient would have wanted or the wishes previously expressed by the patient. If there is no document and no designated decision-maker, then the first-order relative makes decisions (usually spouse, then adult children, then siblings but this may vary by state). Finally the opinion of other relatives can be considered. If none of the above exists, then the physician's judgment can be used to determine the best treatment for the patient.

Practical Considerations Before Providing Enteral/Parenteral Nutrition and Hydration

Decision making regarding the initiation or discontinuation of tube feeding is never easy. Practical matters may be more likely to influence the decision regarding feeding than ethical principles. In an imminently terminal patient the usual goal of care should be aggressive efforts at optimizing comfort.

This means managing the symptoms of the disease or side effects of the treatment while maintaining optimal quality of life. Thus, the goal of nutrition support in this phase of illness should be to optimize energy and strength while being attentive to potentially negative quality of life effects of coercive feeding or artificial nutrition and hydration. During this time, the clinician will be most effective if they seek to understand the caregiver's feelings and offer input. The caregiver may feel frustrated over the inability to find and prepare foods that are tolerated by the patient. They may also sense that the food they are offering is not providing the comfort that they were hoping for. The caregiver should be educated to understand that the loss of appetite and the inability to eat are common experiences in the terminally ill. Also, physical and emotional changes influence the ability to eat. For example, the disease itself, medications, fear, or depression may make it difficult to eat. Changes in the sense of smell, diarrhea, constipation, and nausea or vomiting also decrease the patient's appetite. Thirst and hunger often are diminished in the dying process. Practical options in caring for the terminally ill include eliminating most dietary restrictions and giving only the amounts of foods and liquids tolerated or accepted. Finally, the patient should be assisted with meals, but not forced to eat. It can be helpful to share with caregivers that (1) withholding nutrition and hydration at the end of life can be beneficial with regard to patient comfort, and (2) the injudicious use of ANH may aggravate symptoms. Without hydration there are less oral and airway secretions, less congestion, coughing and fewer symptoms associated with ascites and edema. In addition, terminal patients cannot always cough secondary to weakness; therefore, aspiration risk increases. Peripheral edema may increase pain and predispose the patient to pressure ulcers. Finally, increased gastrointestinal fluids can cause nausea and vomiting, especially for patients with intestinal strictures or obstruction from neoplasms. During the dying process, dehydration occurs from inadequate intake and losses from GI, renal, skin, and pulmonary secretion. Fluid deprivation at this stage rarely causes headache, nausea, cramps, or vomiting. Dehydration leads to mental changes, which may decrease the patient's awareness of their suffering. Families are sometimes concerned about the dry mouth that occurs as a person dies. Ice chips, sips of liquid, lip moisteners, salivary substitutes, mouth swabs, hard candy, and routine mouth care may all help to relieve the xerostoma (dry mouth) that occurs.

Potential Ways to Assist Families and Surrogate Decision-Makers Regarding Feeding Options for Advanced Dementia Patients

In a previous study of family members whose relatives died of dementia, 71.6 % participants stated that there was no decision about feeding tubes [45]. Furthermore, 13.7 % reported that there was no discussion about feeding tube insertion and 41.6 % stated that discussion about feeding tube was less than 15 min [45]. Family members of patients who died with a feeding tube felt that end-of-life care was suboptimal. These findings led to two studies conducted in 24 skilled nursing home facilities in North Carolina that showed that use of audio, audiovisual, or printed decision aids on feeding options for patients with advanced dementia significantly improved surrogate knowledge of feeding options for their loved ones and reduced decisional conflict regarding assisted oral feeding or tube feeding [46, 47]. Topics discussed in the audio, audiovisual, or printed aid included surrogate decision making, and clinical course of dementia, including development of feeding problems. It also discussed advantages and disadvantages of feeding tubes or assisted oral feeding. This intervention led to higher mean knowledge score about dementia and feeding options as well as increase the frequency of surrogates discussing feeding treatment with a physician, nurse practitioner, or physician assistant. After 3 months, the interventional group used assisted oral feeding more than the control group [47]. Investigators felt that a combination of audiovisual, audio, or printed decision aids and provider discussion may further improve the quality of decision making for surrogates about feeding options.

Conclusion

Caring for patients with a terminal illness such as cancer or advanced Alzheimer's disease is difficult for the family and the physician. The issues surrounding feeding are some of the hardest to resolve. This chapter defines the problems and offers broad guidelines for addressing these challenges.

Decisions regarding nutritional support in end-of-life care should be consistent with treatment goals and patient preference. Case law regards enteral nutrition as medical treatment rather than basic care. With the exception of head and neck cancer and esophageal cancer, no studies have demonstrated improved survival in cancer or advanced dementia with enteral support. In advanced cancer patients, nausea and pain should be addressed and corticosteroids and progestational agents considered. In advanced dementia, emphasis should be placed on oral food intake, allowing adequate time for feeding, avoiding distractions, and using verbal cueing. Every person, family, and physician must decide for himself/herself to what extent to nourish a person with a terminal illness based on available information about the risks and benefits.

Recommendations for Clinicians

1. Before deciding on a specific form of nutritional support, establish treatment goals.
2. In most cases, artificial nutritional support in cancer patients does not improve survival or tumor response, decrease toxicity, or decrease surgical complications.
3. Artificial nutritional support may be appropriate in head and neck cancer patients and esophageal cancer patients who are unable to swallow properly and still have an appetite.
4. Current data do not demonstrate that artificial nutritional support improves survival or quality of life in advanced dementia patients.

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Part IV
Contemporary Diet-Focused Concerns

Chapter 20
Anti-aging Effects of Nutritional Modification: The State of the Science on Calorie Restriction

L. Anne Gilmore, Eric Ravussin, and Leanne M. Redman

Key Points

- Calorie restriction (CR) is a dietary intervention hypothesized to improve quality of life and extend lifespan.
- Prolonged CR has been shown to extend both the median and maximal lifespan in a variety of animal species.
- Mechanisms of this CR-mediated lifespan extension possibly involve alterations in energy metabolism, oxidative damage, insulin sensitivity, and functional changes in both the neuroendocrine and sympathetic nervous systems.
- CALERIE is a randomized controlled trial that is testing the effects of prolonged CR in humans on biomarkers of aging and the rate of living theory hypothesis.

Keywords Calorie restriction • Caloric restriction • Humans • Longevity • Metabolism • Quality of life • Physical activity • Aging • Hormones • Weight loss

Introduction: Calorie Restriction and Lifespan

Aging is considered to be either "primary," that is, the inevitable deterioration of cells and tissues structure and function that occurs independent of disease, lifestyle, and environmental causes, or "secondary," where the decline in tissue structure and function occurs as a result of external influences, including diseases [52]. Attenuation of primary aging results in an increase in maximal lifespan, whereas delays in the progression of age-related disease or secondary aging increase mostly average lifespan. Calorie restriction (CR) has been shown since the 1930s by McCay et al. to retard the aging process [1], extending the median and maximal lifespan in various models and species [2].

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While the exact mechanisms through which CR is able to extend the lifespan have yet to be fully elucidated, CR reduces metabolic rate and oxidative damage, improves markers of age-related diseases such as insulin resistance in diabetes, and has been shown to alter neuroendocrine activities in animals [3]. Results from studies in rhesus monkeys suggest that prolonged CR can also oppose many age-associated pathophysiological changes including learning and behavior changes, plasma insulin concentrations, and resting energy expenditure [4–6]. Since many changes associated with prolonged CR are important to the health and survival of humans, and excessive caloric intake is associated with morbidity and development of chronic diseases, it has become an important research objective to assess the feasibility, the safety, and the effects of prolonged CR in well-controlled human trials.

Calorie Restriction May Alter the "Rate of Living" and "Oxidative Stress"

The aging process may be influenced by CR through a reduction in the "rate of living," [7] leading ultimately to reduced oxidative damage. The rate of living theory suggests that increased metabolism and thus increased production of ROS leads to a shorter life span. An ongoing controversy among investigators appears to be whether chronic CR leads to "metabolic adaptation," a reduction in the metabolic rate that is greater than what is expected for the diminished metabolic mass of the organism [8]. Results from rats and monkeys suggest that most of the collected data should be reevaluated using appropriate methods of normalizing the metabolic rate for changes in metabolic size to truly test this theory [9]. For example, Blanc et al. recently calculated a 13 % reduction in resting energy expenditure after adjusting for fat-free mass in an 11-year-long study of energy restricted monkeys [4]. Recently, however, Selman et al., using doubly labeled water to measure total energy expenditure, reported that calorie-restricted rats expended 30–50 % more energy than expected [10]. Yamada et al. explain that while there is a decrease in resting energy expenditure, calorie-restricted monkeys had an increased physical activity level and intensity, leading to a greater than expected energy expenditure [11].

The "free radical theory of aging" or "oxidative stress" hypothesis is one of the well-supported theories of aging. It is widely accepted that the metabolic rate of an organism is a major factor in the rate of aging and is inversely related to its lifespan [12]. Additionally, since 1–3 % of consumed oxygen is associated with the production of reactive oxygen species (ROS), namely superoxide ($O_2^{\bullet -}$), hydrogen peroxide ($H_2O_2^{\bullet -}$), and the hydroxyl ion ($OH^{\bullet -}$) [13], the production of these highly reactive molecules from normal aerobic metabolism is also in direct proportion to an organism's metabolic rate. Many investigators have shown that modulation of the oxidative stress of an organism through prolonged CR is able to retard the aging process in various species, including mammals [14, 15]. As a result of increased oxygen consumption, aerobic exercise is associated with increased production of ROS in muscle tissues [16]. However, exercise training boosts the antioxidant capacity of skeletal muscle, probably resulting in decreased overall oxidative stress [17]. Mitochondria consume the majority of cellular oxygen resulting in the production of ROS [18]. In humans and monkeys, long-term energy restriction has been shown to induce robust increases PGC-1 and mitochondrial biogenesis, which in turn is hypothesized to delay the onsets of sarcopenia, as well as loss of muscle function [19, 20]. Despite an increase in mitochondrial biogenesis, CR results in improved mitochondrial function, decreased total body oxygen consumption, and therefore decreased production of ROS [21].

Calorie Restriction, Cardiovascular Disease, Insulin Resistance, Type 2 Diabetes Mellitus

Elevated levels of LDL, excessive ROS generation, hypertension, and diabetes are all potential causes for the development of endothelial dysfunction, a precipitating event in the progression of atherosclerosis. These factors are believed to initiate an inflammatory response in the injured endothelial tissue.

Long-term CR is associated with sustained reductions in factors related to endothelial dysfunction in humans, such as decreased blood pressure [22], reduced levels of total plasma cholesterol and triglycerides [23], and reduced markers of inflammation such as C-reactive protein, NFκB, and plasminogen activator inhibitor type-1 [24–27]. A long-term CR study in humans supports the feasibility of using CR to protect against atherosclerosis by showing a 40 % reduction in carotid artery intima-media thickness in CR participants relative to a control group [28]. Additionally, long-term CR counters expected age-related cardiac autonomic changes resulting in function equal to that of an average human 20 years younger [19].

Strong evidence shows that long-term CR in lean and obese subjects improves insulin sensitivity, a mechanism by which CR may act to extend lifespan [23, 29]. Improved insulin sensitivity is due in part to the down-regulation of IGF-1/insulin pathway that results in decreased P13K and AKT transcripts in skeletal muscle [27]. Additionally, prolonged CR reduces fasting glucose and insulin concentration, two factors believed to contribute to the aging process due to protein glycation [30] and mitogenic action [31], respectively. This compelling evidence suggests that weight loss due to CR may be the most effective means of improving insulin sensitivity, thereby decreasing the risk for the development of diabetes mellitus.

Why Calorie Restriction?

Since the first report of prolonged lifespan in rodents more than 70 years ago [1], CR has been gaining momentum as an intervention with the potential to ward off age-associated diseases and delay death. While the first observations were reported in rodents, similar observations have been reported across a wide range of species including yeast, worms, spiders, flies, fish, mice, and rats [8]. While the effects of CR in longer-lived species remains unknown, results reported thus far from three nonhuman primate colonies suggest that CR might have a similar effect in longer-lived species. Two of the largest longitudinal studies in Rhesus monkeys agreed that CR was beneficial on several markers of metabolic health, including weight, body composition, blood lipids, and cancer incidence but disagreed that young-onset CR reduced all-cause mortality and age-related death [5, 32]. Differences in diet composition and supplementation are two possible reasons for the conflicting results as well as a slight CR in the control animals, genetic diversity, and age at time of CR initiation. In humans, data from controlled trials is lacking and, no long-term prospective trials of CR have been conducted with survival being the primary end-point [3]. There is, however, a lot that can be learned from controlled trials of CR where biomarkers of aging are measured and a handful of epidemiological and cross-sectional observations in longer-lived humans, centenarians, and individuals who self-impose CR.

Centenarians from Okinawa

Probably the most intriguing epidemiological evidence supporting the role of CR in lifespan extension in humans comes from the Okinawans [33]. Compared to most industrialized countries, Okinawa, Japan has four to five times the average number of centenarians, with an estimated 50 in every 100,000 people [34]. Reports from the Japanese Ministry of Health, Labor and Welfare show that both the average (50th percentile) and maximum (99th percentile) lifespan are increased in Okinawans. From age 65, the expected lifespan in Okinawa is 24.1 years for women and 18.5 years for men compared to 19.3 years for women and 16.2 years for men in the United States [35]. What is interesting about this population is that a low calorie intake was reported in school children on the island more than 40 years ago and later studies confirmed a 20 % CR in adults residing on Okinawa compared to mainland Japan [36]. A recent estimate of the energy balance of a cohort of Okinawa septuagenarians during youth to middle age suggested a 10–15 % energy deficit [37]. This energy deficit can be attributed to laborious occupations and daily

activities as farmers and a diet that was rich in nutrients yet low in energy density [37]. The nutrient-dense diet of the Okinawans allowed for a negative energy balance while providing an abundance of vitamins, minerals, antioxidants, and flavonoids [38]. Unfortunately, with the increase in American presence on Okinawa in recent years (location of US military base and increased availability of fast food chains), unpublished reports suggest that the longevity-promoting lifestyle (i.e., CR and high levels of physical activity) is threatened and may be reversed.

The Vallejo Study

To our knowledge there is only one study that was designed to test the effects of CR without malnutrition in nonobese humans [39]. This was a study of alternate day feeding in 120 men whereby the 60 participants in the CR group received an average of 1,500 kcal per day for 3 years, whereas the 60 others were ad libitum. This amounted to approximately 35 % CR compared to the control group. While the initial report was brief, analyses conducted several years later [40] indicated that the death rate tended to be lowered in the CR group and hospital admissions were reduced in these individuals by approximately 50 % (123 days for CR vs. 219 days for Control).

Unexpected Calorie Restriction in Biosphere 2

The unexpected low availability of food during the 2-year Biosphere 2 experiment provided a unique opportunity to observe the effects of CR in a group of nonobese humans.

Biosphere 2 was an enclosed 3.15-acre ecological laboratory that housed seven ecosystems or biomes resembling the earth: rainforest, savannah, ocean, marsh, desert, and agriculture and human/animal habitats [41]. For 2 years, eight individuals, including Dr. Roy Walford, were completely isolated within this "mini-world," where 100 % of the air and water was recycled and all the food grown inside. Due to unforeseen problems with agriculture early on, food supply became quickly insufficient. Food intake for the eight individuals was projected at ~2,500 kcal/day and estimates from food records maintained by one of the biospherians suggested diets were restricted by ~750 kcal/day in each person during the first 6 months. The resulting ~15 % weight loss in the Biospherians was associated with many physiological, hematological, biochemical, and metabolic alterations [23, 42] consistent with calorie-restricted rodents and primates, including reductions in insulin, core temperature, and metabolic rate (Fig. 20.1) [32].

Randomized Controlled Trials of Calorie Restriction in Nonobese Humans

As for randomized controlled trials, results from a 2-year study of CR in humans will be known shortly. The National Institute on Aging (NIA) is sponsoring a trial, CALERIE (*C*omprehensive *A*ssessment of the *L*ong-term *E*ffect of *R*educing *I*ntake of *E*nergy), which is, for the first time, scientifically testing the effects of 25 % CR in ~150 nonobese healthy men and women aged 25–45 years. Three clinical sites are involved in the trial: Washington University in St. Louis, MO; Tufts University in Boston, MA; and the Pennington Biomedical Research Center in Baton Rouge, LA. The protocol and endpoints for this multicenter trial were developed from experience acquired in three independent Phase 1 trials conducted at each clinical site [3, 43, 44]. The 2-year CALERIE trial (CALERIE 2) was recently completed and data analyses are underway.

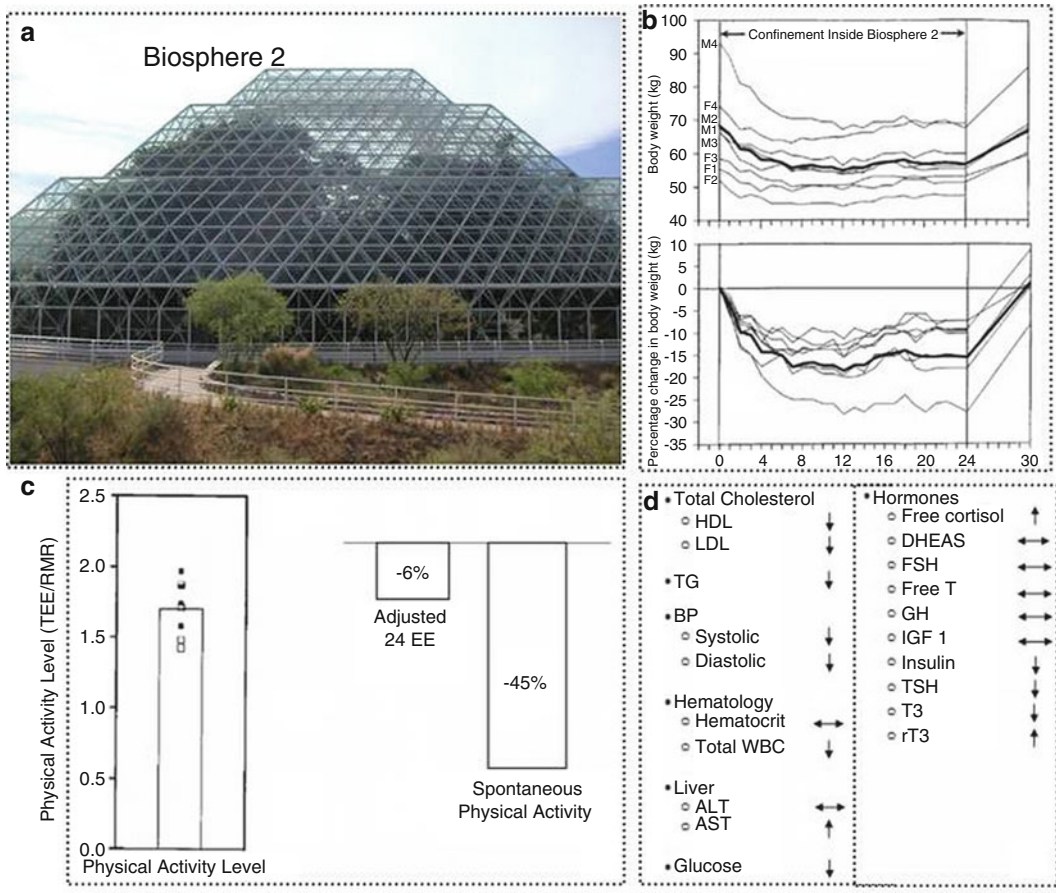

Fig. 20.1 Biosphere 2 (**a**), a 3.15-acre ecological enclosure provided an unexpectedly low availability of food for eight individuals who were housed inside for 2 years in the early 1990s. This study of nature of CR resulted in ~15 % weight loss (**b**), changes in energy expenditure (24 EE) and physical activity measured in a metabolic chamber (spontaneous physical activity) or as the ratio of total daily energy expenditure to resting metabolic rate (TEE/RMR) (**c**) and many hematological, biochemical, and metabolic alterations (**d**) consistent with calorie-restricted rodents and primates including reductions in insulin, core temperature, and metabolic rate [23, 42]

The remainder of this review will concentrate on the results from CALERIE Phase 1 conducted at the Pennington Center. For 6 months, 48 men and women were randomized to one of four treatment groups [21, 45–52]. For the CR group, overweight individuals were restricted to 75 % (a 25 % CR) of their weight maintenance energy requirements assessed by doubly labeled water [53]. The other groups were: (1) CR plus exercise group, for which the calorie deficit was also 25 % from weight maintenance but half (12.5 %) was achieved by CR and half (12.5 %) by increasing energy expenditure with structured aerobic exercise; (2) a low calorie-diet group in which participants consumed 890 kcal/day to achieve a 15 % weight loss and thereafter followed a weight maintenance diet; and (3) a healthy diet control group that followed a weight-maintaining diet based on the American Heart Association Step 1 diet. A sample menu can be found in Table 20.1. The effects of the CR interventions were determined from changes in various physiological and psychological endpoints after 3 and 6 months.

Table 20.1 Sample menus of food provided in the CALERIE Phase I study at 1,500, 1,800, and 2,100 kcal/day

Day 1											
Breakfast				*Lunch*				*Dinner*			
1,500	*1,800*	*2,100*		*1,500*	*1,800*	*2,100*		*1,500*	*1,800*	*2,100*	
1/2 c	2/3 c	3/4 c	Low-fat granola with raisins				Greek wrap	1 c	1 1/4 c	1 1/3 c	Lentils with olives and feta
1 c	1 c	1 c	Skim milk	1	1	1 1/2	10 in. tortilla	1/2 c	2/3 c	3/4 c	Couscous
1	1	1	Banana	2 T	2 1/2 T	3 T	Hummus	1/2 c	3/4 c	3/4 c	Zucchini
				1/2 c	1/2 c	1/2 c	Cucumber	3/4 c	1 c	1 c	Strawberries
				1/3 c	1/3 c	1/3 c	Tomato				
				1 1/2 T	1 1/2 T	1 1/2 T	Onion				
				1 1/4 T	1 1/4 T	1 3/4 T	Olives				
				1 1/2 T	2 T	3 T	Feta cheese				
				1/3 c	1/2 c	1/2 c	Cheddar cheese				
				1 1/3 c	1 2/3 c	1 2/3 c	Red grapes				
Day 2											
Breakfast				*Lunch*				*Dinner*			
1,500	*1,800*	*2,100*		*1,500*	*1,800*	*2,100*		*1,500*	*1,800*	*2,100*	
1/4 c	1/2 c	1/2 c	Oatmeal	1 2/3 c	2 c	2 1/4 c	Pesto pasta	1 c	1 c	1 1/4 c	Greek-style potatoes
2/3 c	2/3 c	3/4 c	Peaches	3/4 oz	3/4 oz	1 1/4 oz	Chicken breast	3 oz	3 oz	3 oz	Salmon steak
1 T	1 T	1 1/2 T	Almonds	1	1	1	Apple	3/4 c	3/4 c	3/4 c	Green beans
1/2 c	1 c	1 c	Skim milk	1	1	2	Dinner roll	3/4 c	1 c	1 c	Mandarin orange

Physiological Effects of Calorie Restriction

Six months of CR produced favorable alterations in physiological and behavioral outcomes.

Body Composition

Throughout the 6-month intervention there was a progressive decline in body weight that reached ~10 % for the CR group at the completion of the study (Fig. 20.2) [45]. Body composition analysis by dual X-ray absorptiometry and multi-slice computed tomography showed that the loss of tissue mass was attributable to significant reductions in both fat mass (CR: −24 ± 3 %) and fat-free mass (CR: −4 ± 1 %). There was a 27 % decrease in both visceral and subcutaneous fat depots, but it was interesting to note that the fat distribution within the abdomen was not altered by CR [45]. We also observed a reduction in subcutaneous abdominal mean fat cell size by ~20 %, a lowering of hepatic lipid by ~37 % but no change in skeletal muscle lipid content [50].

Biomarkers of Longevity

A "biomarker of aging or longevity" is considered to be any parameter that reflects physiological or functional age; it must undergo significant age-related changes, be slowed or reversed by treatments that increase longevity (e.g., calorie restriction), and must be reliably measured. Numerous biomarkers have been identified in rodents and primates, including body temperature and hormones such as DHEA-S and insulin (Fig. 20.3) [54]. In the CALERIE study, two out of the three biomarkers of longevity [54] were improved with 6 months of 25 % CR [3]. Significant reductions were observed in both fasting insulin concentrations (−29 ± 6 %) and core body temperature (−0.20 ± 0.05 °C),

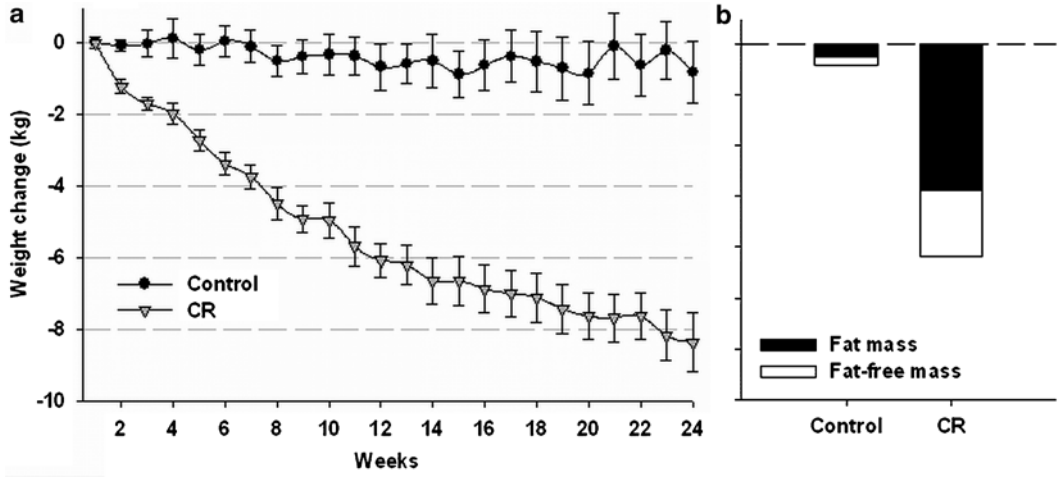

Fig. 20.2 Our 6-month study of 25 % CR resulted in a progressive decline in body weight that reached ~10 % at the completion of the study [45]. Body composition analysis by dual X-ray absorptiometry showed that the loss of tissue mass was attributable to significant reductions in both fat mass (CR: −24 ± 3 %) and fat-free mass (CR: −4 ± 1 %)

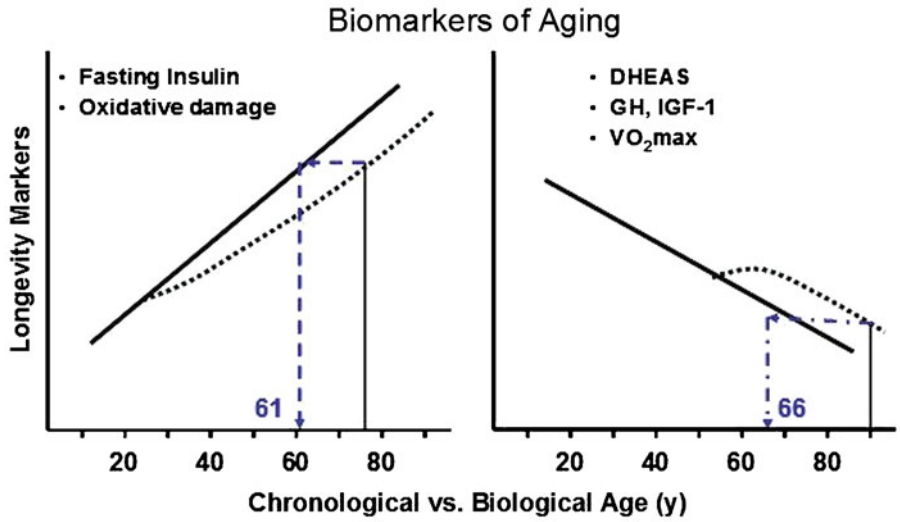

Fig. 20.3 Can CR improve biological age and extend chronological age? This figure summarizes some of the potential biomarkers of aging. It is hypothesized that CR will change the biological trajectory of these biomarkers and therefore improve biological age and extend chronological age. For example, the *left panel* shows an individual aged 75 years. With prolonged CR it is hypothesized that fasting insulin and oxidative damage will be reduced in this individual. The *dotted line* represents the theoretical effects of CR. Therefore, an individual although 75 will have a biological age 17 years younger. Similarly the individual on the *right* at 90 years with prolonged CR will be biologically similar to an individual aged 66 years

whereas DHEA-S was unchanged by the intervention. These findings echo results previously reported in nonhuman primates and rodents on CR and long-lived men in The Baltimore Longitudinal Study of Aging [54].

Cardiovascular and Diabetes Risk Factors

With heart disease and stroke ranked numbers one and three in the causes of death in the United States [55], delaying the progression of atherosclerotic cardiovascular disease may be one potential mechanism by which CR promotes longevity. The risk factors for CVD, including abnormalities in blood lipids, blood pressure, hemostatic factors, inflammatory markers, and endothelial function, are worsened with aging [56, 57]. At least a portion of these age-related changes appear to be secondary to increases in adiposity and/or reductions in physical activity [58, 59] and, therefore, may be amenable to improvements through prolonged CR. Six months CR significantly reduced triacylglycerol (TG) and factor VIIc by 18 % and 11 %, respectively [60]. HDL-cholesterol was increased and fibrinogen, homocysteine, and endothelial function were not changed. According to total and HDL cholesterol (expressed as their ratio), systolic blood pressure, age, and gender, estimated 10-year CVD risk was 28 % lower after only 6 months of CR.

Insulin resistance is an early metabolic abnormality that precedes the development of hyperglycemia, hyperlipidemia, and overt type 2 diabetes. Both insulin resistance and β-cell dysfunction are associated with obesity [61–63]. Calorie restriction reduces fat mass and delays the development of age-associated diseases such as type 2 diabetes. While in obese humans it is well established that CR and weight loss improve insulin sensitivity [64, 65], the effects of CR on insulin sensitivity and,

therefore, diabetes risk are not well understood in overweight and lean individuals. In our study of 6 months CR we observed a 40 % improvement in insulin sensitivity in the CR group, although this did not reach significance ($p=0.08$; p-values assess level of statistical significance. In most cases to be statistically significant a p-value of ≤ 0.05 must be reached) [50]. The acute insulin response to glucose (AIRg), however, was significantly decreased from baseline (CR: 29 ± 7 %, $p<0.01$), indicating an improvement in β-cell responsiveness to glucose.

Metabolic Adaptation and Oxidative Stress

One of the most popular proposed theories by which CR promotes lifespan extension is the "rate of living theory" [66]. It is hypothesized that a lowering of the metabolic rate reduces the flux of energy with a consequential lowering of ROS and rate of oxidative damage to vital tissues [14]. Indeed, CR is associated with a robust decrease in energy metabolism, including an absolute lowering of resting metabolic rate (or sleeping metabolic rate), and thermic effect of meals and a decrease in the energy cost of physical activity. However, as mentioned earlier, whether total energy expenditure is reduced beyond the expected level (i.e., metabolic adaptation) for the reduction in the metabolizing mass (fat-free and fat mass: FFM and FM) following CR is a matter of debate.

As expected, absolute 24-h energy expenditure and sleeping metabolic rate (both measured in a respiratory chamber) were significantly reduced from baseline with CR ($p<0.001$). Importantly, however, both 24-h sedentary and sleeping energy expenditures were reduced ~6 % beyond what was expected for the loss of metabolic mass i.e. FFM and FM [3]. This metabolic adaptation was also observed for RMR measured by a ventilated hood indirect calorimeter [46]. These physiological responses were associated with a reduced amount of oxidative stress as measured by DNA damage. DNA damage was reduced from baseline after 6 months in CR ($p=0.0005$), but not in controls [3]. In addition, 8-oxo7,8-dihidro-2′deoxyguanosine (8oxodG) was also significantly reduced from baseline in CR subjects ($p<0.0001$). These data confirm findings in animals that CR reduces energy metabolism, oxidative stress to DNA, both potentially attenuating the aging process.

Endocrine Adaptations

Thyroid Function

Short-term studies of CR in humans have reported alterations in thyroid function. Four weeks of complete fasting resulted in a decrease in triiodothyronine (T3) and an increase in reverse triiodothyronine (rT3), which was associated with a reduction in metabolic rate [67]. The CRONIES (a self-selected group engaging on long-term CR) have significantly lower T3, but not thyroxine (T4) or thyroid-stimulating hormone (TSH), concentrations compared to age-, sex-, and weight-matched controls [68].

In the CALERIE study, plasma T3 concentrations were reduced from baseline in the CR group after 3 ($p<0.01$) and 6 months ($p<0.02$) of intervention [3]. Similar results were found for the change in plasma T4 in response to the treatment. When the data of the subjects in the three CR groups were combined into one intervention sample, we observed significant linear relationships between the change in plasma thyroid hormones and the degree of 24-h metabolic adaptation after 3 months of intervention (T3; $r=0.40$, $p=0.006$ and T4; $r=0.29$, $p=0.05$) [3].

The Somatotropic Axis

Aging is marked by a reduction in both growth hormone (GH) and insulin like growth factor-1 (IGF-1) concentrations in healthy adults, resulting from a reduced amount of GH secreted at each burst without alterations of burst frequency or GH half-life [69]. Unlike for rodents, weight loss via CR in humans increases GH [70]. After 6 months of CR, 11-h mean GH concentrations were not changed with CR, nor was the secretory dynamics in terms of the number of secretion events, secretion amplitude, and secretion mass (unpublished data). The fasting plasma concentration of ghrelin, a GH secretagogue was significantly increased from baseline, but IGF-1 was unaffected. Despite a significant reduction in weight and visceral fat and an improvement in insulin sensitivity, mean GH concentrations were not altered by the 6 month intervention. In agreement with this observation was the finding that both GH and IGF-1 were not affected by the chronic food shortage experienced by the individuals in Biosphere 2 [23].

DHEA-S

Given the evidence from cross-sectional [71] and longitudinal studies [72] that DHEA-S declines with age, DHEA-S, which is a metabolite of DHEA, an abundant steroid hormone in the body, is considered to be a reliable endocrine marker of human aging and longevity [6]. It was hypothesized that CR will delay or attenuate the age-associated decline in DHEA-S. In our 6-month study in young individuals (37 ± 2 years), we observed no alteration in DHEA-S [3]. Similarly, DHEA-S was not changed with 2 years of energy restriction in the individuals within Biosphere 2 [23]. To our knowledge, there has been no report of DHEA-S levels in those individuals from the Calorie Restriction Society (CRONIES) who are self-imposing CR. The lack of agreement between the human and nonhuman primate data is believed to be due to first, the chronological age of the subjects at the onset of CR, and second, to the duration of CR. Young adult monkeys undergoing CR for 3–6 years had an age-related decline in DHEA-S of 3 % compared to 30 % in monkeys fed ad libitum [73]. In contrast, CR initiated in older animals (~22 years) did not attenuate the age-associated decline in DHEA-S [74]. These explanations remain to be tested in longer term studies of CR in humans.

Leptin

Leptin, which influences body composition and energy balance by regulating energy intake and expenditure, also decreases with CR [75–77]. Metabolic adaptation or a drop in energy expenditure as a result of CR that is greater than what is expected on the basis of changes in weight and energy stores. The CR-mediated change in leptin is an independent determinant of metabolic adaptation. This suggests that leptin response to CR diets could be a possible biomarker for aging [75].

Physical Activity

Daily energy expenditure has three major components: resting metabolic rate (RMR), the thermic effect of food, and the energy cost of physical activity. Investigation of changes in physical activity are important in studies of CR not only because the contribution of physical activity to daily energy expenditure is variable, but also because it is not known if individuals volitionally or nonvolitionally decrease their level of physical activity in an attempt to conserve energy [78]. In our study, we observed no change in spontaneous physical activity in a respiratory chamber [46] consistent with earlier reports of no alterations in spontaneous physical activity [79] or posture allocation in obese individuals following weight loss [80]. These findings are not surprising if the current hypothesis that

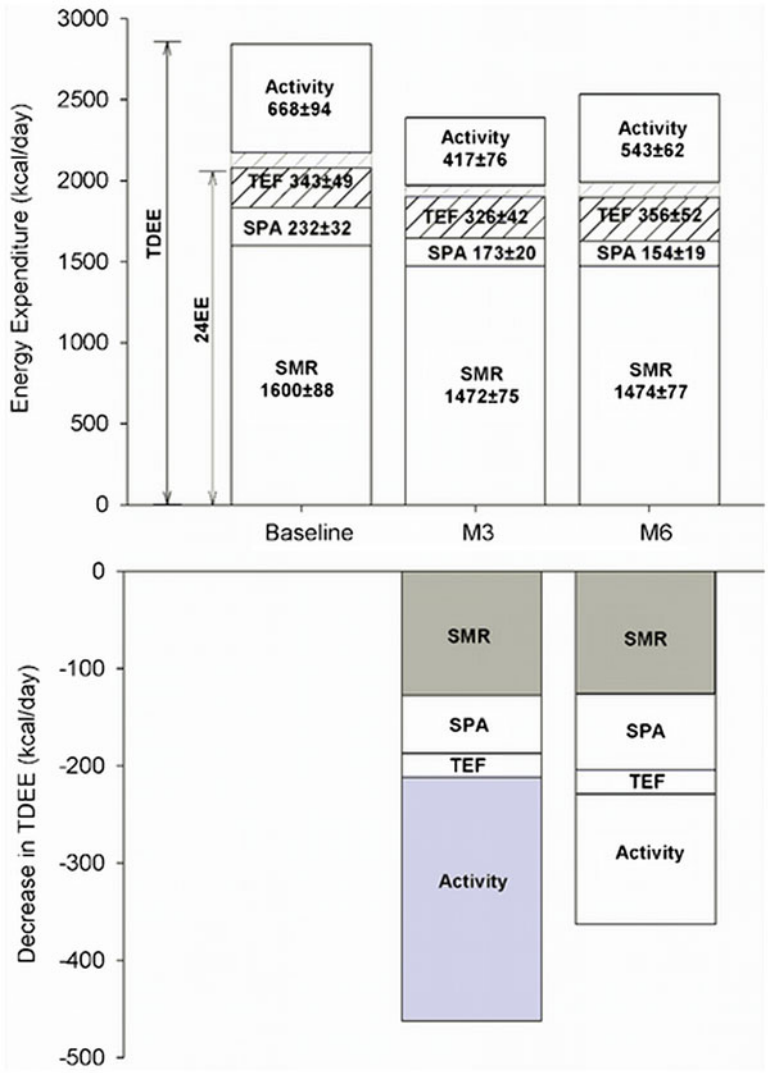

Fig. 20.4 The effect of CR on all components of daily energy expenditure (*top panel*). The components of energy expenditure were determined by combining a measure of sedentary energy expenditure in the metabolic chamber (sleeping metabolic rate, SMR; spontaneous physical activity, SPA; TEF, thermic effect of food) and free-living energy expenditure by doubly labeled water (physical activity); The changes in total daily energy expenditure after 3 and 6 months of CR (*bottom panel*) are shown and those representing a metabolic adaptation (larger than due to weight loss) are *highlighted in grey* [53]. Combining two state-of-the-art methods (indirect calorimetry in the metabolic chamber and doubly labeled water) for quantifying precisely the complete energy expenditure response to CR in nonobese individuals, we identified a reduction in sedentary energy expenditure that was 6 % larger than what could be accounted for by the loss in metabolic size, i.e., a "metabolic adaptation" [3] and a metabolic adaptation in the free-living situation as well. This adaptation comprised not only a reduction in cellular respiration (energy cost of maintaining cells, organs and tissue alive) but also a decrease in free-living activity thermogenesis, *highlighted in blue* (behavioral adaptation)

spontaneous physical activity is biologically determined is true [80, 81]. However with a measure of energy metabolism in free-living conditions (doubly labeled water) we found that a metabolic adaptation exists after 3 months (−386 ± 69 kcal/day) but not after 6 months of CR (Fig. 20.4) [53]. This adaptation was evident even after total daily energy expenditure (TDEE) was adjusted for sedentary energy metabolism (24-h or sleeping energy expenditure) indicating that changes in other components

Table 20.2 Summary of the psychological and behavioral responses to 6 months of CR in humans

Psychological/behavioral responses
Development of eating disorder symptoms
↓ Disinhibition
↓ Binge eating
↓ Concern about body size and shape
↔ Fear of fatness
↔ Purgative behavior
Depressed mood
↓ MAEDS Depression scale
↔ Beck Depression Inventory II
Subjective feelings of hunger
↓ Eating Inventory, Perceived Hunger Scale
Quality of life
↑ Physical functioning
↔ Vitality
Cognitive performance
↔ Verbal memory
↔ Short-term memory and retention
↔ Visual perception and memory
↔ Attention/concentration

of daily energy expenditure, mostly as physical activity and less via diet-induced thermogenesis, are also involved. In support of this, physical activity level calculated by either the ratios of TDEE to RMR or sleeping metabolic rate [46], or TDEE adjusted for sleeping metabolic rate, was significantly reduced at month 3 by 12 % and returned toward baseline values after 6 months of intervention. Interestingly, despite lower physical activity levels, participants reported an improvement in physical functioning, a primary component of quality of life. All the effects of CR on physiological outcomes are summarized in Table 20.2.

Psychological and Behavioral Effects of Calorie Restriction

Calorie restriction in humans might prove to have positive effects on physical health and longevity, resulting in the practice of CR or the identification of CR mimetics. Very little is known about the effect of CR on the quality of life and, furthermore, if people attempt to follow CR for health promotion, important questions must be answered about possible negative effects of CR on psychological well-being, cognitive functioning, mood, and subjective feelings of appetite. Determining the effect of CR on these parameters is critical to learn if adhering to a CR regimen is feasible and if CR has unintended negative consequences that would offset the potential of its health benefits. Phase I of CALERIE provided a unique opportunity to examine the effect of 6 months of CR on psychological and behavioral endpoints. We here summarize the effects of CR on the development of eating disorder symptoms, quality of life, mood (symptoms of depression), subjective ratings of appetite, and cognitive function.

Development of Eating Disorder Symptoms

One of the most pressing concerns about CR is that the adherence to a sustained reduction in food intake will potentiate the development of symptoms of eating disorders. This concern is based in part on the Keys [78] study, which found that 50 % CR for 6 months among healthy men was associated with the development of eating disorder symptoms, e.g., binge eating [82]. Additionally, CR or the intent to restrict intake has been associated with the onset of eating disorders, including anorexia [83], bulimia nervosa [84], and binge-eating disorder [85]. Hence, there is a need to examine both the benefit and potential harm of CR in humans, particularly for people who are not obese, and to answer important safety questions before CR is recommended [86, 87].

In our study, participants completed an assessment battery that included: (1) the Multifactorial Assessment of Eating Disorder Symptoms (MAEDS), which measures six symptom domains associated with eating disorders (binge eating, purgative behavior, depression, fear of fatness, avoidance of forbidden foods, restrictive eating) [88], (2) the Eating Inventory, which measures dietary restraint, disinhibition, and perceived hunger [89], and (3) the Body Shape Questionnaire (BSQ) [90], which measures concern about body size and shape.

As reported by Williamson et al. [51], the three "dieting" groups in CALERIE, including the CR group, reported higher dietary restraint scores in comparison to the Control group at months 3 and 6, but measures of eating disorder symptoms did not increase and some decreased. All groups, except the control group, reported a significant reduction in disinhibition at month 6 whereas binge eating, decreased in all groups at months 3 and 6. Concern about body size/shape decreased at 3 and 6 months among the three dieting groups but did not change in the control group. The Fear of Fatness and Purgative Behavior subscales of the MAEDS did not change during CR.

Subjective Feelings of Hunger

The ability of people to follow CR could be limited by feelings of increased hunger. We evaluated change in appetite ratings during CR using the perceived hunger scale of the Eating Inventory [89] and the Visual Analogue Scales (VAS), which have been found to be reliable and valid measures of appetite: hunger, fullness, desire to eat, satisfaction, and prospective food consumption [91]. During the 6-month study, appetite ratings changed, but the changes among the dieting groups were not different from those in the control group. Moreover, based on the perceived hunger scale of the Eating Inventory, hunger was reduced in the CR group at month 6 [51].

Quality of Life and Mood

The Minnesota Semi Starvation study [78] indicated that CR can negatively affect mood; therefore, the effect of CR on mood and quality of life (QOL) becomes an important factor when considering the feasibility of CR in humans. During CALERIE Phase I, the Medical Outcomes Study Short-Form 36 Health Survey (SF-36) [92, 93] was used to measure QOL, and the Beck Depression Inventory II [94] and depression scale of the MAEDS were used to measure mood. Our results indicate that depressed mood, measured by the BDI-II, did not change during the trial. Additionally, in the CR group, scores on the MAEDS depression subscale decreased at 3 and 6 months in comparison to baseline [51]. Together, the results indicate that CR had no negative effect on mood during this trial and, in fact, symptoms of depressed mood, measured with the MAEDS, decreased in the CR group.

The SF-36 was used to test the effects of CR on two components of QOL—physical functioning and vitality. All dieting groups, but not the control group, had improved physical functioning during the trial. For the CR group, physical functioning was significantly improved at both months 3 and 6 but CR had no significant effect on vitality.

Cognitive Function and Performance

Self-reported dieting or CR has been associated with deficits in cognitive performance (e.g., memory and concentration deficits) [95, 96]. Nevertheless, cognitive impairment is frequently mediated by preoccupation with food and body weight [97], suggesting that obsessive thoughts about food and weight, rather than CR, negatively affect cognitive performance. If CR has negative effects on cognitive performance, the feasibility of CR in humans would be in doubt.

In our trial, cognitive performance was evaluated empirically at baseline and months 3 and 6 with a comprehensive neuropsychological battery [47]. Verbal memory was measured with the Rey Auditory and Verbal Learning Test (RAVLT) [98], short-term memory and retention with the Auditory Consonant Trigram (ACT) [99, 100], visual perception and memory with the Benton Visual Retention Test (BVRT) [101], and attention/concentration with the Conners' Continuous Performance Test-II (CPT-II) [102]. During CR, no pattern of memory or attention/concentration deficits emerged. The degree of daily energy deficit also was not correlated with change in cognitive performance; hence, these data indicate that CR did not have a negative effect on cognitive performance [47]. All the effects of CR on psychological and behavioral outcomes are summarized in Table 20.2.

The psychological and behavioral findings from CALERIE provide important information about the feasibility and safety of CR in humans. Calorie restriction was not associated with the development of eating disorder symptoms, decreased quality of life, depressed mood, or cognitive impairment. In fact, many of these endpoints improved, and changes in subjective ratings of appetite were similar in the CR group to those of the control group. These results suggest that CR might be feasible and have few unintended consequences, at least among overweight individuals. Additional research is needed to determine the feasibility and safety of CR in other samples of the population and over a longer duration.

Could Calorie Restriction Increase Longevity in Humans?

The wealth of CR literature in rodents allows us to address some important questions relating to the practicality and feasibility of CR in humans. Relevant and practical questions are (1) How much CR do we need to improve age-related health and possibly longevity? (2) How long do we need to sustain CR in order to obtain these benefits? Analysis of 24 published studies of CR in rodents (CR up to 55 %) indicated a strong negative relationship between survival and energy intake [103] and a positive relationship between the duration of CR and longevity. Using the prediction equations derived from the rodent data above [103], we and others estimated that a 5-year life extension could be induced by 20 % CR starting at age 25 and sustained for 52 years, i.e., the life expectancy of a male in the United States. However, if a 30 % CR was initiated at age 55 for the next 22 years, the gain would only be 2 months (Fig. 20.5).

Certainly there are individuals who self-impose CR with the CRON (Calorie Restriction with Optimal Nutrition) diet for health and longevity. A group of 18 CRONIES (only 3 women) have recently been studied after 3–15 years of CR [28, 104]. Dietary analysis indicated an energy intake ~50 % less than age-matched controls. In terms of body composition, the mean BMI of the males was

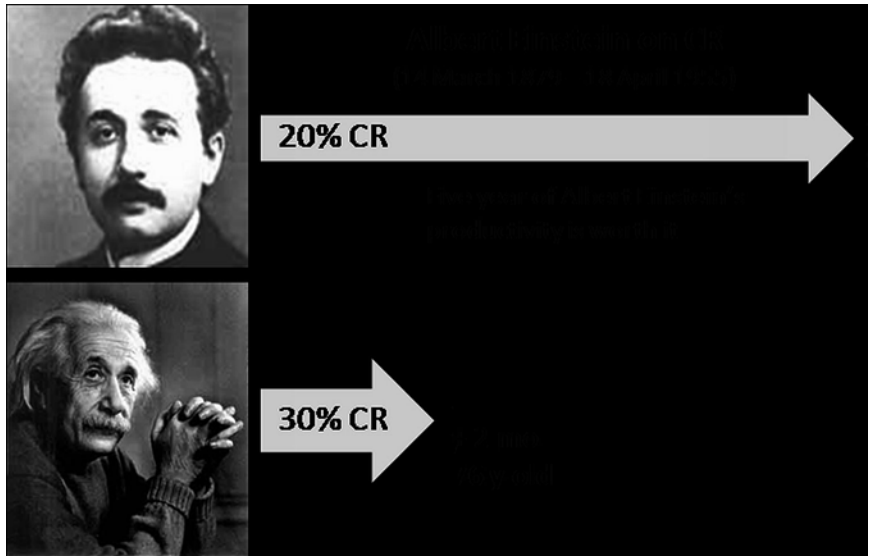

Fig. 20.5 How can CR impact lifespan in humans? By extrapolating the data from rodents to humans [103], one can predict the potential effect of CR in humans [105]. As an example, if Albert Einstein started a 20 % CR diet at 25 years of age, he could have increased his life by approximately 5 years. On the other hand, undertaking a 30 % CR diet 45 years later (age 60) would have extended his life by only 2 months. Therefore, CR needs to be initiated early in adult life to significantly increase life expectancy

19.6 ± 1.9 kg/m^2 with an extremely low percent body fat of ~7 %. Atherosclerosis risk factors including total cholesterol, LDL-c, HDL-c, and triglycerides fell within the 50th percentile of values for people in their age group. This report provides further evidence that longer term CR is highly effective in lowering the risk of developing coronary heart disease and other age-related comorbidities. It remains to be seen if the CRONIES live longer than their age and sex matched counterparts.

Conclusion

While the rodent and primate data indicate that lifespan extension is possible with CR, collective analysis of the rodent data suggest that intensity and onset of CR required to induce these effects is probably not suitable for many individuals [105]. Epidemiological studies certainly support the notion that a reduced energy intake that is nutritionally sound improves age-associated health. While results of the first randomized trials of CR, albeit short in duration suggest a reduction in risk of age-related disease and improvements in some biomarkers of longevity, the ultimate effect of this intervention on lifespan in humans will probably never been determined in the scientific setting. In our short-term study, CR was not associated with the development of eating disorder symptoms, decreased quality of life, depressed mood, or cognitive impairment all probably indicating the feasibility and safety of CR in humans. However, it is a challenge for most individuals to practice CR in an "obesogenic" environment so conducive to overfeeding. Only a very few will be able to practice a lifestyle of CR and probably benefit from it. There is therefore a need for the search for organic or inorganic compounds that mimic the biological effects of CR. If such compounds often called "CR mimetics" (such as resveratrol [106, 107]) prove viable in humans, individuals for the most part will opt to enjoy the effects of anti-aging via a "pill" rather than CR.

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Chapter 21
High-Risk Nutrients in the Aging Population

Katherine L. Tucker

Key Points

- Healthy diet offers tremendous promise for improving health and well-being with age.
- Older adults have lower energy requirements, but higher requirements for some nutrients, making it important to focus on nutrient-dense foods.
- Many older adults fall short of recommended nutrient intakes, placing them at risk of inadequacies that may affect their health.
- Shortfall nutrients include:
  - Macronutrients: protein, n-3 fatty acids, dietary fiber.
  - Vitamins: vitamins B_6, B_{12}, D, E, and carotenoids (vitamin A precursors).
  - Minerals: calcium, magnesium, and potassium.
- Research shows that, in most cases, isolated supplements are not as effective as obtaining the natural combinations of nutrients available in whole foods.
- Exceptions where supplements are often needed include:
  - Vitamin D, which is in few foods and is commonly inadequate in older adults, as they have less exposure to and less-efficient conversion from sunlight.
  - Vitamin B_{12}, which is difficult to absorb with declining stomach acid and interference from common medications.
- Foods to emphasize include fruit, vegetables, legumes, whole grains, nuts or seeds, fish, lean meat, poultry, and low-fat fluid dairy products.

Keywords Older adults • Nutrient intake • Vitamins • Minerals • Protein • Fatty acids • Dietary fiber

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Introduction

With more and more people living longer, an increasing segment of the population has chronic health concerns, including type 2 diabetes, heart disease, osteoporosis, physical frailty, and cognitive decline—all of which require ongoing care and pose an enormous burden to the health care system. Maintenance of nutritional status can go a long way to maximize healthy years of life, while minimizing the personal and institutional burdens of these chronic conditions. As a modifiable risk factor, a focus on healthy diet offers tremendous promise for improving the health and well-being of our aging population.

Unfortunately, national surveys and other research show that we have a long way to go to improve dietary quality in older adults. Relatively recent changes in the food supply and in lifestyle have led to more meals consumed outside of the home, more use of highly processed convenience foods, and relatively lower use of fresh fruit and vegetables, legumes, whole grains, nuts, and seeds. These changes have been paralleled with a rapid increase in obesity and poor nutrient status. Changing age demographics, along with societal changes in family dynamics, place many elders at risk of food insecurity and malnutrition.

Obtaining adequate nutrient intakes in older adults is challenging on several fronts. Although total energy requirement declines with age, requirements for many nutrients actually increase. This is due to declining function in many organ systems, which may affect efficiencies in absorption, conversion to active forms, or metabolism [1]. Several commonly used medications for chronic conditions increase nutrient requirements by interacting in ways that may interfere with absorption or metabolism [2]. Together, this means that it becomes increasingly important for aging adults to consume nutrient-dense diets. Based on national surveys and observational cohort studies, it is clear that intakes of several nutrients are inadequate, relative to dietary recommendations, or with respect to physiologic biomarkers, for a large segment of the older population. These "shortfall nutrients" include macronutrients—protein, n-3 fatty acids, dietary fiber; vitamins—vitamins B_6, B_{12}, D, E, and carotenoids (vitamin A precursors); and minerals—calcium, magnesium, and potassium.

Other nutrients tend to be consumed in excess, increasing risk of obesity, hypertension, and related chronic conditions like type 2 diabetes and heart disease. These include saturated fats (i.e., fatty meats, processed meat, full fat dairy products), *trans* fats (i.e., hydrogenated oils, margarine, shortening, many processed baked products, crackers), refined carbohydrate foods (i.e., soft drinks, fruit drinks, white bread and products with white flour, white rice), and sodium (sodium compounds in canned and other processed foods, table salt). Much has been written about the risks associated with saturated fat, *trans* fat, refined carbohydrates, and sodium, and the need to limit these in the diet is widely understood. Therefore, they will not be discussed further here. A more recently recognized risk nutrient of excess is phosphorus, and a brief discussion of this mineral is included below.

Macronutrients

With age, energy requirements go down, and nutrient density becomes extremely important. To achieve this requires limiting "empty calories" including high fat and sugar or refined carbohydrate-dense foods. Among the macronutrients, it is most important to focus on obtaining sufficient protein, omega-3 fatty acids, and dietary fiber, while limiting saturated and *trans* fat, added sugars, and refined grain products.

Protein

Although there is a common belief that Americans get too much protein, this is not true for many older adults. Research has shown that protein adequacy is critical to maintaining muscle, bone, and functional status with age. Aging is associated with a gradual decrease in muscle mass, called sarcopenia (see Chap. 7) [3]. It is of great importance to maintain muscle to the extent possible, as lower muscle mass leads to reduced muscle strength, lower resting metabolic rate, increased risk of falls, and increased risk of functional impairment. Studies in New Mexico reported the prevalence of sarcopenia, and of sarcopenic obesity (high ratio of body fat to muscle mass), as 15 % and 2 %, respectively, in 60–69 year olds, and 40 % and 10 %, respectively, in those over 80 years [4].

Given evidence of decreasing efficiency of protein synthesis, impaired insulin action, and the high prevalence of muscle loss with aging, some experts argue that protein requirements for older adults should be greater than those currently recommended. Results from one short-term nitrogen balance study suggested that protein intake for older men and women should be 1.0–1.25 g of protein per kilogram of body weight per day [5], rather than the current recommended dietary allowance (RDA) of 0.8 g/kg/day. The need for higher protein was also supported by the longitudinal Health, Aging, and Body Composition Study, which found that older adults with higher protein intake lost less lean body mass over time than those with lower protein intake [6].

One issue that has contributed to the limitation of protein recommendations for older adults is a belief that a high-protein diet will contribute to osteoporosis, by increasing the acid load of the diet and leading to calcium losses [7]. However, more recent studies suggest that the calciuria (loss of calcium in the urine) seen with higher protein intake in controlled studies may be compensated for by higher calcium absorption, with no net negative effect on bone [8]. Further, several observational studies have shown that high, rather than lower, protein intakes were associated with greater bone mineral density [9, 10], and lower risk of hip fracture [11]. A recent systematic review and meta-analysis of protein-feeding trials also showed positive, rather than negative, effects of protein intake on bone [12].

Given the importance of protein intake for both muscle and bone health with aging, one review went as far as to suggest that intakes as high as 1.6–1.8 g/kg/day may be beneficial [13]. Others argue that not only total daily protein, but also the distribution of protein intake across the day can affect muscle protein synthesis, and one group has suggested that 25–30 g of high-quality protein per meal may maximize muscle retention [14].

Another frequently expressed concern that has limited recommendations for higher intake is that high protein intake may increase risk of progression of impaired kidney function [15]. However, a recent international study group noted that the only individuals who should limit protein intake are those with severe kidney disease (GFR <30 mL/min/1.73 m), but who are not on dialysis [16]. For most older adults, the group concluded that daily protein intake should be in the range of 1.0–1.2 g/kg body weight/day, and that it should be higher than this (1.2–1.5 g/kg/day) for those who are exercising or who have acute or chronic disease.

Other considerations for the aging population include particular care to ensure sufficient protein for exercise, and with weight loss—to maximize retention of muscle mass. Data from the National Health and Nutrition Examination Survey (NHANES) 2009–2010 showed that, among adults aged 70 year and older, men consumed a mean 74.4 g and women, 60.1 g of protein per day (Table 21.1). Although this exceeds the currently recommended mean of 56 g/day for the 70 kg reference older man, and 46 g/day for the 58 kg reference older women [17], many aging researchers, as discussed above, believe that most adults aged ≥70 years will benefit from higher protein intakes from healthy sources. Excellent protein sources, that maximize nutrient content and minimize saturated fat, include fish, poultry, lean fresh meats, low fat milk and yogurt, legumes, and nuts (Table 21.2).

Table 21.1 Recommended intakes of shortfall nutrients for older adults, and mean intakes from the 2009–2010 National Health and Nutrition Examination Survey

	Recommended daily allowance (RDA) or adequate intake (AI)[a]		Mean (standard error) daily intake from the 2009–2010 National Health and Nutrition Examination Survey	
Nutrient	Men	Women	Men	Women
Macronutrients				
Protein (g)	0.8/kg/day 56 g	0.8/kg/day 46 g	74.4 (1.8)	60.1 (1.5)
α-Linolenic acid[a], 18:3 (g)	1.6	1.1	1.48 (0.06)	1.34 (0.05)
Eicosapentaenoic acid, 20:5 (g)	0.16	0.11	0.04 (0.006)	0.02 (0.004)
Docosahexaenoic acid, 22:6 (g)			0.02 (0.003)	0.02 (0.001)
Dietary fiber[a] (g)	30	21	17.1 (0.6)	15.2 (0.4)
Vitamins				
Vitamin A, (REA)	625	500	738 (49)	612 (18)
Vitamin B_6 (mg)	1.7	1.5	2.1 (0.1)	1.7 (0.1)
Vitamin B_{12} (μg)	2.4	2.4	5.98 (0.33)	4.18 (0.24)
Vitamin D (μg)	20	20	5.8 (0.4)	4.4 (0.1)
Vitamin E (mg α-tocopherol)	15	15	8.2 (0.4)	6.3 (0.3)
Minerals				
Calcium[a] (mg)	1,200	1,200	895 (35)	813 (13)
Magnesium[a] (mg)	420	320	290 (8)	243 (5)
Potassium[a] (mg)	4,700	4,700	2,800 (7)	2,300 (3)

Estimated Average Requirements from Dietary Reference Intake reports (IOM 1997, 1998, 2000, 2001, 2002/2005, 2010)

Intake data from NHANES 2009–2010 http://www.ars.usda.gov/SP2UserFiles/Place/12355000/pdf/0910/Table_1_NIN_GEN_09.pdf, accessed August 30, 2013

[a]These nutrients do not have an RDA, but have an AI

Table 21.2 Food groups to emphasize or limit to improve nutrient intake in older adults

Increase	*To improve intakes of*
Fruit	Dietary fiber, potassium, carotenoids and other phytonutrients
Vegetables (particularly dark green leafy and dark orange vegetables)	Dietary fiber, carotenoids and other phytonutrients, magnesium
Legumes	Vitamin B_6, magnesium, protein
Low fat fluid dairy (milk and yogurt)	Protein, vitamin D, calcium, vitamin B_{12}, potassium, magnesium
Nuts and seeds, including almonds, sunflower seeds and walnuts	Vitamin E, α-linolenic acid, vitamin B_6, magnesium, protein
Fish (particularly fatty fish) and seafood	DHA and EPA, protein, vitamin B_6, vitamin D
Poultry and lean meats	Protein, vitamin B_6
Whole grains (100 % whole grain breads and cereals)	Dietary fiber, vitamin B_6, magnesium
Fortified breakfast cereals	Vitamin B_{12}
Canola oil	α-Linolenic acid
Limit	*To reduce intake of*
Soft drinks and sweetened juice drinks (particularly cola)	Added sugars (and added phosphorus in cola)
Refined grain products (white bread, baked products, white rice)	Empty calories, rapidly absorbed carbohydrates
Fast food and fried foods	*Trans* and saturated fats, empty calories, sodium, phosphorus
Processed meats (including basted meats)	Phosphorus compounds, saturated fat, empty calories, sodium, heme iron
Liver and red meats	Retinol (preformed vitamin A), heme iron

Omega-3 Fatty Acids

Omega-3 fatty acids are associated with protection against several chronic conditions. Population-based studies have shown associations between fish intake and associated DHA and EPA intakes, with reduced risk of coronary heart disease mortality [18], fatal myocardial infarction [19], stroke [20], and dementia or Alzheimer's disease [21–24]. Mechanistic studies have demonstrated effects of omega-3 fatty acids in reducing inflammation, an important factor in many chronic diseases of aging. They have been shown to reduce membrane phospholipid arachidonic acid in a variety of cells, leading to reduced production of pro-inflammatory mediators [25]; and to downregulate nuclear factor-kappa beta, which is involved in regulating gene expression in inflammatory responses [26], among other anti-inflammatory mechanisms. A recent review concluded that omega-3 fatty acids are cardio-protective through a diverse number of actions, with evidence that they can reduce risk of thrombosis, lower triglycerides, improve endothelial function, slow plaque formation, and have anti-arrhythmic effects [27].

There is also accumulating evidence that fish intake is protective against cerebrovascular events. One systematic review examined 26 prospective cohort studies of fish intake and concluded that consuming two to four fish meals per week (vs. <1) was associated with 6 % reduction in risk of cerebrovascular outcomes and further, that eating fish five or more times per week was associated with 12 % reduction in risk [28]. However, in the same review, a meta-analysis of 12 randomized trials of fish oil supplements, vs. placebo, did not show a significant protective effect of fish oil supplements for cerebrovascular outcomes.

There has also been accumulating evidence for protective effects of fish or omega-3 fatty acids on cognitive function with aging. Importantly DHA is the most concentrated fatty acid in the brain and it is important for neural function. A recent meta-analysis of ten studies with plasma concentrations of fatty acids concluded that EPA, DHA, and total omega-3 fatty acid concentrations were significantly lower in older adults with dementia, relative to similarly aged controls [29]. A recent randomized trial of fish oil supplements (2.2 g/day of long chain n-3 fatty acids) with 65 older adults for 26 weeks led to significantly improved cognitive performance, particularly executive functioning, and visible improvement in measures of brain structure, including white matter integrity and gray matter volume, compared to those taking a placebo [30]. Animal models and in vitro studies have demonstrated protective effects of DHA on learning ability in mice and against amyloid buildup and Aβ fibrillation in brain tissue [31].

Although the marine-based long chain omega-3 fatty acids, DHA and EPA, are thought to be the most active omega-3 fatty acids for health, recent evidence for the beneficial effects of intake the plant based α-linolenic acid, and its sources—specifically walnuts or flaxseed and associated oils—have been accumulating. As a precursor for EPA and DHA, α-linolenic acid is an essential fatty acid. However, its conversion to these other long-chain omega-3 fatty acids is not efficient. A 2008 scientific workshop to consider reference intakes for DHA and EPA concluded that there was clear and consistent evidence for an inverse association between EPA + DHA intake and risk of fatal (and possibly nonfatal) CHD, and growing evidence for protection against cognitive decline [32]. They also concluded that conversion of α-linolenic acid to these fatty acids was so low that protective tissue concentrations could only be obtained by direct consumption of DHA and EPA. It is only relatively recently that evidence for protective effects of α-linolenic acid, itself, has received attention. One review [33] concluded that α-linolenic acid might have direct roles in protecting the heart, modulating the inflammatory response, and protecting central nervous system function. More recent reports have shown reduction of inflammation in brain cells [34], asthma control [35], and reduced risk of diabetes [36].

Due to the limited number of food sources, intakes of these important fatty acids tend to be inadequate in large segments of the population. Adequate Intake (AI) recommendations have been set for α-linolenic acid as 1.6 g/day for older men and 1.1 g/day for older women. The 2009–2010 NHANES

data (see Table 21.1) show mean intakes of 1.5 g/day for men and 1.3 g/day for women, aged 70 years and older, but because these mean intakes are close to the recommendation, many older adults have lower intakes. Sources of α-linolenic acid include flax seeds, walnuts, and certain oils, including canola and, to a lesser extent, soy oils. At this time, there is no AI for DHA or EPA, but individual groups have made recommendations. The workshop on this topic noted above [32] concluded that individuals should consume 0.25–0.5 g/day of DHA + EPA, independent of α-linolenic acid. The American Heart Association recommends that individuals without heart disease eat fish, preferably oily fish, two to three times per week to obtain an average of 0.5 g/day of EPA + DHA, with higher intakes recommended for patients with heart disease or high triglycerides [37]. The major source of long chain omega-3 fatty acids is from cold-water fatty fish, including salmon, mackerel, sardines, and tuna.

Dietary Fiber

Dietary fiber is important for intestinal health and protection against heart disease and metabolic syndrome, as well as adding bulk for a feeling of fullness to aid in limiting energy intake.

There are two primary classifications for dietary fiber, both of which are important for the aging population. Whole grains and the indigestible portions of vegetables contain insoluble dietary fiber, which helps to regulate intestinal transit time, and thereby avoid the common problem of constipation in older adults [38]. Fruits and grains also contain soluble fiber, which has been shown to lower serum cholesterol and reduce the risk of heart disease [39].

Fiber intakes of older men or women in the United States consistently fall well below the AI recommendation of 30 g/day for men and 21 g/day for women. The 2009–2010 NHANES data show mean intakes of 17 g/day for men and 15 g/day for women (see Table 21.1). Although fiber supplements have been widely used, it is important to recognize that fiber from foods is packaged with additional vitamins, minerals, and phytonutrients in the food matrix; therefore increasing intakes of fruit, vegetables, and whole grains is preferentially recommended to increase dietary fiber intakes [40].

Vitamins

With aging, the requirement for several vitamins increases, despite lower energy needs. This is due to declining efficiencies in absorption, metabolism, and retention of certain nutrients. Key shortfall vitamins include several B vitamins, vitamin D, vitamin E, and carotenoids—the latter are vitamin A precursors from plant sources. In contrast, high intake of preformed vitamin A—in the form of retinol—should be avoided, as the body becomes less able to excrete it with age [41].

Vitamin A and Carotenoids

Although dietary assessment reports often suggest that Vitamin A intake is inadequate in older adults, it is important to also avoid excess retinol, the preformed vitamin A found in animal foods, particularly liver, and in some supplements, including cod liver oil. In contrast to many other vitamins, where age-related decreases in efficiencies of absorption and metabolism increase requirements, there is decreased clearance of vitamin A by hepatic and other peripheral tissues with age [42]. High intakes of preformed vitamin A have been linked with bone loss [43] and increased risk of fracture [44]. A recent study also showed that brain retinol concentrations were inversely related to cognitive function, while serum carotenoid concentrations were associated with better cognitive function [45].

It is, therefore, recommended that older adults obtain most of their vitamin A from carotenoids in plant foods; β-carotene, α-carotene, and β-cryptoxantin can all be cleaved to form vitamin A, but this conversion is limited by requirement and therefore provides a natural regulatory mechanism for minimizing the risk of retinol toxicity. Beyond their vitamin A activity, there is increasing evidence that carotenoids offer other health advantages, including strong anti-oxidant activity. Carotenoids from food have been linked with lower risk of heart disease [46] and cancer [47]. Lutein and zeaxanthin (non-provitamin A carotenoids) are found in high concentration in the eye, and have been linked with prevention of cataract- and age-related macular degeneration [48]. Lycopene, another non-provitamin A carotenoid, has been shown to protect against prostate cancer [49]. Despite its importance as an antioxidant, and consistent evidence of protective effects when consumed in foods, high-profile trials providing high doses of β-carotene in the form of a supplement actually saw increased rather than the expected decreased risk of cancers [50–52]. Although the mechanisms are not fully understood, there is growing evidence that carotenoids work optimally when consumed together with other constituents in the food matrix. Therefore, intakes should be maximized from food, and supplements with carotenoids should be generally avoided [53]. The best way to ensure adequate intake of carotenoids, including the provitamin A carotenoids, is to consume a variety of colorful fruits and vegetables. The provitamin A carotenoids are most concentrated in dark orange fruits and vegetables (i.e., carrots, peaches) and leafy green vegetables (i.e., spinach, broccoli). Dark leafy greens are also a major source of lutein, corn is a source of zeaxanthin, and tomatoes and watermelon are sources of lycopene. Benefits of fruit and vegetable intake extend beyond these carotenoids to other beneficial phytochemicals, increasingly being shown to be protective against a variety of age-related health conditions [54].

B Vitamins

B vitamins tend to be plentiful in a diverse natural food supply. Historically, widespread refining of wheat and rice led to B vitamin deficiencies resulting in serious deficiency diseases, such as beriberi, which made their importance to the central nervous system very clear. To avoid these conditions, refined wheat flour and white rice have now long been enriched with vitamins B_1—thiamin, B_2—riboflavin, and B_3—niacin, to add back these vitamins that are removed during milling. Until fairly recently, folate, another B vitamin, was an important shortfall nutrient for the aging population, particularly in relation to its roles in DNA methylation and in lowering homocysteine, a metabolite that has been associated with increased risk of heart disease and stroke [55]. In the 1990s, however, grains in the US food supply began to be fortified with folic acid, primarily to ensure adequate intakes for women of childbearing age (because adequate folate status has been shown to reduce the incidence of neural tube defects). Therefore, dietary inadequacy of folic acid is now relatively uncommon in all age groups. Rather, care should be taken to ensure that intakes do not increase beyond the upper level of 1,000 μg in the form of folic acid. This can easily be done with the combination of vitamin supplements, fortified breakfast cereals, fortified grains, and other foods. Despite the accomplishments of food enrichment and fortification in improving B vitamin nutriture, two B vitamins remain important shortfall nutrients for older adults, vitamin B_6—pyridoxine, and vitamin B_{12}—cobalamin.

Vitamin B_6

Vitamin B_6 (pyridoxine) appears in several related forms in foods, including pyridoxine, pyridoxal, and pyridoxamine. The active form in the body, pyridoxal 5′-phosphate (PLP), plays a role in the function of more than 100 enzymes. As examples of its many activities, PLP is required for protein metabolism, gluconeogenesis from amino acids, the release of glucose from glycogen, synthesis of neurotransmitters, heme synthesis, conversion of tryptophan to niacin, one-carbon metabolism, and

synthesis of nucleic acids [56, 57]. In addition to folate and vitamin B_{12}, inadequate vitamin B_6 contributes to elevated homocysteine concentration, which, in turn, has been linked with increased risk of heart disease and cognitive decline [58, 59]. Several studies have linked low vitamin B_6 with heart disease [60–63]. One prospective study reported a 30 % lower incidence of coronary heart disease for those in the highest, vs. lowest, quintiles of vitamin B_6 intake [64]. In the longitudinal Veterans Administration Normative Aging Study of men, significant declines in cognitive scores were seen among those in the lowest, vs. highest, tertile of baseline plasma PLP [65]. PLP concentration has also been inversely associated with depressive symptomatology [66]. Reduced production of lymphocytes and interleukin-2 has been associated with vitamin B_6 deficiency, illustrating its importance to immune function [67]. Vitamin B_6 is also inversely correlated with markers of inflammation [68, 69], suggesting that this common condition associated with many chronic diseases may increase requirement for the vitamin [70]. Taken together, the literature on vitamin B_6 makes it clear that this nutrient is important for optimization of metabolism, and that inadequate status may have several effects on health.

Although mean intakes of vitamin B_6 in the 2009–2010 NHANES do not appear to be low in the US population (2.11 and 1.66 mg, relative to the RDA of 1.7 and 1.5 mg, for men and women aged ≥70 years, respectively), many individuals fall below the recommended intake level [71]. Plasma PLP concentration ≥30 nmol/L has been defined as normal status [72], but <20 nmol/L is widely used to indicate deficiency. In the Netherlands, from 10 to 45 % of adults aged 65 years and older were found to be deficient in vitamin B_6 [73]. In Massachusetts, 16 % of Hispanic and 11 % of non-Hispanic white adults, aged ≥60 years, had PLP <20 nmol/L. Vitamin B_6 is found widely in whole foods, including liver, fish, pork, chicken, whole grains, nuts and seeds, legumes, avocados, and bananas, but tends to be low in many of the highly processed foods in the American diet.

Vitamin B_{12}

Vitamin B_{12} is a coenzyme in the pathway that converts homocysteine to methionine, required for the synthesis of *S*-adenosylmethionine, a methyl donor needed for DNA methylation. Vitamin B_{12} is also required for energy metabolism and synthesis of hemoglobin. Inadequate vitamin B_{12} leads to elevations in circulating homocysteine and methylmalonic acid, and can lead to megaloblastic anemia. Vitamin B_{12} deficiency has been linked with depression due to the importance of methylation reactions to the synthesis of neurotransmitters [74]. It is centrally important to maintaining neurological function, as it protects the myelin coating of nerves [75]. Early symptoms of deficiency include tingling and numbness in the hands and feet, and reduction in sense of vibration and position. Additional symptoms vary depending on the location of nerve damage, but may include disturbance in gait, memory loss, disorientation, insomnia, incontinence, visual disturbance, and dementia.

Detection of vitamin B_{12} deficiency has traditionally depended on follow-up after diagnosis of megaloblastic anemia, with assessment of plasma B_{12}. A clinical cutoff point of <148 pmol/L has been considered deficient. However, individuals with clinical evidence of deficiency have been documented at higher concentrations [75], and a higher clinical cutoff point, of 250 pmol/L, is now recommended to identify possible deficiency, followed by the measurement of methylmalonic acid, as a specific metabolic indicator of vitamin B_{12} inadequacy [76, 77]. Because high folic acid exposure may correct megaloblastic anemia even if vitamin B_{12} is deficient, there is concern that the fortification of cereal grains with folic acid in the United States may contribute to more undiagnosed vitamin B_{12} deficiency. Further, some studies have noted that vitamin B_{12}-deficient patients without anemia showed more severe neurological complications than those with megaloblastic anemia [78, 79], suggesting that the imbalance between folate and vitamin B_{12} may accelerate the nerve damage from B_{12} deficiency. Importantly, an analysis of post-fortification NHANES data showed that both anemia and cognitive impairment were significantly more likely in older adults with high plasma folate concentration in combination with low vitamin B_{12} concentration, relative to those without high folate, raising concern

that the recent increased exposure to folic acid may be making the problem of vitamin B_{12} deficiency more serious [80].

Unfortunately, vitamin B_{12} deficiency is relatively common among older adults. Many have difficulty absorbing vitamin B_{12}, due to low stomach acid from a progressive, and often undiagnosed, condition called atrophic gastritis. This condition has been estimated to affect as many as 25–40 % of adults aged ≥65 years [81]. Stomach acid is required to separate vitamin B_{12} from protein in food, and without this step, the vitamin B_{12} cannot be absorbed. Therefore, deficiency may exist despite apparently adequate intake. Another contributor to vitamin B_{12} deficiency is the widespread use of acid blocking medications, particularly proton pump inhibitors, which inhibit absorption [82]. Another common medication for diabetes, metformin, has also been shown to lower vitamin B_{12} concentration [83]. Thus, it is advisable to take vitamin B_{12} supplements when using these types of medication.

Although the mean daily intake of total vitamin B_{12} does not appear to be low for most US older adults, relative to the RDA of 2.4 μg—NHANES 2009–2010 mean intakes for men and women, aged ≥70 were about twice this amount (see Table 21.1)—deficiency identified by plasma concentration is common. In the Framingham Heart Study, more than 16 % of older adults had low vitamin B_{12} concentration [84]. In the natural diet, Vitamin B_{12} is found almost exclusively in animal foods, and deficiency of this vitamin is an important concern for strict vegetarians or in populations with limited access to animal products. One study in Latin America [85] found that 51 % of men and 31 % of women had a vitamin B_{12} concentration <148 pmol/L. Because many older adults have difficulty absorbing vitamin B_{12} from food, as discussed above, the Institute of Medicine (IOM) [71] recommends that older adults obtain vitamin B_{12} in its nonbound crystalline form, in either fortified foods (some breakfast cereals) or supplements. The NHANES data now report the amount of added vitamin crystalline B_{12} consumed; in 2009–2010, men and women, aged 70 years and older reported food intakes with 1.5 and 1.0 μg/day, respectively, of added B_{12}. Without additional supplements, this remains short of the 2.4 μg RDA (see Table 21.1). Supplements can help, but do not guarantee adequacy. The Framingham Study found that supplement users were significantly less likely to have low vitamin B_{12} status than nonsupplement uses, but 4.0 % of supplement users were still identified as deficient [84]. Because of the importance of early treatment, older adults with concerns about vitamin B_{12} status should have their concentration measured, and if less than 250 pmol/L (350 pg/mL), should request additional measurement of methylmalonic acid.

Vitamin D

Inadequacy of vitamin D is common throughout the population, but is a particular concern for older adults. Vitamin D is unique in that, in addition to dietary sources, it is made in the skin with exposure to UV radiation from the sun: 7-dehydrocholesterol (7-DHC) in the skin is converted to previtamin D_3 and then to vitamin D_3. Vitamin D_2 or D_3 from the diet, as well as vitamin D_3 from the skin, is converted in the liver to 25-hydroxyvitamin D (25(OH)D), and then in the kidneys to its biologically active form 1,25-dihydroxyvitamin D ($1,25(OH)_2D$). Older adults are at particular risk of vitamin D deficiency for several reasons. They tend to spend less time outdoors, and therefore have less exposure than younger individuals to the sun for skin conversion. Further, even with exposure, the ability of the skin to convert pre-vitamin D_3 to vitamin D_3 with UV light declines with age, as does the efficiency of the liver and kidneys to convert it to the active form [86]. These limitations are compounded in northern latitudes, where studies have shown that sunlight in the winter months is not adequate to stimulate skin formation of vitamin D. A study in Boston, for example, showed clear seasonal declines in vitamin D status in the winter and spring, relative to the summer and fall [87]. The increased prevalence of obesity is another contributing factor to poor vitamin D status. As a fat-soluble vitamin, there is evidence that vitamin D is sequestered within adipose tissues, which limits its availability for other important processes that are detailed in the following paragraphs [88].

Vitamin D has long been recognized as centrally important for calcium absorption and metabolism, and inadequacy of vitamin D contributes to the high prevalence of low bone mass and osteoporosis, and thereby to the incidence of fracture in the older population [89]. Hip fracture is of tremendous importance as, in addition to temporary disability, it leads to loss of muscle mass and is frequently associated with long-term loss of mobility and increased risk of mortality.

More recently, vitamin D deficiency has been linked with a large number of other conditions, and vitamin D receptors have been identified in diverse tissues in the body including neural, gut, and immune cells. Of great importance is accumulating evidence for the role of vitamin D in neurologic and immunologic conditions. Multiple sclerosis, an immune-mediated disease that leads to progressive degeneration of the myelin sheath of nerves, has long been known to be more prevalent in northern climates. Accumulating evidence has recently shown a clear role for vitamin D in the etiology of multiple sclerosis [90, 91]. In addition, ongoing research is suggesting likely important roles of vitamin D in Parkinson's disease, systemic lupus erythematosus, and Alzheimer's disease [92, 93]. More generally, a recent systematic review of 28 cross-sectional and longitudinal studies supported an association between vitamin D status and cognitive decline in the aging population [94, 95]. A recent systematic review showed significant protective associations between vitamin D and cognitive test scores for 18 of 25 cross-sectional studies, and 4 of 6 longitudinal studies with 4- to 7-year follow-up [96].

In addition, vitamin D has been attracting attention in relation to heart disease and diabetes. One longitudinal study found that men in the highest tertile category of serum 25[OH]D concentration had 44 %, and women 68 %, lower risk of incident myocardial infarction relative to those in the lowest tertile [97]. Another analysis from the same study found a 37 % lower likelihood of incident type 2 diabetes across extreme vitamin D tertiles; they noticed that adjustment for inflammatory markers weakened the relationship, suggesting that subclinical inflammation may be a mediating factor [98]. In an Italian study, obese patients in the lowest (vs. highest) quartile category for serum vitamin D concentration were more than four times more likely to have metabolic syndrome [99, 100]. A recent review concluded that there is accumulating evidence that vitamin D may play a role in the pathogenesis of insulin resistance through several vitamin D-related metabolic and immune pathways [101].

The complex roles of vitamin D have also extended to cancer prevention, as vitamin D has been identified as a regulator of cell growth and differentiation. Population-based studies have shown protective effects against incidence rates of colon, breast, ovarian, renal, pancreatic, prostate, and other cancers [102]. Based on cell culture and animal model studies, a recent review described several biochemical mechanisms that explain these complex cancer protective actions, including anti-proliferation, anti-angiogenesis, pro-apoptosis, pro-differentiation and anti-inflammation activities in cells [103].

Food sources of vitamin D are limited in the US diet and the major sources—fatty fish and fortified milk—are not widely consumed by older adults. The RDA for vitamin D intake is currently 20 μg/day (800 IU/day) for men and women aged >70 years, based primarily on evidence to protect bone health [104]. However, given the growing evidence of the importance of vitamin D for a wide variety of chronic conditions, as discussed above, some scientists consider the cutoff point to be too low [105]. Still, current intakes by older adults fall well below the recommended level. The 2009–2010 NHANES reported mean intakes of only 5.8 μg/day in men and 4.4 in women, aged ≥70 years. Plasma measures in the 2001–2006 NHANES, using the IOM definitions of <30 nmol/L as risk of deficiency and 30–49 nmol/L as risk of inadequacy, showed prevalent risk of deficiency for 7 % of men and 11 % of women over age 70 years; and of inadequacy for another 24 % of men and 27 % of women [106]. Importantly, these risks were significantly higher in African Americans and Mexican Americans than in non-Hispanic white adults.

Efforts to improve vitamin D status include increasing intake of fatty fish and fortified foods, including milk, and some yogurt and breakfast cereal brands (check the label). Certain mushrooms, exposed to UV light, contain vitamin D and are becoming available. However, it is difficult for most individuals to obtain sufficient vitamin D from diet alone. Just 10 min/day of sunlight at midday can

make a large difference in vitamin D status. However, many individuals are now using sunscreen, which interferes with this. Therefore many experts now recommend that sunscreen be used only after 10–15 min of exposure. In the winter months at high latitudes, or for individuals who cannot get out, supplements are recommended.

Vitamin E

Current recommendations for vitamin E intake are based on an increasing understanding of the importance of this potent antioxidant in the prevention of age-related declines in a variety of functions. Vitamin E has also been shown to be effective in promoting immune function to fight infection [107, 108]. There is observational evidence of protective effects of vitamin E intakes on plasma status against cardiovascular disease, cognitive decline, cataract, and all-cause mortality [109–113]. However, as with β-carotene, trials with α-tocopherol have been disappointing–showing, for the most part, no benefit for preventing heart disease events, incident cancer or mortality, in large populations of adults on the supplement for 3–10 years, vs. placebo [114–118]. Rather, one trial showed higher risk of heart failure [119], and another, an increased risk of prostate cancer [120] among groups assigned to the vitamin E supplement. A trial of vitamin E supplements to evaluate whether it could reduce risk of Alzheimer's disease also showed no benefit [121].

Vitamin E supplements in the form of α-tocopherol have been shown to reduce plasma γ-tocopherol, which may also be important for optimal health [122]. Vitamin E in nature includes differing forms of tocopherols and also tocotrienols. Although there is evidence that forms of vitamin E other than α-tocopherol are important for many aspects of health [123], including a potential role in prevention of breast cancer [124], the current RDA provides guidance only on α-tocopherol. These findings reinforce the importance of obtaining vitamin E from diet rather than from α-tocopherol supplements.

Most individuals do not come close to meeting the RDA for vitamin E, of 15 mg α-tocopherol per day [125]. Among NHANES 2009–2010 adults aged ≥70 years, the mean vitamin E intakes were 8.2 μg/day for men and 6.3 μg/day for women. Vitamin E is another nutrient that is found in large quantities only in selected foods. The major dietary source is vegetable oil. Nuts and seeds, particularly almonds and sunflower seeds, have the highest concentrations [126]. A dietary simulation, to identify ways to improve vitamin E intake within a healthy dietary pattern, found that it would be very difficult to meet the RDA without the inclusion of nuts and seeds [127].

Minerals

As are vitamins, essential minerals are available in a diverse natural food supply. However, many of these are easily lost with processing and some are concentrated in limited food groups. Inadequacies particularly in calcium, magnesium, and potassium have important health implications for older adults and will be discussed in the following sections. First, however, potential concerns about excessive levels of two essential minerals will be mentioned. Iron, which is a shortfall nutrient throughout most of the life cycle, accumulates with age, and high serum ferritin has been associated with greater risk of coronary heart disease [128]. Thus, care should be taken by older adults to avoid too much iron in the heme form (from red and processed meats) or from supplements. Another essential mineral consumed in excess in our modern food supply is phosphorus. This mineral, which is naturally occurring in protein foods, has been added to a wide array of processed foods, including colas, basted or processed meats, and many fast and convenience foods. Excess intakes appear to be increasingly common and have been linked with adverse effects on

bone, kidney, and heart health [129]. Phosphorus intakes outside the context of natural sources may be particularly harmful, such as in cola drinks where they are not balanced by other nutrients and may have regular periodic negative effects even without large doses. For example, regular consumption of cola drinks has been linked with low bone mineral density in women [130].

Calcium

Calcium is a critically important mineral in the body as an intracellular messenger, regulating diverse cellular processes, and as a cofactor for extracellular enzymes and proteins. It is maintained in tight equilibrium in the extracellular fluid. It is stored primarily in the hydroxyapatite of bone, where it is available for release as needed to maintain plasma concentrations. Adequate calcium intake is, therefore, essential to prevent bone loss associated with aging and related risk of fracture. Bone loss is a concern for all older adults, but accelerates particularly in post-menopausal women due to effects from loss of estrogen. Declines in renal function and impaired absorption of calcium with aging further contribute to bone loss [131, 132]. In addition to the well-known importance for bone status, calcium intake is also important for blood pressure regulation [133].

Few adults meet the intake recommendation of 1,200 mg/day, and milk and low fat dairy products tend to be consumed less frequently by older adults than by younger individuals [134]. Some researchers have questioned the need for this high amount of calcium, and rather, focus on the importance of balancing vitamin D intake with somewhat lower calcium intake levels [135]. Because older adults do not meet dietary recommendations for calcium intake, physicians frequently recommend supplements, which are taken, particularly, by a large proportion of postmenopausal women. However, there is some evidence of harmful effects of high intake of calcium from supplements. For example, one study showed increased risk of heart disease and total mortality among women with calcium intakes greater than 1,400 mg/day, relative to those consuming between 600 and 1,000 mg/day, particularly if they were taking calcium supplements [136]. Other health concerns linked with calcium supplementation include kidney stones [137] and prostate cancer [138], although these remain controversial.

Taken together, the evidence suggests that it is important to balance calcium intake with other nutrients involved in its absorption and metabolism. Whole food sources of calcium, thus, are likely to have better long-term protective effects for bone status and less risk of imbalances that may have negative side effects than calcium supplements. There are many advantages to consuming calcium-rich foods, including low fat dairy products, fish (with bones, like sardines or canned salmon), and leafy green vegetables. Improved intakes of such dietary sources should be encouraged as, in addition to calcium, they also tend to include vitamin D, magnesium, potassium, and other important nutrients.

Magnesium

Numerous metabolic reactions in the body require magnesium. Among these, magnesium is essential for ATP utilization, protein and lipid metabolism, amino acid activation, DNA transcription, membrane fluidity, ion channel function, and calcium metabolism [139]. Although obvious deficiency is rare, subclinical inadequacy may contribute to risk for a variety of chronic conditions, including heart disease, sudden death from cardiac arrhythmia, osteoporosis, and type 2 diabetes [140]. A recent review noted that low magnesium intakes have also been associated with metabolic syndrome, inflammation, hypertension, vascular disease, migraine headache, asthma, and colon cancer [141]. These authors suggest that increasing calcium to magnesium ratios may also factor in the risk for these conditions.

Dietary surveys consistently show that the majority of the adult population falls short of meeting the magnesium intake recommendation [142]. Like vitamin B_6, magnesium is found in many whole foods, but is easily lost with processing. With our increasingly processed food supply, magnesium intakes in the population have been shown to decline over the past century [143]. Importantly, the majority of older adults have low magnesium intakes. Excellent sources include whole grains, nuts, legumes, and fresh vegetables. Increasing intakes of these foods would also improve other nutrient profiles, including B vitamins and dietary fiber.

Potassium

Potassium is the major intracellular cation, and it is tightly regulated in body fluids because of its importance to cardiac rhythm and conduction, and function of skeletal muscle. It is centrally involved in cellular metabolism and transport across cell membranes. Hypokalemia can lead to cardiac arrhythmia and muscle cell necrosis. This condition is usually caused by clinical conditions, including vomiting and diarrhea, rather than by poor intake, but can also result from medications such as diuretics [144]. Subclinical inadequacy due to low potassium intake has been linked to increased risk of hypertension, cardiovascular disease, and renal disease, and to acid–base balance disturbances, glucose regulation disturbances and bone loss [145].

Potassium intake is another mineral that is particularly low in most modern diets. As with magnesium, the majority of older adults have potassium intakes that fall well below recommendations. Fruits, vegetables, and low fat dairy products are excellent sources of potassium that are inadequately consumed by most adults. Increasing intakes of these will also help to improve intakes of vitamin C, dietary fiber, carotenoids, and other antioxidant and anti-inflammatory phytonutrients, calcium, magnesium and, in the case of fortified milk or yogurt, vitamin D.

Conclusion

Evidence of the critical importance of nutrition in protecting against the development and progression of chronic conditions with aging continues to grow. Older adults require less energy, experience less-efficient absorption and utilization of many nutrients, and yet can have greater requirements for many nutrients than younger adults, due to declining organ function, chronic conditions, and medications. At the same time, they face increasing risk for health conditions that may be adversely affected by inadequate or unbalanced nutrient intakes. This poses significant challenges, as many older individuals also experience changes in taste and smell, loss of appetite, dental and chewing problems, and limitations in mobility and access to high quality fresh food.

As noted above, dietary surveys consistently show that older adults fall short in their intake of several individual nutrients. In linking nutrition with chronic disease risk and aging, most studies have focused on the role of single nutrients. This led to trials to test the efficacy of nutrient supplements for reducing risk of heart disease, cancer, osteoporosis, and other important chronic conditions. The failure of many of those trials to show benefit, along with the evidence of protective effects from whole foods, reinforces the importance of emphasizing nutrient-dense foods and varied whole foods dietary patterns, and to work toward improving access to quality foods for the older population.

Relative to food group intake recommendations, older adults tend to report inadequate intakes of fruit, vegetables, legumes, whole grains, nuts or seeds, fish, lean meat, poultry, and low-fat fluid dairy products. Because of lower energy needs, the importance of these nutrient-dense food groups cannot be overstated. Rather, most older adults have excess energy intake from refined grain products,

processed and fatty meats, fried foods, solid fats, and added sugars, which can lead to obesity without providing the nutrients critically needed to maximize health [146].

In some cases, supplements may be helpful, and these are certainly important in the case of nutrient deficiencies, or when health conditions or medications interfere with absorption or effective nutrient utilization of specific nutrients, making it difficult or impossible to obtain adequate intakes from diet alone. Examples of these, as discussed above, include vitamin B_{12} with atrophic gastritis, use of acid blocking medication, metformin or other interfering medications, and vitamin D for individuals who get inadequate sun exposure, and during the winter months in northern latitudes.

In summary, increasing intakes of nutrient-dense whole foods, while reducing energy-dense refined and processed foods, with judicious use of supplements when needed, is of critical importance for optimizing metabolism, protecting cellular and organ function and maintaining health with aging.

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Chapter 22
Physical Activity and Exercise: Important Complements to Nutrition in Older Adults

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Key Points

- Physical activity (PA) is defined as any bodily movement that results in an increase in energy expenditure.
- Exercise (EX) is defined as a distinct subset of PA that is planned, purposeful, and intends to meet a specific health goal.
- Physical activity is essential for the prevention and management of nearly all chronic diseases and conditions, including cardiovascular diseases, cancer, osteoporosis, age-related loss of physical function, and frailty.
- Public health guidelines for physical activity include aerobic exercise, resistance training, and flexibility exercises across the lifespan, with the addition of balance exercise for older adults to decrease the risk of falls.
- Evidence-based programs specifically designed to improve both physical activity and dietary habits of older adults across a range of function are available and can be implemented in community and clinical settings, serving as a resource for clinician referrals.
- Partnerships of clinicians with community-based providers will improve access to both physical activity and nutrition programs, ultimately promoting independence and quality of life for older adults.

Keywords Physical activity • Exercise • Fitness • Cardiovascular disease • Cancer • Osteoporosis • Physical function • Frailty • Functional capacity • Evidence-based programs

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Introduction

Definition of Exercise and Physical Activity

The scientific literature clearly documents that physical movement is beneficial for physical and mental health across the lifespan, especially in older adults. Public health guidelines for physical activity for all Americans have been developed [1], with a specific position stand for older adults [2]. Research is still advancing regarding how much movement (quantity) is needed and what mode(s) of movement (quality) are most effective to obtain health benefits. The ultimate answers to these questions will depend on the individual and their specific health status and the health goal to be obtained. For example, a contemporary topic of research is the influence of sedentary behavior (e.g., sitting time) on health status [3]. Importantly, it appears that leisure-time physical activity does not completely offset the adverse health effects of being completely sedentary [4]. This movement pattern would describe individuals who exercise 30–60 min per day but are sedentary the remaining 23–23.5 h of their day.

To appreciate the topics presented in this chapter, the reader will benefit from understanding the working definitions of physical activity, exercise, and physical fitness that will be utilized [1, 5]. Physical activity (PA) is defined as any bodily movement that results in an increase in energy expenditure. Alternatively, PA includes any activity that is not sedentary or that does not involve quiet sitting or lying down. PA can include leisure time PA, spanning low-intensity activities such as fishing to high-intensity activities such as playing sports and occupational or job-related PA. Exercise (EX) is defined as a distinct subset of PA that is planned, purposeful, and intends to meet a specific health goal. EX activities, especially in older adults, are conventionally completed to enhance or maintain cardiorespiratory fitness, muscular strength, and endurance, flexibility and/or balance. However, many individuals also utilize habitual EX to enhance their psychosocial well-being such as for management of anxiety or mild depression, and to improve their sleep quality. For the purposes of this chapter, the term "PA/EX" will be used, and specific descriptions will be given when needed.

Many definitions of physical fitness exist typically clustering into health-related physical fitness or performance-related physical fitness [5]. Health-related physical fitness is conventionally defined as morphological (e.g., body composition, bone density), muscular, motor (e.g., balance), cardiorespiratory, and metabolic (e.g., glucose tolerance, lipid metabolism). Performance-related physical fitness is related to health-related physical fitness but applies these attributes to perform a task inclusive of competitive sports, military maneuvers, or occupational work. As older adults are primarily concerned with physical function we have chosen to define physical fitness according to the World Health Organization as "the ability to perform muscular work satisfactorily," which recognizes that many aspects of health-related physical fitness influence performance-related physical fitness in daily life. It should be recognized that these terms, although having distinctly different definitions, are often used interchangeably in the literature largely due to the fact that they are so interrelated.

Synergistic Effect of Diet and Exercise

The potential additive or synergistic effects of energy and nutrient intake with PA/EX on numerous health outcomes important for older adults have been well documented. For example, PA/EX combined with energy restriction during intentional weight loss programs promotes desirable changes in

body composition, such as reductions in fat mass, while attenuating the loss of lean mass and bone mineral mass [6]. Also, during intentional weight loss, the interactive effects of EX combined with a higher-protein-energy-restricted diet attenuates loss of lean mass and enhances loss of fat mass compared to a higher-carbohydrate-energy-restricted diet [7–9]. A classic example of the interactive effects of PA/EX with a micronutrient is calcium and vitamin D and the role of PA/EX for optimal bone mineral status [10]. Indeed, when designing a research study or clinical trial exploring bone mineral responses to either novel forms of loading (i.e., EX) or calcium/vitamin D supplementation it is necessary to carefully account for the other factor due to the established independent effects of each factor on bone status [1, 10]. Although the additive and synergistic effects of energy and nutrient intake and PA/EX on the health status of older adults have been documented, additional research is needed. As contemporary scholars and interdisciplinary teams bridge the gap between nutrition and exercise, it is anticipated that more information regarding multimodal interventions will become available. Additionally, as dietary intake and PA/EX practices are essentially behavioral choices, partnerships with behavioral scientists will exponentially advance our understanding of best practice, with the ultimate goal of enhancing the health of older adults through effective and sustainable interventions and programs.

Prevention Versus Management of Disease

PA/EX is not only instrumental in *preventing* chronic diseases and conditions, it is also a powerful strategy for *management* of chronic diseases and conditions. In the US, more than 60 % of adults over the age of 65 have at least two chronic conditions [11] and approximately 50 % of older women aged 70–80 years cannot complete general mobility tasks such as climbing a flight of stairs or completing housework [12]. This low functional status along with the high prevalence of chronic disease indicates that PA/EX may be particularly beneficial for older adults [2].

Overview and Call to Action

This chapter will summarize the literature for PA/EX for older adults regarding (1) the benefits for the main metabolic diseases, including obesity, cardiovascular diseases, diabetes mellitus, and cancer; the primary mental and psychosocial challenges, including cognitive decline and depression; and musculoskeletal challenges, including osteoporosis and physical function; (2) compliance with recommendations; (3) the current public health guidelines; (4) barriers and challenges; and (5) evidence-based programs. The goal of this chapter is to encourage the clinician to embrace the importance of PA/EX as a complement to nutrition to positively influence the health status of older adults. Moreover, if the expert in nutrition is not confident in their PA/EX knowledge, the content in this chapter might facilitate collaborations with PA/EX scholars and other professionals working in community and clinical settings.

Benefits of Physical Activity and Exercise

Engagement in PA/EX positively influences numerous chronic diseases and conditions, health-related physical fitness, and physical function to ultimately enhance quality of life for older adults. Ultimately most chronic diseases and conditions negatively influence physical functional ability, threaten independence in older adults, and impair the quality of life. Moreover, just as chronic diseases and

conditions cluster in prevalence, PA/EX has a beneficial influence on several diseases and conditions that are interrelated. For example, PA/EX expends energy (*obesity*) and simultaneously improves insulin sensitivity (*type 2 diabetes mellitus*) and the lipid profile (*cardiovascular diseases*), increases muscular strength (*physical function*), benefits psychological well-being (*depression*), and ultimately improves *quality of life*. The following section will provide a brief overview of the primary diseases and conditions that are positively influenced by habitual PA/EX in older adults.

Obesity

The relative importance of energy intake versus energy expenditure for risk of obesity remains incompletely characterized. This question will undoubtedly remain unanswered for some time due to (1) the inability to accurately measure either component of the energy balance equation over long periods of time in free-living individuals, and (2) the paradigm that "not one energy balance equation fits all" in that any given energy balance equation is highly individual, although patterns of imbalance exist for given cohorts including older adults. Additionally, the independent effects of PA/EX on health outcomes independent of nutritional factors and adiposity are an active area of interest. In other words, to what degree can an older adult maintain good health when they are "fit" but "fat" and/or have poor diet quality? Obesity is prevalent across the lifespan, including among older adults. In the US, about 35 % of adults aged 65 and over were obese in 2007–2010, which represents over eight million adults aged 65–74 years and about five million adults aged 75 and older [13]. The prevalence was similar between men and women. The forecasted increase in older adults combined with the increase in obesity in younger populations is predicted to have major impacts on our health care system. Notably, obesity is cited as a primary factor in loss of independence and nursing home admissions [14].

The public health goal for weight management is to manage the "energy gap," to control or reduce fat mass, and to maintain or enhance lean and bone mass, the latter two being very important for older adults. Current recommendations [15] indicate that a combination of restriction of energy intake with an increase in energy expenditure is of primary importance for all aspects of the weight management spectrum including weight gain prevention, weight loss, and weight loss maintenance. PA/EX is uniquely positioned for this multifaceted goal as habitual PA/EX both expends energy and assists in the preservation of lean and bone mass. PA/EX contributes to energy expenditure via several mechanisms [16]. First, the direct increased energy demand for muscle force production for movement is well recognized. Aerobic activities involving large muscle groups, often performed rhythmically, are best suited for energy expenditure with higher intensities (e.g., walking faster) and longer durations (e.g., minutes walked) producing greater energy expenditures, other factors being equal. Walking, cycling, and swimming are typical aerobic activities performed by older adults. Second, if the activity was of sufficient intensity (e.g., running) and duration (typically greater than 30 min) then energy expenditure may be influenced through excess post oxygen consumption theorized to be due to energy deficits occurring at the beginning of the exercise bout and perturbations in thermoregulatory and endocrine systems collectively resulting in an elevated metabolic rate after the activity has ceased. Third, habitual higher levels of PA/EX, including both aerobic and resistance training, potentially contribute to a higher resting energy expenditure (REE) and may attenuate the natural decline in REE that occurs with aging. The influence of PA/EX on REE is mediated primarily through lean mass, which is known to explain approximately 80 % of REE. As REE is the greatest contributor to total daily energy expenditure in most adults, especially older adults, comprising about 60–70 % of total daily energy expenditure, the preservation of REE is essential to energy balance [16].

Although long-term weight loss is achieved by both moderating energy intake and participating in habitual physical activity, the question always is how much PA/EX is enough? Current guidelines indicate that 60 min/day of moderate intensity activity is the target level to prevent weight gain,

whereas 60–90 min/day might be a more important goal to prevent weight regain following significant weight loss [17]. Resistance training does not enhance weight loss, but may increase fat-free mass and decrease fat mass and is associated with reductions in health risk and preservation of functional independence. The long-term implication of resistance exercise for weight management, especially in older adults, is not well studied. Finally, the importance of PA/EX for weight management is essential for older adults. As detailed in Chap. 10, the combined modes of endurance and strength training under conditions of dietary energy restriction are critical for the preservation of lean and bone mass in older adults undergoing weight loss [6, 18]. Due to the high risk of osteoporosis and sarcopenia in older adults, maintaining bone and lean mass with weight loss is of primary importance.

Cardiovascular Disease

It is well established that habitual PA/EX reduces the risk of cardiovascular diseases, our major public health challenge. As age is an independent risk factor for both of the primary cardiovascular diseases, coronary heart disease (CHD) and stroke [19], prevention and treatment of CHD and stroke are essential for older adults. Independent of other risk factors, PA reduces risk for CHD [19, 20], and PA/EX is a primary component of cardiac rehabilitation. PA/EX alters several modifiable risk factors for CHD, including high blood cholesterol and triglycerides, high blood pressure, diabetes mellitus, stress, and obesity. Regular participation in moderate-to-vigorous leisure time PA reduces risk for ischemic and hemorrhagic stroke by about 30 % in older adults [1]. Similar to CHD, PA/EX is a primary component of the rehabilitation from a cerebrovascular event, although the health goal differs in that physical rehabilitation is primarily used to recover physical function [21].

The mechanisms responsible for the independent effects of PA/EX on CHD are thought to be related to myocardial oxygen supply and demand mediated in large part by direct effects on the vascular wall with enhanced endothelial function and reductions in hemostatic and inflammatory biomarkers [22]. These beneficial effects are in addition to the established reduction in modifiable risk factors for CHD (e.g., lipids, blood pressure). First, regular EX lowers the oxygen demands of the heart during a given physical task of a fixed demand (i.e., intensity), and thus reduces risk of ischemia during physical work or other stress. With a chronic overload of exercise stress, cardiorespiratory fitness increases from both central and peripheral mechanisms, effects that have been demonstrated in individuals of all ages, including older adults. In addition to peripheral adaptations that occur in the trained muscle that enhances oxygen uptake and utilization, increases in plasma volume and remodeling of the left ventricle combine to enhance stroke volume, leading to a reduction in heart rate for a given bout of EX, thereby decreasing work demand on the heart. Second, risk of coronary thrombosis is also reduced by this increased plasma volume, possibly through a series of events including reduced blood viscosity, which may decrease platelet aggregation and clotting, the latter known to cause most myocardial events. Third, beneficial changes in endothelial function in response to exercise also occur. Normal endothelial function allows the appropriate vasodilation of arteries, most notably the coronary arteries, in response to increased metabolic demand. The nitric oxide system is critical in the vasodilatory response to exercise allowing the atherogenic effects of inflammation to be attenuated. Exercise stimulates nitric oxide synthase, improving endothelial function. Finally, inflammation is associated with increased blood clotting and endothelial dysfunction. The role of chronic inflammation in several age-associated chronic diseases, especially CHD, is of high contemporary research and clinical interest in older adults [23]. Importantly, PA/EX, in addition to optimal nutrition, is a key for the management of chronic inflammation [23].

Hypertension, along with being considered a primary risk factor for stroke and CHD, is also considered a widespread cardiovascular disease with approximately 70 % of individuals 65 years and older having hypertension in the US [24]. The positive effects of PA/EX and cardiorespiratory fitness

on blood pressure are well documented [1]. The magnitude of the effect of habitual PA/EX on hypertension is on the order of about 7 mmHg and 6 mmHg for systolic and diastolic blood pressure, respectively, after controlling for other risk factors [25]. The mechanisms responsible for the anti-hypertensive effects of PA/EX are likely multifactorial, including the anti-inflammatory and endothelial effects described previously, along with potential beneficial changes in the sympathetic nervous system and renin-angiotensin-aldosterone system. Exercise guidelines to prevent CHD, stroke, and hypertension are all geared toward enhancing both leisure time PA and cardiorespiratory fitness. The latter requires a higher training intensity typical of EX (60–75 % compared to 40–60 % maximal capacity for leisure time PA) and continuous EX (about 30 min). Resistance training also reduces blood pressure in both normotensive and hypertensive adults [25].

Metabolic Syndrome (MetS), Type 2 Diabetes Mellitus (T2DM), and Dyslipidemia

Metabolic syndrome is a cluster of pathophysiological conditions related to insulin resistance and encompasses abdominal obesity, hypertriglyceridemia, low high-density lipoprotein cholesterol, hyperglycemia, and hypertension [26]. MetS is a major precursor to both CHD and T2DM. Although the classification of risk factors for MetS continues to be debated, what is well established is that habitual PA/EX and high cardiorespiratory fitness are protective against MetS, T2DM, and dyslipidemia. Older adults are prime candidates for these health challenges, as over 50 % of men and women over 60 years of age have MetS [26]. Although these diseases/conditions are also influenced by weight status and dietary intake, PA/EX is known to reduce risks for MetS and T2DM independent of the effects of adiposity or dietary habits [27].

Obesity, MetS, and T2DM share the same underlying pathology described above for CHD of chronic low-level inflammation and endothelial dysfunction, along with insulin resistance. Individuals with some combination of MetS and T2DM have altered insulin function with a classic resistance pattern resulting in hyperinsulinemia and potentially hyperglycemia (classic diagnostic criteria for T2DM). Increased energy metabolism within skeletal muscle increases the demand for glucose (and other energy sources), stimulating glucose uptake even in the absence of insulin. With habitual PA/EX additional mechanisms contribute to this enhanced glucose disposal including adaptation of metabolic enzymes and mitochondrial density within skeletal muscle. Thus, PA/EX increases glucose uptake and insulin sensitivity at rest and during PA/EX [28]. Additional changes occur to enhance fat metabolism, which can benefit the serum lipid profile. LDL and cholesterol are less responsive to PA/EX compared to dietary manipulations; however, HDL cholesterol and triglycerides are positively influenced by PA/EX. Note that the two latter lipoproteins are associated with MetS. PA/EX also influences the postprandial lipemia (PPL) response, which is the surge in lipoproteins that is present after a meal that is dependent on the fat ingested within the meal. PPL is linked to the incidence of myocardial infarction and stroke through its influence on coagulation ability. It is well established that acute and chronic PA/EX decreases the length and amount of the PPL response from a meal [28].

The recommendations for EX/PA to reduce or treat MetS and T2DM are similar to that recommended for CHD in that the activity should be aerobic in nature involving large muscle group activities (e.g., walking, cycling, swimming) with an intensity being moderate to vigorous for 60 min per day, which may be divided into shorter sessions but not less than 15 min per bout and one session per week should be greater than 30 min. As the cellular adaptations that occur to enhance insulin sensitivity are transient, it is highly recommended that some PA/EX be performed daily. In addition, the energy expenditure in PA/EX should be greater than 2,000 kcal/week. Resistance exercise can be used as a supplement to the aerobic exercise. Importantly, higher intensity and longer duration EX is needed for beneficial changes in HDL cholesterol to be realized [27, 28].

Cancer

Although there is a growing interest in obesity and the link to many types of cancers, the independent benefits of PA/EX on cancer are less well-established than cardiovascular and metabolic diseases. Almost half of men and one-third of women in the US will develop some form of cancer during their lifetimes [29]. Importantly, although all cancers involve the malfunction of genes that control cell growth and replication, only about 5 % of cancer is strongly hereditary, which means that primary and secondary prevention of cancer is a high public health priority [29]. As age is an independent risk factor for cancers of all types, older adults are concerned with prevention, as well as with successful cancer treatment and survivorship issues. It is well established that PA/EX can positively influence cancer-related treatment and survivorship concerns in many ways including fatigue, depression, and quality of life [30]. The strongest and most consistent evidence for the beneficial effects of PA/EX relate to the prevention of cancer of the colon and breast. As evident from the protective mechanisms described below, the optimal PA/EX guidelines for cancer prevention relate to the prevention of obesity and insulin resistance as described previously.

Although the exact mechanisms whereby PA/EX prevents colon cancer have not been fully elucidated, there are several potential theories. First, the initial theory is that PA/EX results in a shortened gastrointestinal transit time, which results in less exposure of the mucosal lining of the colon to potential carcinogens, although more recent studies do not embrace this theory. Second, insulin resistance may be an important link of PA/EX with colon cancer. The protective effects of PA/EX occur over a wide range of weight statuses. The hyperinsulinemia of insulin resistance serves as an important growth factor for colon cancer cells [31]. Third, chronic low-grade inflammation may play an important role in the link between PA/EX and colon cancer. Finally, limited evidence suggests that positive changes in immune function (acquired, innate, or both) and reduction of prostaglandin levels may also contribute to the protective effects of PA/EX on colon cancer [1].

Similar to colon cancer, the exact mechanisms whereby PA/EX reduces risk for breast cancer are not known. In addition to the beneficial effects on the immune system, several theories also suggest that the beneficial effects of PA/EX on breast cancer risk are through reductions in insulin, insulin-like growth factor, and inflammation, which similar to colon cancer, are known to promote tumor cell growth [32]. As cumulative lifetime exposure to circulating ovarian hormones, especially estrogens, is a well-established risk factor for breast cancer, the influence of PA/EX on sex hormones is also an important theory. For example, strenuous exercise during adolescence can delay menarche and is also associated with longer menstrual cycles due to a longer follicular phase during the reproductive years, which may in part by driven by the reductions in adiposity that occur with physical training. PA/EX may also influence menopausal status as active women are leaner and obesity is associated with a later age at menopause thereby increasing estrogen exposure. Thus, it is difficult to ascertain if the beneficial effects of PA/EX on risk for breast cancer are due to a direct effect on the activity of ovulatory cycles or an indirect effect through diet, body composition, and caloric expenditure or some combination thereof.

Osteoporosis and Physical Functional Capacity

More so than cardiovascular or metabolic diseases, osteoporosis, frailty-related bone fractures, and loss of physical functional capacity almost exclusively occur in older adults. Of significant concern are falls [33], which can lead to traumatic brain injury, hip fracture, and other fractures. Such severe injuries in older adults can rapidly progress to loss of independence or death. It is estimated that 44 million Americans ages 50 or older, 80 % of which are women, or 55 % of our adult population, have

either osteoporosis or osteopenia [34]. Physical limitations and risk for disability are influenced by many factors, including comorbidities (e.g., cancer, cardiovascular diseases, obesity, osteoporosis), psychosocial factors (e.g., depression, self-confidence, motivation), and sensory impairments (e.g., vision), as well as muscular fitness. According to the CDC, physical limitations can be defined as difficulty performing one of any of the following activities: walking a quarter mile; walking up ten steps without resting; standing or being on your feet for about 2 h; sitting for about 2 h; stooping, bending, or kneeling; reaching up over your head; using your fingers to grasp or handle small objects; or lifting or carrying something as heavy as 10 lb [12]. Current estimates indicate that 23 % of individuals 60–69 years of age report one or more physical limitations and that the presence of physical limitations increases linearly with age [12].

Functional capacity and osteoporosis are strongly related to each other. Bone and physical functional capacity encompass the morphological, muscle, and motor components of health-related fitness and ultimately determine performance-related fitness, which in the case of an older adult is the "performance" of activities of daily living. Risk for fracture can be conceptualized as a combination of bone-dependent and bone-independent risk factors. Undeniably, proper nutrition influences both bone status and physical function, with a large literature documenting the benefits of calcium and vitamin D on bone health, as well as protein intake on muscle mass and quality. Here we highlight the most salient mechanisms whereby PA/EX positively influence bone status, muscle capacity, and physical function.

The skeleton adapts to loading, with the two primary means to load including gravity or ground reaction forces and muscle and tendon interactions or joint reaction forces, which occur during muscular contraction, ambulation, and the maintenance of posture. Although genetics largely determine bone geometric properties, environmental factors, mainly diet, hormones, and PA/EX, greatly influence bone mass, bone mineral density (BMD), and bone architecture (i.e., trabeculae) through their influence on bone resorption and formation. The two primary bone-dependent strategies to reduce risk of bone fracture are to (1) maximize peak bone mineral mass and BMD during childhood and adulthood, and (2) minimize the reduction in bone mass and BMD that occurs after the age of about 40 years [35]. The positive benefits of influence of PA/EX on bone mass and BMD across the lifespan are well documented, even in older adult populations [35]. Although not fully understood, bone adaptations are largely thought to align with Wolff's law that posits that mechanical loading impacts the microstructural architecture remodeling [36]. The biomechanical mechanism whereby mechanical strain translates into an increase in BMD is not completely characterized; however, it is thought to include piezoelectric potentials, increased blood flow, and hormonal response involving prostaglandins, nitric oxide, and growth factors [36]. Importantly, PA/EX effects on bone are maximized in the presence of optimal nutrition and the hormone milieu.

Another important component of bone fracture, especially for hip fracture, is the risk of falling, which is related to physical functional capacity. Although the aging process is known to influence muscle capacity (see Chap. 7), including muscle strength, endurance, and power (the ability to move force quickly), PA/EX can greatly attenuate the decline in muscle performance. Physical inactivity is directly linked to reduced muscle mass and quality and reductions in physical functional ability; habitual PA has been consistently associated with improvements in physical function [1, 2]. The benefits of physical activity include a prolonged time until mobility disability and loss of independence occurs in the lifespan, as well as clinically meaningful improvements in physical function testing scores in the research laboratory. Mechanisms responsible for increased muscle capacity in response to PA/EX include improved neural activation and hypertrophy of muscle fibers although hypertrophy responses are reduced compared to younger individuals. Importantly, both functional training (e.g., activities of daily living such as chair rises) and resistance training are effective training strategies in older adults, but adaptations are task-specific.

The optimal PA/EX regimen to enhance bone status involves dynamic, high peak loads that are frequent, intermittent, and novel. However, for the typical older adult, this type of loading could cause injury to osteoporotic bones, joints and/or muscles. Therefore, the safest overload strategy for the older adult is through joint reaction forces obtained from strength and/or resistance training. An EX program that is multimodal and inclusive of both resistance exercise and functional training will provide muscle capacity benefits to attenuate declines in functional capacity. High levels of PA along with cardiorespiratory and/or aerobic EX are also important to prevent other comorbidities (e.g., obesity, CHD), which also indirectly contribute to declines in physical function.

Cognition and Depression

Although the positive effects of PA/EX on the physical health status of older adults are well documented and appreciated, a physically active lifestyle also confers benefits to mental health and psychological well-being. The most salient of these conditions for the older adult are cognition and depression. Importantly, although PA/EX has been shown to positively influence cognition and depression, impairments in cognition and depression can also reduce the likelihood that an older adult will participate in PA/EX. Thus, it should be appreciated that PA/EX has multifaceted direct and indirect benefits for mental and psychological health, which are briefly highlighted below.

Literature summarizing prospective studies supports that PA delays the incidence of dementia and the onset of cognitive decline associated with aging [1]. Additional studies documenting the benefits of regular exercise and cardiorespiratory fitness on cognitive functioning suggest that the greatest effects are on executive control tasks related to goal-oriented decision-making behavior [37]. Mechanisms through which PA/EX improves cognition may include plasticity and survival of brain neurons, increased brain blood flow, and enhanced neural circuits. The most studied type of EX is aerobic cardiorespiratory in nature, which strongly suggests that these benefits are realized when changes in cardiorespiratory fitness occur.

The prevalence of depression is high among older adults and treatment is often inadequate. A rich literature base of various research designs documents that higher levels of PA are associated with lower odds of depressive symptoms in all ages, including older adults [38, 39]. Mechanisms to explain the effect of PA/EX on depressive symptoms include cognitive-related social and/or biological factors [40]. The primary neurobiological mechanisms speculated to be associated PA/EX-related reductions in depression include (1) endorphin hypothesis, (2) brain blood flow hypothesis, (3) hypothalamic-pituitary-adrenocortical (HPA) axis that regulates the body's response to stress but has also been associated with depression, (3) improved sleep, and (4) monoamine hypothesis, which focus on the neurotransmitters dopamine, norepinephrine, and serotonin. Importantly, moderate and high levels of PA reduce the odds of depression similarly. An increase in fitness is not necessary to provide the effect. Aerobic and resistance exercise training provide similar benefits for individuals diagnosed with mild to moderate depression [40].

Mortality and Quality of Life

A large body of observational studies strongly support that those with higher levels of PA/EX and higher levels of fitness have a lower incidence of premature mortality than their inactive or unfit counterparts [41]. The strength of this association is consistent among men and women and among different racial-ethnic groups, although the data on the latter are limited. As greater than 50 % of deaths

occur due to CHD, stroke, and cancer, the biological plausibility is well established. It is plausible that higher PA/EX enhances quality of life in older adults through reduction in chronic conditions as described previously, and attenuates physical functional decline thereby preserving independent living. Multimorbidity, defined as the coexistence of two or more chronic conditions, is associated with disability, poor functional status, and poor quality of life [11]. As mortality rates have declined and the population has aged, multimorbidity will undoubtedly increase in the future. Habitual PA/EX are critical throughout the lifespan for optimal physical and mental health but more so for older adults to prevent or manage chronic conditions and preserve their physical functional ability. Importantly, it is never too late to begin a PA/EX program. Position statements [1, 2] regarding PA/EX have been built on the extensive literature that documents the adaptability of the human body to PA/EX with much of the research being performed in individuals in the eighth and ninth decades of life [2].

Prevalence of Physical Activity in Older Adults

A comprehensive exercise program incorporates multiple components, including aerobic exercise, resistance training, flexibility, and balance exercises. According to the 2011 Behavioral Risk Factor Surveillance System (BRFSS), 48.9 % of older adults in the United States did not engage in the recommended amounts of aerobic exercise [42]. A larger percentage (78.1 %) did not engage in the recommended amounts of resistance training exercise, and nearly 84 % of older adults in the United States did not engage in the recommended amounts of aerobic and resistance training activity. In spite of these statistics, data from BRFSS indicate a positive shift in the number of older adults engaging in regular physical activity. In 1996, only 19.9 % of older adults obtained 30 min of physical activity five or more days per week. By 2005, this percentage doubled, such that nearly 40 % of older adults reported at least 30 min of moderate intensity physical activity five or more days per week or 20 min of vigorous activity three or more days per week [42]. Even though a well-balanced exercise program includes multiple components, there is little data regarding the percentage of older adults engaging in adequate amounts of flexibility and balance training.

Public Health Guidelines for Physical Activity in Older Adults

2008 Physical Activity Guidelines for Americans

One of the most widely recognized and recommended physical activity guidelines with recommendations specific to older adults is from the US Department of Health and Human Services (DHHS) [1]. The 2008 Physical Activity Guidelines for Americans focus on aerobic and muscle-strengthening activities across the lifespan. The DHHS PA guidelines for older adults are the same as those recommended for the general adult population, but additionally include balance training for those older adults at risk of falling. Furthermore, DHHS states that older adults with chronic conditions be as active as those conditions allow. Each type of physical activity (aerobic, muscle-strengthening, and balance) provides individuals with significant health benefits and whenever possible should all be included in a comprehensive PA/EX program.

A key recommendation from DHHS for older adults is to avoid inactivity. Any activity is better than none. The accumulation of chronic conditions may prevent an older adult from reaching the recommendations, yet an individual should be as active as their conditions allow. Specifically, in order to obtain substantial health benefits, DHHS recommends older adults acquire at least 150 min of

moderate-intensity aerobic physical activity per week, or 75 min of vigorous-intensity aerobic physical activity per week, or an equivalent combination of moderate and vigorous-intensity aerobic physical activity [1]. On a scale of 0–10, with a 0 equivalent to sitting in a chair and a 10 representing a maximal effort, moderate intensity activity would be a 5 or 6. Moderate intensity activities should increase breathing and heart rate. Using the same scale, a vigorous intensity activity would be a 7 or 8 and cause large increases in both breathing and heart rate. The total amount of aerobic physical activity can be accumulated in 10 min bouts, spread throughout the week. Additional health benefits can be gained by exceeding these recommendations. The most commonly recommended aerobic activity is walking as it requires little equipment and is a common and familiar activity for most older adults. Other forms of aerobic exercise include dancing, swimming, water aerobics, bicycle riding, gardening activities (raking leaves, pushing a lawn mower), and aerobic dance classes.

Muscle-strengthening activities are also a key component to a comprehensive physical activity program. The DHHS recommends that older adults engage in muscle-strengthening activities of moderate to high intensity on at least 2 days per week. These activities should involve all major muscle groups of the body, including the muscle of the legs, hips, back, chest, abdomen, shoulders, and arms. Bands, hand weights, or resistance training machines are common examples of equipment used for muscle-strengthening. Calisthenic exercises such as wall push-ups, climbing stairs, or chair squats utilize an individual's own body weight and provide an easy way to engage in muscle-strengthening activities with limited equipment. Other alternatives include carrying groceries, digging or lifting when gardening, and some yoga and Tai chi exercises. One set of 8–12 repetitions for each of the major muscle groups is effective, but two to three sets may be more beneficial to build and maintain muscular strength.

Balance is an important component in an exercise program for older adults, because it helps reduce the risk of falling. The DHHS recommends that older adults who are at increased risk of falls or have fallen in the past, engage in balance activities. Older adults should engage in balance training three or more days per week. Examples of balance exercises include walking backwards or sideways, heel or toe walking, and standing from a sitting position. Balance exercises can be made more challenging by progressing from using a stable support while completing the activities to completing them without any support. Less is known about the type, intensity, and frequency of balance activities that are necessary to achieve health benefits.

Warm-up, cool-down, and flexibility exercises should also be included in a physical activity program for older adults. A warm-up allows the heart rate and breathing to increase gradually before beginning aerobic exercise and a cool-down allows the heart rate and breathing to decrease gradually after ending aerobic exercise. Though flexibility alone has no known benefits for prevention of the major chronic diseases (e.g., heart disease), maintaining adequate flexibility is essential to the performance of activities of daily living. Last, safety is a crucial element in an exercise program for older adults. Depending on an individual's health status, it may be recommended that exercise occur under supervision of qualified professionals.

ACSM Position Stand: Exercise and Physical Activity for Older Adults

In 2009, the American College of Sports Medicine (ACSM) published a Position Stand entitled Exercise and Physical Activity for Older Adults [2]. The purpose was to provide a summary of concerns critical to understanding the importance of physical activity in older adults, including functional changes associated with normal aging, the interaction of physical activity and aging, and the short-term and long-term benefits of physical activity on health and physical function. The document provides an in-depth review of the literature regarding these topic areas and may be a helpful resource for

practitioners seeking evidence-based research studies. The strength of evidence for each physical activity recommendation is also provided, ranging from A (overwhelming evidence from randomized controlled trials and/or observational studies, which provides a consistent pattern of findings on the basis of substantial data) to D (panel consensus judgment that the strength of evidence is insufficient to place it in categories A through C).

In general, the ACSM Position Stand recommendations for physical activity for older adults are consistent with the 2008 DHHS Physical Activity Guidelines for Americans. ACSM also recommends 150 min per week of aerobic activity for health benefits, but provides daily recommendations of at least 30–60 min of moderate-intensity aerobic exercise, 20–30 min of vigorous-intensity aerobic exercise, or an equivalent combination of moderate and vigorous activity, which can be accumulated in 10-min bouts [1, 2]. Despite some discrepancies in terminology, the recommendations for resistance training/muscle-strengthening activities are consistent across the DHHS and ACSM recommendations. The Position Stand provides more guidance regarding flexibility and balance training. According to ACSM position stand, flexibility training is recommended at least 2 days per week at moderate intensity (5–6 out of 10 on an intensity scale), including any type that maintains or increases flexibility using sustained stretches rather than ballistic movements, such as bouncing, which may cause injury. Balance training is recommended for individuals with a history of previous falls or mobility limitations. A lack of studies prevent specific recommendations regarding frequency, intensity, or type of balance exercises, but ACSM encourages progressively difficult postures that gradually reduce the base of support (e.g., two-legged stand, semitandem stand, tandem stand, one-legged stance), dynamic movements (e.g., tandem walk, circle turns), stressing the postural muscle groups (e.g., heel stands, toe stands), and reducing sensory input (e.g., standing with eyes closed). In general, there is strong evidence (evidence ratings of A or B) to support the benefits of aerobic exercise on exercise capacity, cardiovascular effects, body composition, metabolic effects, and bone health in previously sedentary individuals. Also, strong evidence (evidence ratings of A or B) exists to support the benefits of resistance training on muscular strength, muscle power, muscle quality, and bone health in previously sedentary individuals.

The National Institute on Aging provides free publications that can be viewed online, ordered in a hard copy form, or downloaded in the form of an audio book. For example, the handbook entitled *Exercise and Physical Activity*: *Your Everyday Guid*e [43] describes the benefits of physical activity for older adults, provides example exercises with pictures and descriptions, and addresses some frequently asked questions regarding exercise for older adults.

Physical Activity Barriers and Challenges for Older Adults

Despite the numerous physical and psychosocial benefits of regular physical activity, the majority of older adults remain inactive. Inactivity may be due to actual and perceived barriers that are specific to an older adult population. Identifying and addressing the unique challenges faced by older adults may increase adherence to physical activity programs and allow more older adults to lead active lifestyles. In the general population, the most commonly cited reason for not engaging in a regular exercise program is a lack of time; however this does not seem to be the most common barrier among older adults. Older adults most commonly report limitations due to current health conditions and pain, environmental issues, lack of advice from physicians, and a general lack of knowledge regarding physical activity [44]. Other barriers identified by older adults include a lack of time and energy, fear of injury, low motivation, and safety issues.

Among older adults of all ages, current health status is the most common barrier to physical activity. In the US, 80 % of older adults have at least one chronic condition [45] and more than 60 % have at least two chronic conditions [11]. Furthermore, BRFSS data indicate that the percentage of adults

reporting limitations in activities due to physical, mental, or emotional problems increases with age, such that current data indicate that over one-third of older adults report these limitations. The Centers for Disease Control and Prevention (CDC) recommend that older adults with chronic conditions speak with their physicians to find out if their health condition would in any way limit their ability to be active. If an older adult is considering beginning an exercise program, it is recommended that they assess their ability to safely engage in exercise. One commonly used tool is the PAR-Q, or physical activity readiness questionnaire. The PAR-Q contains seven questions, which require a "yes" or "no" response. If an older adult answers "yes" to any of the questions, it is recommended that they speak with their physician before beginning an exercise program. It is also important to bear in mind that the most common chronic health conditions in older adults (heart disease, diabetes, and arthritis) are improved by regular physical activity and may reduce an older adult's risk of developing other conditions. Even if an older adult cannot meet the minimum physical activity guidelines due to health problems, they are encouraged to be as active as possible, bearing in mind their chronic conditions and current health status.

An older adult's physical environment may also pose a challenge to engaging in a regular physical activity program. For example, an individual's built environment may discourage physical activity if there are poorly maintained or no sidewalks. Additionally, older adults who prefer walking outdoors are more active when they perceive that they are safe in their own neighborhood. Other environmental barriers to physical activity include geographical distance to a local recreational facility, gym, park, or swimming pool. Overcoming barriers in the built environment is challenging, but recommendations are being made by CDC, AARP, World Health Organization, and others to create environments that are safe and encourage physical activity in one's community by improving access to parks, public transportation, and walking paths.

Older adults commonly cite a lack of knowledge as a barrier to initiating a physical activity program. Individuals may lack understanding of the adequate amounts and intensities of physical activity that are necessary for health benefits. Additionally, many older adults may believe that their normal activities of daily living provide enough exercise for disease prevention. Older adults' physicians can play a key role in promoting exercise among this population. Despite the fact that older adults tend to visit physicians more often than the general population, the majority of physicians do not regularly counsel their patients about physical activity. In 2010, 41.9 % of individuals 65–74 years of age received exercise recommendations from their physician or another health professional, but this percentage decreased as age increased, 32.9 % of individuals 75–84 years of age and only 28.9 % of individuals 85 and older received exercise recommendations from physicians or other health professionals [46]. Understanding the pivotal role that physicians can play in overcoming barriers to physical activity for older adults, the American College of Sports Medicine and the American Medical Association recently introduced a health campaign, Exercise is Medicine [47]. This program encourages physicians to assess and review every patient's physical activity habits at each visit and provides physicians with tools and methods to counsel individual patients. The *Exercise is Medicine* website (http://www.exerciseismedicine.org) provides free guides for physicians and other healthcare providers that can be downloaded, printed, or emailed. For example, the Health Care Providers' Action Guide suggests that physicians begin by asking their patients if they currently exercise. If yes, physicians are encouraged to query regarding the type of activities, duration, intensity, and frequency and to record this information. If the answer was no, it is suggested that the physician ask why and determine if the patient is willing to begin an exercise program. Additionally, the guide includes a physical activity readiness questionnaire, exercise prescription and referral forms, and physical activity clearance forms.

In order to encourage older adults to initiate a physical activity program or improve adherence to a program, it is important to remove perceived and actual barriers. Multiple methods have been effective at removing or mitigating common barriers. For example, it is important to highlight the social support and positive interactions that can be gained through regular physical activity programs in

group settings among older adults. Exercising among peers creates a less stressful environment for older adults and involves a social component, which improves physical activity adherence in the long-term. Building self-esteem and self-efficacy is also important for older adults and has been shown to be related to older adults' physical activity patterns. Education and knowledge transfer about how to safely engage in exercise and the benefits of physical activity improve older adults' adherence and enjoyment in exercise. Finally, it is important to bear in mind that among some older adults, barriers may also act as motivators. For example, failing health, which can cause physical activity to be more challenging and is often viewed as a barrier, can serve as motivation for an older adult to become more active. Helping older adults identify their own distinct barriers and motivators towards exercise is a helpful tool used to create individualized programs that are both safe and effective. Practitioners should keep in the mind that the ultimate goal is to encourage older adults to remain active throughout their lifetime.

Conclusion: Evidence-Based Physical Activity Programs for Older Adults

This chapter concludes by translating our knowledge base about the benefits of physical activity by summarizing accessible, practical, and evidence-based programs for older adults. Clinicians must be equipped to provide knowledge, support, and encouragement for older adults to engage in physical activity. Providing basic education regarding the health benefits of physical activity, as well as encouragement is straightforward for most clinicians, but recommending specific modes of exercise appropriate for older adults with varying chronic conditions and experience levels is more complex. Fortunately, there are many evidenced-based physical activity programs that clinicians can recommend or utilize with confidence.

The National Council on Aging (NCOA) and the National Institute on Aging (NIA) at the National Institute of Health (NIH) support the use of evidence-based physical activity programs for older adults and provide resources for connecting with many program providers on their websites [48–50]. Title IIID of the Older Americans Act (OAA) authorizes funds from the Department of Health and Human Services (DHHS), Administration on Aging (AoA) specifically for use in implementing evidence-based health promotion and disease prevention programs (e.g., physical activity, smoking cessation, falls prevention) and to leverage other funds, particularly through partnerships, to support these programs [49]. AoA uses a tiered set of criteria (minimal, intermediate, and highest-level criteria) to define evidence-based programs suitable for consideration for OAA Title IIID funding. AoA, NCOA, and NIA promote the use of evidence-based physical activity programs because of their proven effectiveness in the target population and readiness for translation and implementation by a variety of types of organizations and clinicians [49]. These programs are particularly successful because they address many of the barriers to physical activity for older adults (e.g., safety, knowledge, accessibility, chronic disease management).

For example, *Healthy Moves for Aging Well*, a Title IIID highest-tier criteria qualified physical activity program, addresses safety concerns by providing chair exercises for frail individuals or those with functional limitations in addition to advanced level exercises [51, 52] (Table 22.1). Most of these NCOA, AoA, and NIA recommended programs involve instruction, demonstration, and supervision by a lay person or health professional, which can be reassuring for the apprehensive older adult. Barriers to transportation can be overcome by community-based senior centers that provide both transportation and physical activity programs, while many group living situations provide physical activity programs on-site such as in long-term care facilities, nursing homes, assisted living facilities, and independent living communities. About 90 % of community-based senior centers offer at least one evidence-based program, many of which include physical activity [48]. Moreover, some physical activity programs are designed for use in the home with guidance from instructional booklets and DVDs.

Table 22.1 Evidence-based physical activity and nutrition programs for older adults[a]

Program	Nutrition	Physical activity	Program goals	Program description	Target population	Organization and contact
Eat Better, Move More	✓	✓	Increase daily consumption of fruits and vegetables, fiber, and calcium Eat sensible portions for healthy weight Accumulate at least 30 min physical activity on most days of the week	12-week group-based education sessions (≤30 min) on nutrition and physical activity lead by health professional Step counters used for motivation	Older adults of any health and fitness level (with physician clearance)	Florida International University, National Resource Center on Nutrition, Physical Activity, and Aging http://nutritionandaging.fiu.edu/You_Can/index.asp
Active Living Every Day (ALED)		✓	Integrate more physical activity into their daily lives	12-week group-based education Book with optional online companion materials	Adults interested in integrating physical activity into their daily lives	Human Kinetics www.ActiveLiving.info/ OR 800-747-4457
Healthy Eating Every Day (HEED)	✓		Improve eating habits for optimal health, set realistic goals and rewards, and cope with triggers for unhealthy eating	12-week group-based education OR online individual course Book with online companion materials	Adults interested in improving nutritional health	Human Kinetics www.ActiveLiving.info/ OR 800-747-4457
Diabetes Prevention Program	✓	✓	Prevent or delay onset of type 2 diabetes by improving nutrition and meeting DHHS 2008 Guidelines for physical activity	1-year program Lifestyle coaches provide 22 group education sessions Training provided by DTTAC[b]	Adults interested in preventing or delaying the onset of type 2 diabetes	CDC and private partners http://www.cdc.gov/diabetes/prevention/about.htm

(continued)

Table 22.1 (continued)

Program	Nutrition	Physical activity	Program goals	Program description	Target population	Organization and contact
Stanford School of Medicine Chronic Disease Self-Management Program	✓	✓	Improve chronic disease self-management through education regarding nutrition, physical activity, stress-management, interpersonal communication, medication management, and behavioral concerns	6 weeks 2.5 h per week in community centers, churches, libraries, hospitals Program provides information and teaches practical skills on managing chronic health problems	Adults with one or more chronic diseases	Stanford School of Medicine http://patienteducation.stanford.edu/programs/cdsmp.html
Eat Smart, Live Long	✓	✓	Improve fruit and vegetable consumption (at least 3.5 cups/day) Participate in at least 30 min of moderate-intensity physical activity most days of the week	4 interactive sessions lead by a community member Leaders Guide and Session Guides provide self-assessment tools and education CD of reproducible participant handouts	Able-bodied older adult (60-74 y) participants of USDA FNS nutrition assistance programs (SNAP[c], SFMNP[d], OAA[e] Congregate Meals Providers)	USDA Food and Nutrition Services http://www.arthritis.org/resources/community-programs/walk-with-ease/
Walk With Ease		✓	Reduce the pain and discomfort of arthritis Increase balance, strength and walking pace Build confidence in ability to be physically active Improve overall health	Certified instructor leads 1-h group classes 3days/week for 6 weeks Participant guidebook provided with fitness routine, stretching exercises, heart-rate monitoring techniques Companion online tools, videos, and social media	Older adults with arthritis who can be on their feet for at least 10 min without increased pain	Arthritis Foundation http://www.arthritis.org/resources/community-programs/walk-with-ease/ OR call 1-800-283-7800

Healthy Moves for Aging Well		✓	Help maximize independence by building strength, increasing flexibility, and helping to reduce the risk of falls	In-home physical activity intervention (chair bound and advanced exercises) Exercises practiced 3–5 days/week One 15-min goal setting and instructional session between care manager and participant	Frail, sedentary adults ≥65 years currently enrolled in a care management program; need assistance with 2–4 ADLs[f]	Partners in Care Foundation http://www.picf.org/landing_pages/22,3.html
Project Enhance (Enhance Fitness, Enhance Wellness)		✓	Enhance Fitness: Improve functional fitness of older adults	(EF) Group physical activity sessions focused on stretching and flexibility, low impact aerobics, strength training, and balance; 1 h sessions offered 3 days/week	(EF) Older adults seeking to maintain or improve their physical functioning	Senior Services (Seattle, WA) and University of Washington
			Enhance Wellness (EW): Behavior modification for those with chronic conditions	(EW) Health professionals work with participant and physician to develop behavioral goals and action plan	(EW) Older adults with chronic conditions	www.projectenhance.org/EnhanceFitness.aspx
Go4Life	✓	✓	Improve physical activity uptake	Individual level physical activities Workout to Go: Sample exercise routine (13 exercises) can be ordered or downloaded for print Guidebook and video, tip sheets, exercise audio book, healthy aging brochures and pamphlets	Adults ≥50 years	National Institute on Aging (NIA) at the National Institute of Health http://go4life.nia.nih.gov/

[a]Adapted from DHHS AoA Title III-D Highest Tier Evidence-Based Health Promotion/Disease Prevention Programs: http://www.ncoa.org/improve-health/center-for-healthy-aging/content-library/Title-IIID-Highest-Tier-Evidence-FINAL.pdf [52]
[b]Diabetes Training and Technical Assistance Center (DTTAC) at Emory University
[c]Supplemental Nutrition Assistance Program (SNAP)
[d]Senior Farmers Market Nutrition Program (SFMNP)
[e]Older Americans Act (OAA)
[f]Activities of Daily Living (ADL)

Programs such as the *Stanford Chronic Disease Self-Management Program* encourage lifestyle changes, including increased physical activity, applicable to prevention and management of multiple chronic diseases, while other evidence-based programs are disease specific, such as the *Walk With Ease* Program that specifically targets alleviating arthritis discomfort [51, 53].

Clinicians should also contact other local organizations, such as faith communities, health systems, colleges and universities, and local fitness centers, including the YMCA, to identify existing physical activity programs and explore forming partnerships to offer these programs [54]. For example, the SilverSneakers program is offered by several Medicare health plans and provides membership with many fitness centers, including both corporate gyms and YMCAs, and access to a SilverSneakers® Program Advisor and SilverSneakers® exclusive classes [55]. The SilverSneakers program also provides personalized fitness programs for those older adults who do not have convenient access to a SilverSneakers® provider at a fitness center [55].

Table 22.1 highlights several evidence-based health promotion/disease prevention physical activity and nutrition programs, of which many are endorsed by NCOA and NIA and qualify for OAA Title IIID funding [51]. As physical activity and nutrition provide synergistic benefits for health and well-being, programs that target both, such as Florida International University's *Eat Better Move More* and Human Kinetics' companion programs *Active Living Every Day* and *Healthy Eating Every Day*, may be optimal for improving the health and well-being of older adults. With readily available evidence-based resources, clinicians can be instrumental in encouraging older adults to become more physically active.

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Chapter 23
Dietary Supplements in Older Adults

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Key Points

- There are times when food alone cannot meet all the nutrient requirements of older adults, and certain dietary and medical foods can help maintain health.
- However, an established need for supplements is highly variable depending upon the nutrient, e.g., strong for vitamin D and calcium to prevent osteoporosis versus unclear for B-vitamins to protect blood vessels.
- Factors increasing the likelihood of needing supplements include osteoporosis, alcohol abuse, gastrointestinal abnormalities, renal insufficiency, cardiovascular disease, nutritional anemias, or any situation in which food intake is chronically inadequate.
- Health care providers should routinely screen elderly clients for both the need to use dietary supplements and the risks of excessive supplement intake, which may include economic difficulties as well as interactions with medications and other supplements.

Keywords Dietary supplements • Vitamins • Minerals • Botanicals • Herbals

Introduction

This chapter focuses on the rationale and evidence base for the use of dietary supplements for both maintaining health and decreasing the risks of some common chronic diseases. This review also updates the information in a review of data through 2009 on nutritional supplements for older adults [1] by summarizing evidence published in 2009–2013 from systematic reviews and meta-analyses of randomized clinical trials with disease endpoints. The chapter concludes with recommendations for assessing dietary supplement use in older persons and suggestions for counseling them. We have categorized these supplements according to their active ingredient(s), and we pay particular attention to

Note: The findings and views reported in this chapter represent those of the contributing authors and not necessarily those of the National Institutes of Health and are not intended to constitute an "authoritative statement" under the Food and Drug Administration rules and regulations.

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claims on supplement labels about these products' effects on health conditions or the health of specific parts of the body.

Sound dietary patterns are vital to maintaining health and well-being. However, there are times when food alone cannot meet all nutrient requirements, or physiological limitations due to disease alter nutrition needs. Under such circumstances, certain dietary and medical foods can help maintain health. For example, the need for supplemental vitamin D and calcium to prevent osteoporosis in older adults is well established [2–7]. In contrast, the effectiveness of the use of supplements containing B-vitamins, such as folic acid and vitamins B_6 and B_{12}, in preventing blood vessel diseases in older adults is not clear [8–10]. The reason why some dietary supplements are not effective in reducing disease risk might be that, with a few exceptions, clinical deficiency of vitamins or minerals (other than calcium and possibly vitamin D [7, 11] and iron) is uncommon in the United States, except in certain high-risk groups such as the elderly. In other cases, excessive amounts of nutrients from fortificants or supplements might have adverse effects. For example, very high doses of vitamin D that some elderly individuals take in hope of preventing osteoporosis may give rise to health problems, such as kidney stones [12].

Dietary supplements marketed today include many ingredients other than essential nutrients, such as extracts of herbs and other plants. Older Americans use these products to prevent, manage, or lessen the impact of age-associated disorders and conditions. Such use might be inappropriate for certain conditions and diseases [13]. In one recent analysis of data on adults older than 19 from the 2007–2010 National Health and Nutrition Examination Survey (NHANES), only 23 % of supplements were used in accordance with health care providers' recommendations [13]. Although approximately 25 % of all drugs used today are derived from plants [14], very few of the botanical supplement products on the market have been rigorously tested in clinical studies for efficacy and toxicity. Another concern is the risk of interactions between dietary supplements and other medications used by the elderly [15].

The Dietary Supplement Marketplace

According to the 2012 edition of *Nutrition Business Journal*, supplement sales in the United States now total more than $30 billion each year, fueled in large part by consumers' desires for health and wellness [16]. The top five dietary supplement companies include pharmaceutical companies (Pfizer, Bayer Group, and Pharmavite) and contract manufacturers (such as Perrigo) that produce a variety of products for a variety of companies, specialty product manufacturers (such as Glanbia, Schwabe NA, and Integrative Therapeutics) that do so for a more limited group of products, and holding companies (such as the Carlyle Group).

Types of Dietary Supplements

Dietary supplements are categorized in many ways. For example, marketers may group them by source (i.e., animal or plant), nutrition researchers by their essentiality to human health or chemical composition (e.g., vitamin, mineral, or protein), epidemiologists by prevalence of use, regulators by their purported health benefits (e.g., for bone health or heart health) or manufacturing or production processes used (e.g., use of organic ingredients, production using traditional methods, or synthesis from artificial ingredients); or a combinations of these categories. However, marketers frequently promote supplements based on their purported health benefits, even if these products' efficacy has not been demonstrated.

The doses of bioactive ingredients that supplements contain can vary greatly; some supplements contain 100 % or more of the reference daily value (DV) per serving and some contain much less. "High-potency" nutrient products (containing 100 % of more of the DV per serving) and non-nutrient supplements containing large amounts of single ingredients or concentrated extracts have the potential for adverse interactions with other dietary constituents and drugs [15, 17]. These interactions can lead to health problems in elderly persons taking many medications.

Motivations for Dietary Supplement Use

The recent analysis of the 2007–2010 NHANES found that American adults use supplements to "improve" (43 %) or "maintain" (33 %) their overall health rather than to supplement intakes of nutrients from food [13]. Condition-specific use, such as for "bone health" or "heart health or to lower cholesterol" is also high. Adults older than 60 years are more likely than younger people to report motivations for using dietary supplements that are related to specific health conditions or the health of parts of the body, such as the heart, bones, joints, or eyes.

Dietary Supplement Use by Older Americans

About half of all adults and 70 % of those older than 71 years in the United States use dietary supplements [18]. Among older Americans, slightly more women (75 %) than men (66 %) use supplements. Multivitamin/multimineral (MVM) supplements are by far the most popular among older persons (46 % report using them in the past month), whereas fewer (17 %) report using botanical supplements [18]. Among older adults, prevalence of use of supplements containing at least one of the following vitamins is as follows: 41 % for vitamin C, 40 % for vitamin E, 37 % for vitamin A, 36 % for vitamin B_6, and 28 % for vitamin K. Prevalence of use for minerals in this age group is 36 % for zinc, 35 % for magnesium, 32 % for selenium, 29 % for chromium, and 16 % for iron. In addition, more older adults use supplements containing one or more vitamins and/or minerals than those containing botanical or other ingredients [19].

Adults who take more herbal and other botanical products often use these products to treat specific health conditions, such as upper respiratory tract infection or anxiety [20]. In a recent study using data from the National Health Interview Survey, individuals with more severe diabetes were more likely to use complementary and alternative medicines, including diet-based interventions and nonvitamin/nonmineral dietary supplements, than those with less severe disease [21].

Surveys on dietary supplement use do not readily lend themselves to comparisons between studies because patterns of use change from year to year, the collection instruments or methods are different (e.g., telephone versus online surveys, 24-h recall versus food frequency questionnaires), participants might be queried about different time periods of use (e.g., over the last week versus the last month), and respondents might be confused about what types of supplements are relevant to a given question.

Current Market Trends in Supplements

The nutrient-containing supplements on the market today vary in their forms as well as the nutrient doses they provide. These products include: (1) MVM products; (2) multivitamins, such as B-complex vitamins or combinations of antioxidant vitamins; (3) calcium-containing products with

or without other minerals or vitamins, such as calcium, calcium and vitamin D, and Tums and other antacids with calcium as a primary ingredient; (4) multimineral preparations, such as magnesium and zinc; (5) single-vitamin/mineral or single-mineral supplements, such as supplements providing vitamin A or iron; (6) omega-3 and omega-6 fatty acids, such as fish oils, docosahexaenoic acid (DHA), and flaxseed; (7) products containing protein, amino acids, and nitrogenous ingredients, such as creatine, lysine, arginine, or creatinine; and (8) products with fiber as the primary ingredient or fiber used as a laxative, including over-the-counter products with dual labeling, such as Metamucil and Citrucel.

In the 1990s, the use of herbal products and high-dose vitamins became much more common [22]. During this period, sales of condition-specific and other specialty supplements, such as sports nutrition products, also grew rapidly, and many consumers switched from single-nutrient supplements to combination and condition-specific products [16, 23].

In marketing dietary supplements, manufacturers often make claims about these products' effectiveness in promoting the health of various organs. Marketers also promote combinations of supplements and prescription medications for specific conditions in drugstore chains, health food stores, grocery stores, and magazines, although such efforts are not always successful. Nevertheless, vitamin, multivitamin, and mineral supplements are among the items most frequently purchased with a heart-related prescription drug in drugstores and grocery stores [24].

The number of different dietary supplement products sold in the United States is not known, although the U.S. Food and Drug Administration (FDA) has estimated the total to be at least 55,000 [25]. Dietary supplements are produced in many different parts of the globe and are sold through many channels, including the Internet, drugstores, supermarkets, and grocery stores, health food stores, and fitness centers, as well as in some healthcare providers' offices. New supplements constantly appear on the market. The compositions, quality, and prices of supplements vary greatly, and even those with similar formulations can differ markedly from one producer to another.

Advertising themes closely track changes in population demographics, such as the greater number of older persons and emerging trends in science. Dietary supplements are marketed so imaginatively that it is easy for older Americans to infer that supplements can do far more than simply add to dietary intake, such as preventing or treating chronic diseases. Indeed, the latest compilation of the trade publication *Nutrition Business Journal's* annual statistics on the sales of supplement marketed in the United States today suggests that there are no ills or miseries of mankind for which there is not a condition-specific supplement on the market [16]. People who counsel the elderly should be aware of the current marketing appeals and be ready to discuss the actual safety with their patients and address the often quite different efficacy of these products from advertised claims.

Multivitamins are among the dietary supplements marketed today with appeals to general health. Manufacturers claim that many supplements have anti-aging effects, appealing to the desire for an enhanced appearance and youthful looks or allaying fears about memory loss. Coenzyme Q10 (CoQ10) is currently popular for anti-aging. In their marketing claims, CoQ10 manufacturers often mention telomere length (a marker of biological age) and "telomere health," which is supposedly improved by ingredients such as resveratrol; omega-3 fatty acids; and vitamins C, D, and E. However, there is little evidence that these claims are factual.

Many condition-specific supplements appeal to elders. Brain health and mental acuity also seem to have a special appeal, and nearly half the sales of products in this category are of fish and animal oils high in omega-3 fatty acids [16]. Manufacturers claim that supplement ingredients (including vitamins B, D, and E; zinc; phosphatidylserine; CoQ10; *Ginkgo biloba*; St. John's wort; SAM-e; and kava) improve cognition, reduce anxiety and depression, and slow the onset of dementia and the progression of Alzheimer disease. In addition, many supplements, such as multivitamins and 5-hydroxytryptophan, are sold for mood disorders, such as depression. For people with trouble sleeping, manufacturers claim that herbs, such as valerian, and other ingredients, such as melatonin, provide relief from stress and insomnia.

Cardiovascular/heart heath condition-specific supplement sales are also growing rapidly, particularly for omega-3-rich fish and animal oils [16]. Sales fell for folic acid and vitamin E after large clinical trials showed few benefits [26–33], but the supplement industry keeps marketing others, such as potassium, magnesium, and calcium for high blood pressure. Some products, such as CoQ10 and proathocyanidins (naturally found in dark chocolate, tea, and Concord grape juice), are being tested in clinical trials, but they are already being marketed before results are available.

For the millions of older Americans living with osteoporosis, arthritis, osteoarthritis of the knee, and chronic joint and bone pain, glucosamine/chondroitin products marketed for these conditions are widely available. For bone health, calcium is the most commonly marketed product, with vitamin D and vitamin K close behind [16]. Elderly people worry about vision and eye health, particularly advanced age-related macular degeneration that leads to vision loss and cataracts [34]. Among vision health supplements, lutein is the most popular. Sales of diabetes and metabolic syndrome condition-specific supplements are also growing rapidly, with vitamin B and biotin being the biggest sellers in this category.

Regulation of Dietary Supplements

The safety and efficacy of dietary supplements are critical to consider when dealing with the health of older Americans. Although most dietary supplements are both safe and effective, they are not tested as rigorously as prescription drugs. As with conventional foods, Congress gave the FDA the authority to regulate dietary supplements once they are on the market. However, unlike medical devices, the FDA does not have the authority to regulate dietary supplements before they are marketed. Members of the American public, including elders, are likely to believe that the FDA reviews the safety and effectiveness of dietary supplements before they are marketed. Therefore, it is important for those who counsel elders to understand what the law does and does not say. A brief review of the relevant statutes follows.

The Dietary Supplement Health and Education Act (DSHEA; Public Law [PL] 103-417) laid the foundation for the current regulatory framework for dietary supplements in the United States. This law amended the Federal Food, Drug, and Cosmetic Act of 1938 "to establish standards with respect to dietary supplements." DSHEA defines a dietary supplement as "a product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients: 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 the ingredients described above]."

Under DSHEA, the FDA regulates the safety and manufacturing of, and information about, dietary supplements, such as claims in product labels, package inserts, and accompanying literature. The FDA cannot require testing of dietary supplements prior to marketing (except for new dietary ingredients). However, although DSHEA prohibits manufacturers from selling dangerous products, it permits the FDA to remove a product from the marketplace only when the agency proves that the product is dangerous to the health of Americans. If in the labeling or marketing of a dietary supplement product a claim is made that the product can diagnose, treat, cure, or prevent disease, such as "cures cancer," the FDA determines that the product is an unapproved new drug and its sales are thus illegal.

Regulations requiring good manufacturing practices for dietary supplements and finished products have been in place since 2007 [35]. The Public Health Security and Bioterrorism Preparedness and Response Act of 2002 (PL 107-188) requires registration of manufacturers, processors, and packers of foods and dietary supplements with the FDA. The Dietary Supplement and Nonprescription Drug Consumer Protection Act (commonly known as the Adverse Event Reporting, or AER, law; PL 109-462) of 2006 requires manufacturers of dietary supplements and over-the-counter products to submit

serious adverse event reports to the FDA. The Food Safety Modernization Act of 2011 (PL 111-353) provides the FDA with mandatory recall authority for adulterated dietary supplements and foods containing undisclosed allergens.

The process for removing an unsafe dietary supplement from the market is still cumbersome, with the burden of proof falling on the FDA, even after the FDA received mandatory recall authority. Congress and the FDA continue to balance the often-conflicting goals of safety and effectiveness; access to up-to-date, complete, and unbiased information on dietary supplements; accurate reporting of adverse events; and consumer choice [36].

Health Claims for Supplements

The Nutrition Labeling and Education Act of 1990 (PL 101-535) that allowed conventional foods and dietary supplements to be labeled with health claims also permitted health claim labels for supplements that met the specified criteria. In this context, health claims are statements describing relationships between a food or food component and a disease, such as cardiovascular disease, or a health-related condition, such as hypertension, that is considered to be a surrogate marker for a disease (in this case, for cardiovascular disease). Health claims are limited to claims about disease risk reduction and cannot suggest that a product cures, mitigates, treats, or prevents a disease.

The FDA may use several ways to determine which health claims may be used on a label or in labeling for dietary supplements. The FDA website provides details on these processes (http://www.fda.gov/Food/GuidanceRegulation/). In some cases, the FDA approves health claims based on evidence that a nutrient or dietary supplement influences a biomarker in a way that is associated with reduced disease risk.

When evidence suggests that a product has a potential benefit but the FDA does not consider the evidence to be strong, it might permit a qualified health claim. Qualified health claims must be accompanied by language such as "FDA has determined that this evidence is limited and not conclusive."

The FDA has authorized 16 health-disease-related claims for foods, including 8 for cardiovascular disease, 4 for cancer, 2 for dental caries, 1 for neural tube defects, and 1 for osteoporosis-related conditions. Only three approved health claims are authorized for dietary supplements: one for osteoporosis, one for neural tube defects, and one for cardiovascular disease. The FDA has approved 17 qualified health claims for foods: 7 for cardiovascular disease, 5 for cancer, 1 for cognitive function, 1 for atopic dermatitis, 1 for hypertension, 1 for neural tube birth defects, and 1 for diabetes-related conditions. The qualified health claims for supplements include at least 2 for cardiovascular disease, 6 for cancer, 1 for cognitive function, 1 for hypertension, 1 for neural tube defects, and 1 for diabetes.

Manufacturers may make structure-function claims on the labels of conventional foods and dietary supplements to describe the role of ingredients intended to affect a normal structure or function in humans. The FDA does not review or authorize structure-function claims prior to their use. For this reason, these claims must carry a disclaimer statement.

Effectiveness and Safety of Nutrient Supplements for the Elderly

Evaluations of the associations between supplements, health, and disease risk are complicated because the formulations used vary so much from study to study. Furthermore, supplement users and nonusers have varied demographic, lifestyle, and other characteristics that affect their health. Nevertheless, some conclusions can be drawn, as we show in this section.

Space does not permit a complete discussion here of all of the essential nutrients provided in dietary supplements, so we have given priority to the recent evidence for or against the efficacy of the most popular dietary supplement ingredients among older Americans. We discuss these ingredients roughly in the order of their prevalence of use.

Supplements Containing Combinations of Vitamins

MVMs

There is no regulatory definition of what nutrients or how much of certain nutrients must be included in MVMs. Many different products with various levels of nutrients and other ingredients are in the marketplace today. The most common MVMs contain vitamins that are generally at levels close to their daily values (DVs), but they contain much lower amounts than their DVs of some minerals that would otherwise add bulk to the products. The special "silver" formulations for elders usually provide the same vitamins and minerals as those marketed to all adults but in amounts that are closer to the recommended dietary allowance (RDA) levels for older individuals. High-potency preparations contain greater amounts of both vitamins and minerals than standard MVMs. Specialized "condition-specific" supplements appealing to elder concerns, such as immune function or maintenance of memory, contain several vitamins and minerals in combination with other ingredients.

MVMs: Supplementing Nutrients in the Diet

One of the reasons why older people take MVMs is to ensure that they are obtaining adequate amounts of nutrients to maximize their health [13]. Taking MVMs does increase intakes of the nutrients these products contain. However, the nutrients in MVMs might not be those that are low or lacking in the user's diet, or the amounts present might not suffice to meet the user's nutrient needs. Also, MVM users tend to have good diets with relatively high nutrient intakes, so they might not need MVMs. Furthermore, some nutrients might already be present in plentiful or excessive amounts in users' diets. If many "high-potency" MVM supplements are taken daily, excessive intakes may result. Paradoxically, elders who are most likely to benefit from MVMs because of low micronutrient intakes are least likely to take them [18].

MVMs: Chronic Disease Prevention

Some older people take MVMs to prevent or treat chronic degenerative diseases and other ills. In 2006, the Office of Medical Applications of Research and Office of Dietary Supplements at the National Institutes of Health sponsored a systematic review of randomized controlled trials (RCTs) that assessed the risks and benefits of MVMs for many chronic diseases [37]. An expert committee evaluated the state of the science and concluded that "the present evidence is insufficient to recommend either for or against the use of MVMs by the American public to prevent chronic disease." The U.S. Preventive Services Task Force also found that the evidence was insufficient to determine whether MVMs can prevent cancer or cardiovascular disease [38]. In its 2007 report, *Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective*, the World Cancer Research Foundation and American Institute for Cancer Research recommended against using supplements to prevent cancer; instead, these organizations recommended that people meet their nutritional needs through diet alone, which would maximize the proportion of the population achieving nutritional adequacy without supplements [39].

MVMs: Mortality

Whether MVM supplements increase or decrease mortality risk in older adults continues to be debated because higher mortality rates have been reported for subgroups in some cohorts [40]. A meta-analysis of 21 randomized controlled trials (RCTs) that included approximately 91,000 individuals (average age 62 years) and 8,800 deaths found no significant effects of MVMs on all-cause mortality (relative risk [RR]: 0.98; 95 % confidence interval [CI] 0.94, 1.02) [41]. In the 13 primary prevention trials included in the analysis, MVMs had no effect on mortality due to cancer (RR: 0.96; 95 % CI: 0.88, 1.04) or vascular causes (RR: 1.01; 95 % CI: 0.93, 1.09).

MVMs: Cancer

In an analysis of cohort and case-control studies of MVMs and breast cancer, eight studies in more than 355,000 women who took MVMs for 3–10 years at least twice a week were studied [42]. Neither longer duration of use nor greater frequency of use was significantly associated with decreased risk of breast cancer in the meta-analysis of the pooled data from five cohort studies (RR: 0.10; 95 % CI: 0.60, 1.63). An analysis of data from 14 RCTs, case-control studies, and cohort studies in 230,000 men aged 40 and older also found no convincing evidence of effects of multivitamins on prostate cancer incidence, severity, or death [43]. A pooled analysis of 13 prospective cohort studies of the associations between intakes of vitamins A, C, and E (including intakes from multivitamins) and colon cancer risk included more than 676,000 adults and 5,400 colon cancer cases [44]. Intakes of the vitamins from food were not associated with colon cancer risk, even after adjustment for total folic acid intakes. However, multivitamin use was inversely associated with colon cancer risk (RR: 0.88; 95 % CI: 0.81, 0.96).

Two large RCTs have linked beta-carotene and vitamin A supplements to an increased risk of lung cancer in smokers [45]. Smokers and possibly former smokers should therefore avoid MVM products providing large amounts of these nutrients.

MVMs: Infection

Infections are major causes of morbidity among elderly people. A systematic review of 20 RCTs in more than 35,000 adults found no differences in the number of episodes of infection in people over 65 years who did or did not take MVM supplements (weighted mean difference [WMD]: 0.06; 95 % CI: −0.04, 0.16) [46]. However, the results did suggest that undernourished older people might benefit from taking supplements for at least 6 months (WMD: −0.67; 95 % CI: −1.24, −0.10).

MVMs: Cognition

A systematic review included ten RCTs that tested the effects of MVM supplements for at least 1 month on any valid cognitive outcome in 3,200 adults older than 18 with normal cognitive function [47]. MVMs enhanced immediate free-recall memory (standardized mean difference: −0.32; 95 % CI: 0.09, 0.56; $p < 0.01$) but had no effect on delayed free-recall memory or verbal fluency. An RCT testing daily MVMs for 12 months in 900 persons older than 65 years living in the community (450 in each treatment arm) also found no evidence of change in several domains of cognitive function, including digit span forward (an assessment of immediate memory) and verbal fluency (an assessment of executive function) [48].

MVMs: Conclusions

In summary, for some older persons whose dietary intakes are low or inadequate, taking MVMs containing approximate DV levels of the micronutrients that their diets do not provide in sufficient quantities might be helpful. The evidence is still weak on whether taking MVMs prevents chronic disease or decreases mortality risk among older persons. More high-quality studies are needed before MVM use can be recommended for these purposes.

Supplements Containing Calcium and Vitamin D

Many calcium-containing supplements with or without other vitamins and minerals are marketed to older people. In its 2011 report on the dietary reference intakes (DRIs) for calcium and vitamin D, the Food and Nutrition Board of the Institute of Medicine summarized the evidence for the association of vitamin D and calcium with various chronic degenerative disease outcomes [49]. The 2011 DRIs are based on the amounts of calcium and vitamin D required to decrease the risks of osteoporosis and fractures.

Calcium-containing supplements with and without vitamin D are extremely popular among older Americans, in part because many elders do not obtain enough of these nutrients from food alone [50]. The RDA is 1,200 mg for calcium and 800 IU (20 μg) for vitamin D for women and men over age 71. According to an analysis of 2010 NHANES data, the prevalence of use of calcium supplements was 65 % among women aged 71 years or older and 56 % among men [50]. These intakes contributed a mean of 608 mg/day to intakes in women and 372 mg/day in men. The prevalence of use of vitamin D supplements in elders aged 71 years or older was 49 %, and these supplements contributed about 11 μg/day. Total food and supplement intakes for both of these nutrients were lower than the adequate intake (AI) for this age group, but intakes in users of calcium and vitamin D supplements were closer to the AI than in nonusers.

Calcium and Vitamin D: Osteoporosis

More than 99 % of total body calcium is stored in bones and teeth to support their structure [51]. Consuming adequate amounts of calcium and vitamin D throughout infancy, childhood, and adolescence and engaging in weight-bearing exercise maximizes bone strength and bone density, which helps prevent osteoporosis and fractures later in life. In 1993, the FDA authorized a health claim for food labels about calcium and osteoporosis in response to scientific evidence indicating that an inadequate calcium intake contributes to low peak bone mass and is a risk factor for osteoporosis [52]. The claim states that "adequate calcium intake throughout life, as part of a well-balanced diet, may reduce the risk of osteoporosis." Manufacturers may also make health claims about calcium and osteoporosis and about calcium, vitamin D, and osteoporosis for dietary supplements. An example of these claim statements is, "Adequate calcium and vitamin D, as part of a well-balanced diet, along with physical activity, may reduce the risk of osteoporosis."

More than 1.5 million fractures per year in the United States are linked to osteoporosis, and they generate high healthcare costs [53]. The U.S. Surgeon General's report on bone health and treatment noted the importance of calcium and vitamin D supplementation to reduce bone loss and fracture risk in some populations [54]. However, data on the efficacy of calcium supplements for preventing bone fractures in healthy postmenopausal women remain equivocal. An analysis of data from the Women's Health Initiative, which followed more than 36,000 postmenopausal women aged 50–79 years,

showed that, compared to placebo, daily supplementation with calcium carbonate (1,000 mg) and vitamin D_3 (400 IU) for up to 10 years resulted in a small but significant improvement in hip bone density (1.06 %; $p<0.01$) but did not significantly reduce the number of hip fractures (hazard ratio [HR]: 0.88; 95 % CI: 0.72, 1.08) [4].

In its clinical practice guideline for managing osteoporosis in men, the Endocrine Society suggested testing men aged 70 and older and younger men who have many risk factors for osteoporosis [55]. The authors also recommended that men with osteoporosis or who were at risk for this condition consume 1,000–1,200 mg/day calcium and, in those with low vitamin D levels, vitamin D supplements.

Calcium and Vitamin D: Bone Mineral Density

Since the publication of the 2011 DRIs, additional information has become available that is relevant to older persons. One of the better surrogate measures of fracture risk is bone mineral density (BMD). A review of 32 RCTs in 3,200 postmenopausal women from Australia found that daily calcium supplements (700–2,000 mg/day) for at least a year slowed bone loss but only when supplement doses were higher than 700 mg/day [56]. The effects became weaker after 4 years of treatment. Doses higher than 1,000 mg had no significant beneficial effects compared to doses of 1,000 mg/day. However, a review of 15 RCTs of calcium supplementation (750–1,200 mg/day) with or without vitamin D (400–800 IU/day) in more than 47,000 mostly postmenopausal women showed that greater increases in BMD at the lumbar spine were not necessarily associated with larger reductions in fracture risk [57].

Calcium and Vitamin D: Fractures

A 2011 meta-analysis that included 11 RCTs found that combined supplementation with vitamin D (300–1,100 IU/day) and calcium (500–1,200 mg/day) reduced fracture risk (pooled RR: 0.88; 95 % CI: 0.78, 0.99) in 53,000 adults, of which 69 % were postmenopausal women from the Women's Health Initiative [12]. However, the effects differed considerably by the setting, being greatest in institutional settings (RR: 0.71; 95 % CI: 0.57, 0.88) and somewhat lower among community-dwelling elders (RR: 0.89; 95 % CI: 0.76, 1.04), probably due to adherence differences among settings. Older women occasionally experienced adverse events, including increased risk of kidney and urinary tract stones.

Calcium and Vitamin D: Mortality and Other Outcomes

A recent study in Canada examined the association between total calcium and vitamin D intakes and mortality in a population-based longitudinal cohort of 9,033 men and women who were at least 25 years old [58]. The associations between higher calcium intakes and lower mortality risk were inconclusive for both men and women. Use of calcium supplements was associated with reduced mortality risk (HR: 0.78; 95 % CI: 0.66, 0.92) in female supplement users compared to nonusers but not in male users.

In summary, for older persons whose dietary intakes from food and fortified foods are low, vitamin D supplements, either as vitamin D_2 (ergocalciferol) or D_3 (cholecalciferol) may help to achieve intake levels approximating the RDA of 600 IU (15 μg) per day for those 51–70 years, and 800 IU (20 μg) per day for those greater than 70 years. Usual intakes over 4,000 IU (100 μg) per day from any source should be avoided because of risks of toxicity.

Some physicians use a blood measure of vitamin D status, specifically serum levels of 25-hydroxyvitamin D, and base their recommendations on this measure. Levels are stated either in nanomoles per liter (nmol/L) or nanograms per milliliter (ng/mL), where 1 nmol/L = 0.4 ng/mL. In general, levels below 30 nmol/L (12 ng/mL) are too low for bone or overall health, and when these are present vitamin D supplements may be prescribed. Serum levels of 50 nmol/L (20 ng/mL) are sufficient for most of the population. There is no known benefit of levels above about 50 nmol/L (20 ng/mL) for bone or other health outcomes. Serum levels above 125 nmol/L (50 ng/mL) are probably too high and should be avoided since emerging evidence links potential adverse effect to such high levels, particularly when they exceed 150 nmol/L (60 ng/mL).

Older women 51–70 years of age should aim to consume at least 1,200 mg calcium per day and males at least 1,000 mg/day. Individuals of both sexes who are more than 70 years of age should consume at least 1,200 mg/day from all sources. Dietary supplements may be helpful for those whose intakes of food and fortified food do not reach these levels. More studies are needed on the effects of very large amounts of calcium; the current UL should not be exceeded. It is also important to ensure that vitamin D intakes are adequate, and that usual intakes of 2,000 mg/day or more be avoided because of possible adverse effects such as kidney stones from excessive calcium.

Combinations of Vitamins, Minerals, and Other Nutrients

Prostate Cancer

Blood levels of prostate-specific antigen (PSA) are often elevated in men with prostate cancer. PSA is also used as a marker of cancer progression because increases in PSA after treatment sometimes indicate that the cancer has returned. Some supplements might decrease PSA levels, but there is no evidence that they decrease cancer progression. A 2013 systematic review of RCTs on the use of nonherbal dietary supplements and vitamins found that in two RCTs, a combination of dietary supplements (including isoflavones, lycopene, minerals, phytoestrogens, and vitamins) significantly decreased PSA levels compared to placebo [59]. However, six other studies found that supplements with various ingredients had no significant effects on PSA. Therefore, use of supplements such as these cannot be recommended as effective treatments for patients with prostate cancer.

Eye Health

Supplements containing combinations of vitamins, minerals, and other nutrients are widely marketed to the elderly for "eye health," but there is little evidence that dietary supplements can prevent or treat the eye diseases that many elderly people experience. The Age-Related Eye Disease Study (AREDS) examined the clinical course of age-related macular degeneration (AMD) and lens opacities and included an RCT to test the use of dietary supplements for 5 years to reduce the progression of these diseases in 3,540 participants aged 55–80 years [60]. The supplements contained the antioxidants vitamin C (500 mg), vitamin E (400 IU), and beta carotene (15 mg); zinc (80 mg as zinc oxide) and copper (2 mg as cupric oxide); antioxidants plus zinc; or placebo. Participants who were at high risk of developing advanced AMD, had intermediate AMD, or had advanced AMD in one eye only at baseline benefited from the supplements. Among these participants, those taking antioxidants plus zinc had the lowest risk (20 %, compared to 22 % for those taking zinc only, 23 % for those taking antioxidants only, and 28 % for those taking placebo) of advanced-stage AMD and its accompanying vision loss at 5 years. However, these dietary supplements had no significant effect on development or progression of age-related cataracts. The AREDS formula was the first evidence-based treatment for people at high risk of AMD.

The Blue Mountains Eye Study was an Australian population-based cohort study of 3,654 participants aged 49 years or older at baseline who were followed for 10 years [61]. This study found that higher zinc intakes are associated with a lower risk of AMD (RR for top decile of intake compared to the rest of the population: 0.56; 95 % CI: 0.32, 0.97). However, unlike AREDS, the study did not show that a combination of high doses of zinc, beta-carotene, and vitamins C and E prevented advanced-stage AMD.

Preliminary animal studies suggested that omega-3 fatty acids or other antioxidants might prevent cellular damage in the retina by reacting with free radicals produced in the process of light absorption. Therefore, experts hoped that supplementation with omega-3 fatty acids or other antioxidants might prevent or slow the progression of AMD. AREDS 2 was a multicenter, Phase III RCT of 4,200 participants aged 50–85 years who were at risk of advanced AMD to assess the effects of oral supplementation with lutein (10 mg/day), zeaxanthin (2 mg/day), and the omega-3 long-chain polyunsaturated fatty acids docosahexaenoic acid (DHA, 350 mg) and eicosapentaenoic acid (EPA, 650 mg/day) on the risk of progression to advanced AMD [62]. Adding lutein and zeaxanthin, DHA and EPA, or all of these ingredients to the AREDS formula did not reduce the risk of advanced AMD more than the original AREDS formula.

Some more recent trials of combinations of vitamins to treat or prevent AMD have also had negative results. A 2012 Cochrane review of antioxidant vitamin and mineral supplements for slowing AMD progression that included four RCTs in 62,520 healthy people found that vitamin E and beta-carotene supplements alone or in combination did not decrease the incidence of acute AMD (pooled RR: 0.98; 95 % CI: 0.89, 1.08) or advanced AMD (RR: 1.05; 95 % CI: 0.80, 1.39) [63]. A systematic review and meta-analysis of six longitudinal studies found that dietary intakes of lutein and zeaxanthin from foods had little association with risk of early-stage AMD but were associated with a reduced risk of late-stage AMD (RR: 0.74; 95 % CI: 0.57, 0.97) and of neovascular AMD (RR: 0.68; 95 % CI: 0.51, 0.92) [64]. More research is needed on the use of lutein and perhaps other carotenoids to prevent late-stage AMD.

Vitamins

B-Complex Vitamins

Manufacturers often market supplements containing B-complex vitamins with claims that these supplements improve cardiovascular health, prevent cancer, improve cognitive function, and decrease mortality risk.

In the United States, B-vitamin deficiency is rarely caused by a low dietary intake but, rather, by diseases, such as pernicious anemia or atrophic gastritis, bariatric surgery, or other gastrointestinal factors that affect absorption. These illnesses are more common with aging. Furthermore, proton pump inhibitors are commonly used by elderly people, and these medications also decrease gastric acidity and thereby lower vitamin B_{12} absorption from food. The Institute of Medicine recommends that people older than 50 take vitamin B_{12} in unbound form either in fortified foods or as oral supplements in DV amounts. Such oral supplements are efficacious for treating vitamin B_{12} deficiency and can prevent the need for B_{12} injections to prevent deficiency in healthy elders [65, 66].

Folic Acid: Mortality

A meta-analysis of cause-specific mortality in eight RCTs included more than 37,000 individuals at increased risk of cardiovascular disease (CVD) who were treated with folic acid supplements for a

median of 5 years [67]. Folic acid supplements (0.8–40.0 mg/day) had no effects on cancer mortality (rate ratio: 1.00; 95 % CI: 0.85, 1.18) or all-cause mortality (rate ratio: 1.02; 95 % CI: 0.97, 1.08) during the treatment period or in the years following treatment.

Folic Acid: CVD

There is contradictory information about whether supplements containing B-vitamins can reduce the risk of CVD by lowering levels of homocysteine, an amino acid that might act as a vascular toxin when present at high levels [68–72]. For example, in the meta-analysis of cause-specific mortality in eight RCTs discussed above, treatment with 0.8–40.0 mg/day folic acid had no effect on vascular outcomes, including major vascular events (rate ratio: 1.01; 95 % CI: 0.97, 1.05), major coronary events (rate ratio: 1.03; 95 % CI: 0.97, 1.10), and stroke (rate ratio: 0.96; 95 % CI: 0.87, 1.06), even though supplementation reduced homocysteine levels by 25 % [67]. A systematic review and meta-analyses of 16 RCTs also found that although folic acid supplementation (0.8–40 mg/day) could lower homocysteine levels, the supplements had no effects on rates of major cardiovascular events, myocardial infarction, all-cause mortality, or stroke [73]. In another systematic review, folic acid supplementation did not affect the risks of primary cardiovascular clinical endpoints (RR: 1.02; 95 % CI: 0.93, 1.13) or stroke (RR: 0.95; 95 % CI: 0.84, 1.08) [74]. However, a meta-analysis that included ten RCTs involving more than 43,000 individuals living in areas with little or no folic acid fortification of the food supply found that folic acid supplementation (0.4–0.8 mg/day) reduced stroke risk by 11 % (RR: 0.89; 95 % CI: 0.82, 0.97); the effects were even greater in populations with lower use of statins [75].

Although supplementation might have had a small effect on CVD risk, this effect was unlikely to be dramatic, especially in countries (such as the United States) where folic acid fortification of flour and use of MVM supplements containing folic acid are common and blood levels of folic acid are already high. Also in such countries, use of statins is very common, making it difficult to detect any small additional effects of folic acid.

In summary, a healthy diet and, if needed, other measures are probably more appropriate to prevent CVD and hypercholesterolemia in the United States than supplementation with folic acid or other B-vitamins.

Folic Acid: Possible Risks of Excess Amounts

The relationships between diet, dietary supplements, and health are complex. There are concerns about the increased folic acid blood levels resulting from folic acid fortification of enriched, uncooked cereal grains in the United States and Canada since 1998 and the increased use of folic acid-containing dietary supplements. Data from NHANES show that in 2003–2006, total folate and folic acid intakes from foods and supplements were highest in those aged 50 years or older, and about 5 % of those aged 50–71 years had total intakes exceeding the UL's [76]. Folic acid fortification has achieved its goal of reducing the number of births complicated by neural tube defects. However, whether the hoped-for cardiovascular benefits have occurred is unclear, and concerns have been raised about cancer risk.

Folate is important for DNA synthesis, is a known cofactor in one-carbon transfer reactions, and might modulate colorectal cancer development [77]. Epidemiologic studies have suggested an inverse relationship between folate intake and incidence of colorectal cancer [78]. However, animal studies have suggested that the timing and dose of folic acid supplementation might influence its effect on development or inhibition of colorectal cancer [77]. When folate fortification began in the United States and Canada in the mid-1990s, the downward trend in colorectal cancer incidence was reversed before it began to decline again a few years later, causing some researchers to speculate that the

phenomenon had a cause-and-effect association [79]; this association, however, has not been confirmed. In normal epithelial tissue, folate deficiency might promote neoplastic transformation, whereas moderate folate supplementation might suppress tumor development [77]. But the opposite could be true in established tumors or microscopic neoplasms. Animal studies suggest that folate deficiency might inhibit, and supplementation might promote, progression of established colorectal neoplasms.

The Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, which collected observational data on 25,400 women aged 55–74 years at baseline, showed that high folate intakes could increase the risk of breast cancer [80]. Women who ingested at least 400 μg/day of supplemental folic acid had a 19 % greater risk of developing breast cancer than those who did not consume supplemental folic acid (95 % CI: 1.01, 1.41). Participants in the highest folate quintile for total folate intakes had a 32 % greater risk of breast cancer than those in the lowest quintile (95 % CI: 1.04, 1.68). These data suggest that folate has dual modulatory effects on cancer development. Although the data are not definitive, they do warrant continued population-based monitoring of free folic acid levels in blood, as the NHANES survey does.

B-Complex Vitamins: Cognition

B-complex vitamins are advertised as promoting "brain health" and cognition. However, many confounding factors are associated with cognitive decline in later life. These factors include current tobacco use, presence of certain genotypes (e.g., apolipoprotein E epsilon-4 genotype), multi-infarct dementia, and some medical conditions. However, a systematic review of 127 observational studies, 22 RCTs, and 16 systematic reviews found little clear evidence that nutritional factors play a role in maintaining cognitive function [81].

Vitamin B_{12} deficiency has well-known adverse effects on cognitive function, including difficulties with concentration, disorientation, and dementia [82]. Folic acid supplementation can mask the presence of vitamin B_{12} deficiency and, by delaying treatment for this deficiency, can allow progression of the associated neurological symptoms, including mood and cognitive disorders [83]. For this reason, there is concern about high-dose folic acid supplements in elders who might be vitamin B_{12}-deficient.

Folic acid supplements decrease homocysteine levels somewhat, and some evidence indicates that high homocysteine levels are associated with an increased risk of dementia and Alzheimer's disease [83]. But there is little evidence that the other B-vitamins affect cognition or that folic acid supplements with or without vitamin B_{12} are useful in preventing dementia in healthy elders or treating those suffering from dementia. For example, an analysis of data from the Framingham study on 1,092 participants (mean age 76 years) without dementia found that those who had homocysteine levels greater than 14 mmol/L had almost twice the risk of developing Alzheimer disease 8 years later as people with lower homocysteine levels (95 % CI: 1.3, 2.5); for each 5 mmol/L elevation, risk their increased by 40 % (95 % CI: 1.1, 1.9) [84]. An observational cohort study in 816 dementia-free adults (mean age 74 years) assessed rates of newly diagnosed dementia and Alzheimer disease [85]. After 4 years, the risk of dementia and Alzheimer disease was higher in those who had baseline levels of homocysteine higher than 15 μmol/L (HR for Alzheimer disease: 2.11; 95 % CI: 1.19, 3.76; HR for dementia: 2.08; 95 % CI: 1.31, 3.30) and those who had folate levels of 11.8 mmol/L or lower (HR for Alzheimer disease: 1.98; 95 % CI: 1.15, 3.40; HR for dementia: 1.87; 95 % CI: 1.21, 2.89). However, whether hyper-homocysteinemia was a risk marker or risk factor for dementia was not clear.

If a high level of homocysteine is a risk factor, reducing this level by increasing intake of folic acid or vitamin B_{12} might decrease the risk of dementia. However, if hyper-homocystinemia is a marker for dementia, lowering homocysteine levels is not likely to affect risk of this disease. One RCT found that supplementation with vitamin B_{12} (1,000 μg/day) with or without folic acid (400 mg/day) for 24 weeks in 195 elders with mild vitamin B_{12} deficiency had no effect on cognitive function [86].

Another RCT compared the use of folic acid supplements (800 μg/day) to placebo for 2 years in 818 participants aged 50–70 years with high plasma homocysteine and normal serum vitamin B_{12} levels [87]. The supplements improved global functioning (weighted mean difference [WMD]: 0.05; 95 % CI: 0.004, 0.096; $p = 0.033$), memory (WMD: 0.132; 95 % CI: 0.032, 0.233; $p = 0.06$), and information-processing speed (WMD: 0.087; 95 % CI: 0.016, 0.158; $p = 0.016$). In both studies, the supplements decreased homocysteine levels.

The authors of a 2009 Cochrane review of the use of folic acid supplements (400 μg to 15 mg/day) with or without vitamin B_{12} (1,000 μg to 1 mg/day) for preventing or treating dementia concluded, based on eight RCTs, that the evidence showing that such supplements can prevent declines in cognitive function or mood in healthy elderly people is inadequate [88]. Of the four trials reviewed that tested supplementation in people with cognitive impairment, one found that folic acid supplements (1 mg/day) significantly improved responses to cholinesterase inhibitors, typically given to patients with Alzheimer's disease (odds ratio: 4.06; 95 % CI: 1.22, 13.53; $p = 0.02$), and scores of instrumental activities of daily living and social behavior measured by a subscale of the Nurse's Observation Scale for Geriatric patients. The other three trials found no benefit of folic acid supplements with or without vitamin B_{12} on cognitive function. A 2012 meta-analysis of 19 RCTs also found that supplements containing vitamin B_{12} (0.5–1 mg/day), vitamin B_6 (25 mg/day), and folic acid (0.8–15 mg/day) alone or in combination for 60 days to 24 months did not improve cognitive function in 5,398 people aged 50 years or older who were healthy or who had mild cognitive impairments [89]. The results did not seem to vary by folic acid status or by study duration or size. A systematic review of 22 RCTs that tested the effects of supplements with at least one kind of vitamin, mineral, or omega-3 fatty acid on various cognitive tests in 3,400 persons aged 65 or older concluded that B-vitamin supplements had no significant effects on global cognitive functions [90]. The authors found no significant effects of B-vitamins on global cognitive function.

Vitamin D

The effects of calcium and vitamin D on bone and on mortality are discussed above. The evidence on the effects of vitamin D supplements on health issues that are particularly relevant to older people is reviewed in this section.

A 2007 Agency for Healthcare Research and Quality (AHRQ) review included 167 studies (112 RCTs, 19 prospective cohort studies, 30 case-control studies, and 6 before-and-after studies) on the association between circulating 25-hydroxyvitamin D [25(OH)D] concentrations and bone health outcomes [91]. The authors found that in 22 RCTs whose investigators reported whether vitamin D supplements had toxic side effects (including 17 RCTs in older adults), intakes of vitamin D that were higher than current DRIs were generally well tolerated, although the most relevant trials were not adequately designed to assess the long-term risks of adverse events. Although some studies found that high intakes of vitamin D were associated with an increased risk of hypercalcemia and hypercalciuria, these effects were not clinically significant.

Vitamin D: Bone Health

The 2007 ARHQ review [91] and a 2006 National Institutes of Health (NIH) conference entitled "Vitamin D and Health in the 21st Century: An Update" [87] revealed that the effects of vitamin D supplements alone, independent of calcium intake, could not be evaluated in most of the trials conducted to date. In most trials reviewed in the AHRQ report, daily supplementation with 700 IU vitamin D_3 and calcium compared to placebo had a small beneficial effect on BMD and reduced the risk of fractures and falls, although the benefit was sometimes confined to specific subgroups [92].

The authors of the AHRQ report also noted that determining which blood levels of markers for vitamin D status are optimal for bone health is difficult. One challenge is that current methods, which measure serum 25(OH)D levels, have yielded highly inconsistent results in many studies, in part because of the lack of commercially available standard reference preparations for calibrating measurements between laboratories.

A 2011 meta-analysis of 13 RCTs of vitamin D supplementation without exercise interventions in adults aged 60 years and older found that supplements decreased postural sway (standardized mean difference: −0.20; 95 % CI: −0.39, −0.01), decreased time to complete the Timed Up and Go Test (−0.19; 95 % CI, −0.11, 0.20), and improved lower extremity strength (0.05; 95 % CI: 0.11, 0.20), but had no effect on gait [93]. All of the studies in which daily vitamin D doses were 800 IU or more showed that the supplements improved balance and muscle strength.

A systematic review and meta-analysis of 26 RCTs that enrolled more than 45,700 participants, most of whom were elderly women, who had a median risk of falling of 50 %, found that the use of supplements containing vitamin D (200–1,100 IU/day, 10,000 IU weekly, 100,000 IU every 10 weeks, or 100,000–600,000 IU once) reduced the risk of falls (odds ratio [OR] of at least one fall: 0.86; 95 % CI: 0.77, 0.96) [94]. The effect was especially striking in patients who had lower levels of 25(OH)D at baseline and those who took both calcium and vitamin D supplements.

Several other reviews have found that vitamin D supplements can reduce the risk of falling in older adults. For example, a systematic review and meta-analysis of ten RCTs found that vitamin D supplementation (200–1,000 IU) for 1–36 months reduced the number of falls by 14 % (RR: 0.86, 95 % CI: 0.79, 0.93) compared to calcium supplements alone (200–1,200 mg/day) or placebo [95]. The effects were statistically significant, especially for those who lived in the community, were younger than 80 years, took adjunctive calcium supplements, had no history of fractures of falls, used the supplements for longer than 6 months, or received a dose of 800 IU vitamin D or more. A Cochrane review of 60 RCTs that tested interventions to reduce falls in care facilities and hospitals found, based on five trials in 4,603 participants, that vitamin D supplementation (200–1,100 IU/day or 10,000 IU weekly) for 3–5 months reduced the rate of falls (rate ratio: 0.63; 95 % CI: 0.46, 0.86) but not the risk of falling (rate ratio: 0.99; 95 % CI 0.90, 1.08) [96].

However, other studies have not found vitamin D supplementation to be effective for preventing falls. A Cochrane review of trials of interventions to prevent falls in community-dwelling older people found that vitamin D supplementation (200–2,000 IU/day or 300,000 IU once) did not appear to reduce the number of falls (rate ratio: 1.00, 95 % CI: 0.90, 1.11 based on 7 trials in more than 9,300 participants) or the risk of falls (rate ratio: 0.96; 95 % CI: 0.89, 1.03 based on 13 trials in more than 26,700 participants), except possibly among individuals who had lower intakes of vitamin D before treatment. Supplements did not reduce the risk of falling (rate ratio: 0.96; 95 % CI: 0.89, 1.03) [97].

Some evidence indicates that vitamin D supplementation can improve muscle strength. For example, in a systematic review of 17 RCTs involving 5,072 participants (who were mostly older than 60 years), supplementation with vitamin D (400–1,000 IU/day vitamin D_3, 60,000 IU/week vitamin D_3, 150,000 IU/month vitamin D_3, or 300,000 IU once vitamin D_3, 2,000–9,000 IU/day vitamin D_2, or 600,000 IU once vitamin D_2) did not have a significant effect on muscle strength (as measured by grip strength or proximal lower limb strength) in adults whose baseline levels of 25(OH)D were higher than 25 nmol/L, but supplements in people with lower levels of 25(OH)D improved hip muscle strength [98].

The evidence on the use of vitamin D supplements to reduce the risk of fractures is mixed. A 2012 pooled analysis included participant-level data from 11 RCTs that compared oral vitamin D supplements (199–846 IU/day) with or without calcium (84–830 mg/day) to calcium alone or placebo for preventing fractures in 31,022 mostly female adults aged 65 years or older [99]. Virtually all of the women who were randomly assigned to receive vitamin D compared to those assigned to control groups experienced a nonsignificant (10 %) reduction in risk of hip fracture (HR: 0.90; 95 % CI: 0.80, 1.01) and a 7 % lower risk of nonvertebral fracture (HR: 0.93; 95 % CI: 0.87, 0.99). Risks of fracture

were only evident at the highest levels of intake (equivalent to a median of 800 IU/day). People with higher baseline D levels might not require such high doses of supplements to prevent fractures. The optimal intake level probably depends on the individual's baseline nutritional vitamin D status, which varies greatly from country to country.

Vitamin D: Cancer

A meta-analysis of studies that evaluated the use of vitamin D supplements with or without calcium to prevent cancer or fractures included three RCTs lasting 4–7 years in healthy postmenopausal women or in men and women aged 71 years or older and 28 observational studies focused on cancer prevention [12]. Limited data from the RCTs suggested that 1,000 IU/day vitamin D supplements might reduce the risk of cancer, but the data from the observational studies suggested that higher blood 25(OH)D concentrations might be associated with an increased cancer risk. A mixed-effects, dose-response meta-analysis in this analysis showed that each 10 nmol/L increase in blood 25(OH)D concentration was associated with a 6 % reduced risk of colorectal cancer (95 % CI: 0.03, 0.09), but no significant dose-response relationship was evident for breast or prostate cancer. A meta-analysis of prospective studies that evaluated the association between vitamin D intakes from foods and supplements in 6,466 individuals (nine studies) or blood levels of 25(OH)D in 2,767 cases and 3,948 controls and colorectal cancer risk found an inverse association between vitamin D intake (pooled RR: 0.88; 95 % CI: 0.80, 0.96) and blood 25(OH)D levels (pooled RR: 0.67; 95 % CI: 0.54, 0.80) and risk of colorectal cancers [100].

Vitamin D: Cognition and Dementia

A review of 37 studies (21 cross-sectional studies, 10 case-control studies, 1 before-and-after study with a comparison group, 2 prospective cohort studies, and 3 RCTs) that evaluated the association of vitamin D concentrations with cognition and dementia in adults older than 18 years found that lower vitamin D concentrations were associated with poorer cognitive function and a higher risk of Alzheimer disease [101]. However, the authors suggested that the results might have been due to association rather than causation because most of the studies were prospective. In both a systematic review and meta-analysis of two longitudinal and five cross-sectional studies on the association between vitamin D deficiency and cognitive impairment in 7,688 elderly individuals, people with low vitamin D levels had an increased risk of cognitive impairment compared to those with normal vitamin D levels [102]. However, whether vitamin D deficiency caused the impairment could not be determined.

Vitamin D: Other Chronic Diseases

Many other associations between vitamin D levels and chronic diseases have been suggested but not proven. For example, in a systematic review and meta-analysis of 51 RCTs that assessed the associations between vitamin D supplements (200–3,332 IU/day, 8–10 μg/day, 10,000–100,000 IU weekly, 50,000 IU twice weekly, 12,000 IU every 2 weeks, 100,000 IU every 4 months, or single injections of 100,000–300,000 IU) with or without calcium (500–1,000 mg/day) and/or other nutrients and cardiovascular outcomes in adults, the supplements had no significant effects on risk of death (RR: 0.96; 95 % CI: 0.93, 1.00; $p = 0.08$), myocardial infarction (RR: 10.02; 95 % CI: 0.93, 1.13; $p = 0.64$), or stroke (RR: 1.05; 95 % CI: 0.88, 1.25; $p = 0.59$) [103]. A meta-analysis of 12 RCTs that assessed the effects of vitamin supplements on blood lipid levels in 1,346 individuals found that vitamin D

supplements (800 IU/day or 100,000–200,000 IU once) had small effects (e.g., 1–6 mg/dL) on low-density lipoprotein (LDL) cholesterol levels [104]. A systematic review and meta-analysis of 15 RCTs that assessed the effects of vitamin D supplements on glycemic control and insulin resistance in adults who were healthy or had type 2 diabetes or insulin resistance found that supplements had no significant effects on fasting glucose, hemoglobin A1c levels, or insulin resistance, and, in patients with diabetes or impaired glucose tolerance, only small effects on fasting glucose (−0.32 mmol/L; 95 % CI: −0.57, −0.07) and insulin resistance (standard mean difference [SMD]: −0.25; 95 % CI: −0.48, −0.03) [105]. The effects of vitamin D supplements (200–600 IU/day) on systolic blood pressure were also quite small (2.44 mmHg; WMD: −2.44; 95 % CI: −4.86, −0.02) in a review of four RCTs in 429 adults (mean age 64 years) who had normal or high blood pressure [106]. A systematic review and meta-analysis of eight RCTs in hypertensive patients in western Europe found that although vitamin D supplements or ultraviolet radiation reduced systolic blood pressure compared to placebo, the results were not significant (−3.6 mmHg; 95 % CI: −9.0, 0.7) [107].

Vitamin E

Vitamin E is a popular vitamin that elders often taken in very large doses in the hope that it will improve their cardiovascular health. Various forms of vitamin E are available in supplements; alpha-tocopherol is considered the most active form. Unlike other vitamins, the form of alpha-tocopherol made in the laboratory and found in many supplements (all Rac-alpha-tocopherol) is not identical to the natural form (RRR-alpha-tocopherol) and is less active than the natural form. The vitamin E RDA of 15 mg equals 22 IU of natural and 33 IU of synthetic vitamin E. Studies suggest that daily doses of vitamin E ranging from 200 to 1,200 IU are safe when taken by healthy adults for up to 4 months [108–110].

Vitamin E: Cardiovascular Health

Reactive oxygen species promote atherogenesis. As an antioxidant with inflammatory properties, vitamin E might mediate free radical reactions that oxidize LDL cholesterol and initiate or promote atherosclerosis [111, 112].

The Women's Health Study indicated that taking 600 IU vitamin E every other day for approximately 10 years did not decrease the risk of major cardiovascular events in healthy women aged 45 or older (RR: 0.93; 95 % CI: 0.82, 1.05; $p=0.26$), but the supplements were associated with a 24 % reduction in the incidence of cardiovascular deaths (primarily sudden death in women aged 65 years or older; RR: 0.76; 95 % CI: 0.59, 0.98; $p=0.03$) [28]. The Heart Outcomes Prevention Evaluation (HOPE) trial, which examined the effect of vitamin E supplementation on major cardiovascular events in 9,541 people with vascular disease or diabetes aged 55 years or older, demonstrated that vitamin E supplementation (400 IU/day for 4.5 years, on average) did not reduce the risk of a composite measure of myocardial infarction, stroke, and cardiovascular death (RR, 1.05; 95 % CI: 0.95, 1.16; $p=0.33$) and was not associated with any adverse effects [113]. The results of a 7-year passive follow-up of the HOPE trial in 738 participants suggested that vitamin E supplementation failed to prevent major cardiovascular events (RR: 1.04; 95 % CI: 0.96, 1.14; $p=0.34$) [27].

The results of clinical trials have not supported a role for vitamin E in either the primary or secondary prevention of heart disease. The weakness of evidence supporting a treatment role for vitamin E for CVD led the FDA to reject health claims for vitamin E. It might be too optimistic to expect a single-vitamin supplement to overcome the effects of poor dietary habits and a sedentary lifestyle on known risk factors, such as hypertension and hypercholesterolemia, for heart disease [112].

Additional studies are needed to further explore the benefit of vitamin E in treating and/or preventing heart disease. Older persons at high risk of developing CVD or who have CVD should discuss the benefits of taking a supplement containing vitamin E at a dose that not exceed the UL of 1,000 IU/day with their cardiologist or primary physician. This amount of vitamin E is not available in most multivitamin preparations and usually requires a vitamin E supplement.

Vitamin E: Cancer Prevention

The evidence on the benefits of vitamin E supplements in cancer prevention is also uncertain, at best. Vitamin E supplements (600 IU every other day for 10 years) did not prevent cancer (RR: 1.01; 95 % CI: 0.94, 1.08; $p = 0.87$) in the Women's Health Study, an RCT of 39,876 healthy female health professionals (median age 54.6 years) [28]. However, the follow-up phase of the Alpha-Tocopherol Beta-Carotene study, which randomly assigned 29,133 50–69-year-old male smokers from Finland to 50 mg alpha-tocopherol, 20 mg beta-carotene, both, or a placebo for 5–8 years, demonstrated a 32 % decrease in incidence (95 % CI: −0.47, −0.12) and a 41 % decrease in mortality (95 % CI: −0.65, −0.01) from prostate cancer among participants who received alpha-tocopherol supplements [114]. Six years after the trial ended, follow-up data continued to indicate that alpha-tocopherol supplements were associated with a lower risk of prostate cancer (RR: 0.88; 95 % CI: 0.76, 1.03) [115]. Interestingly, an analysis of 19 years of follow-up data on intakes found that men in the higher quintiles of baseline serum alpha-tocopherol levels had a lower risk of death due to cancer (RR: 0.79; 95 % CI: 0.72, 0.86) than those in the lowest quintile, suggesting that higher circulating concentrations of alpha-tocopherol within the normal range had health benefits [116]. The authors of a pooled analysis of eight prospective studies of intakes from North America and Europe examining correlations between intakes of vitamin antioxidants, multivitamins, and lung cancer concluded that regardless of smoking habits and lung cancer cell type, the available data do not support an association between intakes of vitamin E and lung cancer risk (pooled multivariate RR: 0.86; 95 % CI: 0.76, 0.99) [117].

One of the largest recent studies of vitamin E and cancer was the Selenium and Vitamin E Cancer Prevention Trial (SELECT), which included 35,533 men with a PSA level of up to 4.0 ng/mL who were aged 50 or older for black men and 55 or older for other men in the United States, Canada, and Puerto Rico [118]. The men were randomly assigned to supplementation with vitamin E (400 IU/day), selenium (200 μg/day), both, or placebo. After 7–12 years, not only did vitamin E supplements not reduce prostate cancer incidence, but they were associated with an increased risk of prostate cancer compared to placebo (HR for vitamin E supplements alone: 1.17; 99 % CI: 1.004, 1.36; $p = 0.008$).

At present, there does not appear to be evidence that vitamin E supplements can help prevent prostate or other cancers. In their recommendations regarding nutrition and cancer, the American Cancer Society [119] and World Cancer Research Federation/American Institute of Cancer Research [39] do not recommend that older people take vitamin E supplements. At this time, there is insufficient evidence to recommend vitamin E supplements for older adults.

Minerals

Potassium

In the 2010 Dietary Guidelines for Americans, potassium is described as a nutrient of public health concern because very few Americans consume the AI amount of 4,700 mg/day [120].

Potassium: CVD

The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure notes that diets that are rich in potassium can reduce blood pressure, and the American Heart Association recommends increasing potassium intakes to 4,700 mg/day to lower blood pressure [121]. Combining an overall healthy diet with weight loss, lower salt intake, and higher potassium intake is thought to prevent and treat hypertension on the basis of some studies [122]. Healthy people who eat eight to ten servings of fruits and vegetables each day can achieve an intake of 4,700 mg/day, but this intake might be too high for those with impaired kidney function or congestive heart failure and not in line with many peoples' food choices. A diet containing 75 mEq (i.e., approximately 3,500 mg of elemental potassium) daily might help reduce the risk of stroke. However, potassium supplements are neither necessary nor recommended for the general population. Potassium supplements at high doses are not sold over the counter, and those containing more than the small doses included in a MVM preparation should only be taken under the guidance and instruction of a physician.

Selenium

Selenium supplements are popular among older men who take them to prevent prostate cancer. Selenium is available in supplements as selenomethionine and as yeast grown in a selenium-rich medium (selenized yeast). This yeast provides up to 1,000–2,000 μg/day of selenium, the vast majority of which is in the form of selenomethionine. The RDA for selenium is only 55 μg/day, and mean intakes from foods and supplements appear to be above that level [123, 124]. Older adults whose dietary selenium intake is inadequate might benefit from MVM supplements providing 100 % of the RDA for selenium. The UL for selenium is 400 μg/day.

Selenium: Cancer

The FDA approved a qualified health claim recognizing the anticarcinogenic potential of selenium [125]. However, selenium supplements provide no anticarcinogenic benefit in people whose diets provide adequate amounts of selenium, and people whose total intakes from food and supplements are excessive could be harmed by taking selenium supplements. Older adults who are unable or unwilling to increase their dietary selenium intake to RDA levels might benefit from an MVM supplement providing 100 % of the RDA/DV for selenium.

Selenium is incorporated in approximately 25 selenoproteins. Two selenoproteins, thioredoxin reductase and glutathione peroxidase, are antioxidant enzymes that provide protection from free radicals. Researchers have hypothesized that selenium compounds and selenoproteins might prevent cancer by modulating free radical metabolism, among other biologic mechanisms [126]. Furthermore, the incidence of some cancers has been lower among people with higher blood levels or intakes of selenium in some studies [127, 128].

In the early 2000s, there was great hope that selenium and vitamin E either alone or in combination might decrease the incidence of prostate cancer. Experts believed that intakes higher than the RDA level might be needed to maximize the selenium content of all selenium-containing proteins based primarily on the known antioxidant activity of selenium and vitamin E, secondary analyses of large-scale chemoprevention trials, and human observational studies showing that these compounds might decrease cancer risk. SELECT, described in the "Vitamin E" section above, was designed to test this hypothesis [118]. Unfortunately, after 7 years, supplements containing selenium alone (200 μg/day) or selenium and vitamin E (400 IU/day) were not associated with reduced prostate cancer incidence in high-risk men [129]. In retrospect, although the supplement doses, supplement formulations, study

design, or cohort characteristics might have been faulty, the most likely explanation of the SELECT results is that any anticarcinogenic effects of selenium supplements might be confined to certain subpopulations of men [130]. The challenge is identifying these subpopulations, including their baseline selenium status, age, and perhaps genotype of specific selenoproteins to maximize results.

At present, there is little support for taking high-dose selenium supplements for prostate health, and doing so might have some adverse effects.

Selenium: Excessive Amounts

The threshold between adequate and excessive selenium amounts is small, and NHANES III cross-sectional data suggest that high levels of serum selenium are positively associated with diabetes risk [131]. In addition, two secondary analyses of data from the Nutritional Prevention of Cancer trial found that supplementation for an average of 7 years with 200 μg/day of selenium did not prevent CVD [132] and might have increased the risk of type 2 diabetes mellitus [133].

Omega-3 and -6 Fatty Acids

Should older Americans take omega-3 fatty acid supplements in addition to eating a healthful diet? Marketers claim that these supplements improve cardiovascular health, protect people from vision loss, improve cognition, and prevent cancers. The polyunsaturated fatty acids include alpha-linolenic acid (ALA), an omega-3 fatty acid, and linoleic acid, an omega-6 fatty acid. Linoleic acid is converted in the body to arachidonic acid. ALA is converted in the body to the fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), and these are all metabolized along the same biochemical pathways. The diet must supply these nutrients because the body cannot make them. Most American diets provide more than ten times as much omega-6 as omega-3 fatty acids.

AHRQ conducted an extensive systematic evidence-based review of many putative benefits of omega-3 fatty acids in 2004 and 2005 [134–144]. The review identified little evidence that omega-3 fatty acids had beneficial effects for most of the indications, other than possible cardiovascular benefits.

Omega-3 Fatty Acids: CVD

Essential omega-6 lipids promote development of pro-inflammatory eicosanoids, and essential omega-3 lipids promote development of anti-inflammatory eicosanoids. The anti-inflammatory effects of omega-3 fats might partially explain their cardioprotective benefit because incorporation of these fats in cell membranes promotes vasodilation, stimulates antiarrhythmic effects, and promotes vascular patency [145, 146].

Several large diet studies in the 1990s supported the cardiovascular benefits of omega-3 fats. The strongest evidence for a benefit was in secondary prevention of CVD. By far the largest secondary prevention trial was the GISSI-Prevenzione Study that enrolled 11,324 persons in Italy (of which about half were aged 60 years or older) who had survived a myocardial infarction for a median of 16 days [147]. Researchers examined the effects of daily supplementation for 3.5 years with 850–882 mg EPA and DHA (average EPA-DHA ratio of 1:2), and 300 mg vitamin E using a factorial design. Treatment with EPA and DHA reduced total mortality by 20 %, predominantly by reducing the incidence of sudden cardiac death by 45 %.

Few studies have focused on the effects of omega-3 fatty acid supplements for primary prevention of CVD. The Japan EPA Lipid Intervention Study, a primary prevention trial, randomly assigned

18,645 patients (mean age 61 years) with hyperlipidemia to receive 1.8 g/day EPA and a statin or a statin only [148]. At baseline, 20 % of the participants had a history of coronary artery disease. After an average of 4.6 years, the incidence of major coronary events was significantly reduced by 19 % in the EPA group ($p=0.011$). A 2006 meta-analysis of 48 RCTs, most of limited size and duration, in 36,913 participants followed for 6 months to 6 years found that supplementation with omega-3 fatty acids (0.4–7 g/day) was associated with smaller, nonsignificant reductions in total mortality (13 %; 95 % CI: 0.73, 1.03) and total CVD events (5 %; 95 % CI: 0.82, 1.12) [149]. A meta-analysis of 16 RCTs in 901 participants (baseline mean age 9–66 years) found that omega-3 supplements (0.45–4.5 g/day for a median of 56 days) lowered blood triglyceride levels in a dose-dependent manner, which might have reduced atherosclerosis risk [150]. In a meta-analysis of 11 RCTs and 7 cohort studies, supplementation with fish oils (1–3 g/day) or dietary consumption of fish for 5 days to 18 years had no impact on risk of atrial fibrillation (pooled odds ratio [OR]: 0.79; 95 % CI: 0.56, 1.12; $p=0.19$ for RCTs; pooled OR 0.83; 95 % CI: 0.59, 1.16; $p=0.27$ for cohort studies) [151]. In the AHRQ review of 123 studies that assessed the effects of omega-3 fatty acids on cardiovascular risk factors, omega-3 supplements reduced blood pressure by approximately 2 mmHg [142].

The most recent review of RCTs on the use of omega-3 fatty acids to prevent CVD included 20 primary and secondary prevention trials in 68,680 patients treated for more than 1 year with either omega-3-rich foods or supplements [152]. The omega-3 fatty acid supplements (0.24–3.4 g/day) had no statistically significant effects on all-cause mortality (RR: 0.96; 95 % CI: 0.91, 1.02), cardiac death (RR: 0.91; 95 % CI: 0.85, 0.98), sudden death (RR: 0.87, 95 % CI: 0.75, 1.01), myocardial infarction (RR: 0.80, 95 % CI: 0.76, 1.04), or stroke (RR: 1.05, 95 % CI: 0.93, 1.18) when all the trials were analyzed together. Moreover, factors such as prevention setting, the presence of implantable cardioverter-defibrillators in patients, or dose of omega-3 fatty acids did not appear to have affected the results.

Another meta-analysis was problematic. It included 14 secondary prevention RCTs in 20,485 adults (mean age 63 years) with a history of CVD who were followed for approximately 2 years or less [153]. Omega-3 fatty acid supplements (0.4–4.8 g/day) for 1–4.7 years had no significant effects on the overall incidence of cardiovascular events (RR: 0.99; 95 % CI: 0.89, 1.09), all-cause mortality (RR: 0.96; 95 % CI: 0.90, 1.02), sudden cardiac death (RR: 0.92; 95 % CI: 0.66, 1.30), myocardial infarction (RR: 0.81; 95 % CI: 0.65, 1.01), congestive heart failure (RR: 0.92; 95 % CI: 0.71, 1.17), or transient ischemic attack and stroke (RR: 1.13; 95 % CI: 0.77, 1.66). However, the authors found a small reduction in the number of cardiovascular deaths (RR: 0.91; 95 % CI: 0.84, 0.99) that disappeared when they excluded an open-label study without a placebo. Subgroup analyses also showed no significant associations by history of CVD, use of concomitant medications, trial quality, treatment duration, EPA or DHA dose, use of fish oil supplementation only, country, or area within a country. Although the authors found no association between dose of omega-3 fatty acids and clinical outcomes, the doses in most of the studies reviewed were very high (more than 1 g/day). The findings of this meta-analysis were later criticized because it included studies that were small, used an inappropriate placebo, lacked sufficient statistical power, or were of poor quality and excluded large studies that were not placebo controlled.

The 2004–2005 AHRQ review found only weak evidence that omega-3 fatty acids might have beneficial effects in tertiary prevention, such as on coronary artery re-stenosis after angioplasty and improved exercise capacity in patients with coronary atherosclerosis [142]. More high-quality, well-powered, well-controlled RCTs would be helpful for addressing these issues.

The FDA has approved a prescription form of omega-3 fatty acids (Lovaza, GlaxoSmithKline) for treatment of very high triglyceride levels [154]. The prescription product contains 0.84 g EPA and DHA in each 1 g capsule. Approximately 2–4 g EPA and DHA per day are required to lower triglyceride levels. EPA/DHA capsules are also available without a prescription, but the American Heart Association advises people with hypertriglyceridemia to undergo therapy with EPA and DHA only under a physician's care [155].

The American Heart Association and American College of Cardiology recommend an intake of 1 g/day of omega-3 fatty acids in people with atherosclerotic vascular disease to manage lipid levels [156]. However, the National Heart, Lung, and Blood Institute (NHLBI), American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons do not recommend omega-3 supplements for people with or at risk of CVD, although NHLBI suggests eating at least two meals that include fish each week for people with high cholesterol levels [157, 158].

If older adults wish to use omega-3 fatty acid supplements, they should discuss this option with a qualified healthcare provider. Together, patients and providers should review the advantages and disadvantages of various treatment options, individual needs, and potential interactions (such as with blood thinners, including warfarin).

Omega-3 Fatty Acids: Cancers

Researchers have suggested that omega-3 fatty acids might be useful in cancer prevention, but the evidence for such an effect remains weak. The rationale is that omega-3 fatty acids suppress biosynthesis of arachidonic acid-derived eicosanoids that influence angiogenesis, apoptosis, cell proliferation, inflammation, immune cell function, and other mechanisms [159]. Some preclinical research has suggested that a nutrition intervention with omega-3 fatty acids might improve cell sensitivity to chemotherapy [160].

However, available epidemiologic data on omega-3 fatty acids and the risk of cancer continues to be inconsistent. In a review of 38 reports examining the effects of dietary consumption of omega-3 fatty acids on cancer risk in 20 prospective cohorts that included more than 700,000 participants, the results did not provide evidence for a significant association [141]. The authors concluded that dietary supplementation with omega-3 fatty acids is unlikely to prevent cancer.

In one large meta-analysis of seven studies in 489,465 adults on dietary consumption of omega-3 fatty acids and colon cancer prevention, overall effects were null but the results of a subgroup analysis showed a trend toward reduced risk of colorectal cancer among men (RR: 0.87; 95 % CI: 0.75–1.00) in four cohort studies [161]. The results of meta-analyses of studies on the effects of fish consumption or dietary alpha-linoleic acid intakes on prostate and gastric cancer risk were also negative [162–164]. Based on an ongoing systematic review, the World Cancer Research Foundation and American Institute of Cancer Research do not recommend omega-3 fatty acids for cancer prevention [39].

Omega-3 Fatty Acids: Cognition

Many elderly people take omega-3 fatty acid supplements to improve or prevent declines in cognitive function, but the evidence that this nutrient has these effects is inconclusive. Little has changed since the 2004–2005 AHRQ review to clarify its beneficial effects in the last few years [138].

A meta-analysis of ten RCTs on the effects of omega-3 fatty acid supplements (20–1,670 mg/day EPA and/or 40–1,550 mg/day DHA) on various domains of memory among healthy people, individuals with mild forms of cognitive impairment with no dementia, and those with Alzheimer disease found no effects when all of these patients were pooled and analyzed together (Hedge's g effect size: 0.04; 95 % CI: −0.06, −0.14) [165]. However, among people with cognitive impairment but without dementia, the results showed a small but statistically significant effect on immediate recall (Hedge's g effect size: 0.16; 95 % CI: 0.01, 0.31). In contrast, no benefit was evident in either healthy elders or

those who already had Alzheimer disease. Omega-3 fatty acid supplements in patients with Alzheimer disease did not improve scores on the Mini Mental State Examination or Alzheimer Disease Assessment Scale-Cognitive Subscale. In a Cochrane review of three RCTs lasting at least 6 months of omega-3 fatty acid supplements (200–1,093 mg/day EPA and 160–847 mg/day DHA and, in one study, 2 g ALA) in 3,536 participants, omega-3 fatty acid supplements had no effect on incident dementia [166]. However, many of these studies were small, of short duration, and of poor quality.

Although larger studies of longer duration might show effects, the quantity and strength of evidence is inadequate today to conclude that omega-3 fatty acid supplements protect cognitive function with aging or decrease the incidence or clinical progression of dementia, including Alzheimer disease. However, omega-3 fatty acid supplements at the doses studied appear to be safe, with few reported adverse events.

Effectiveness and Safety of Non-nutrient Supplements for the Elderly

Recent meta-analyses of the evidence supporting the use of a select number of these supplements that are popular are summarized below. These examples demonstrate the uncertainties that remain and the difficulties in making evidence-based recommendations regarding the use of these products.

Herbals and Botanicals

Botanical dietary supplements, which are made from plants, are sold in many forms, including fresh, dried, liquid, or solid extracts; tablets; capsules; powders; and tea bags. These products contain one or more botanical or herbal ingredients, such as *Gingko biloba* and St. John's wort, with or without vitamins and minerals. Experts do not understand how many botanical preparations work or what their active components are. The presence of adulterants or undeclared drugs also might be toxic.

Soy Protein and Soy Isoflavones

Soy contains three aglycones, or hydrolyzed forms of isoflavones—genistein, daidzein, and glycitein—and their respective glycoside forms esterified to either malonic or acetic acid. Isoflavones in American foods are primarily present as glycoside conjugates. The levels of aglycones in supplements and foods tend to be very low unless the food has been fermented. The term "aglycone isoflavone equivalents" best describes the bioactive form of isoflavones. Hence, drawing generalizable conclusions about the health effects of soy from soy studies is very difficult without a complete description of the intervention [167]. This shortcoming plagued many of the early studies of the health effects of soy.

Soy Protein and Soy Isoflavones: CVD

One of the first health claims that the FDA permitted on food packages, in 1999, was that foods containing at least 25 g of soy protein could prevent coronary heart disease (although the validity of this claim has been challenged in recent years). However, later studies summarized below showed that these foods did not lower LDL levels.

In 2006, a science advisory panel of the American Heart Association determined, on the basis of 22 RCTs, that soy (25–135 g/day for soy proteins and 40–318 mg/day for soy isoflavones) reduced

LDL levels to a very small extent (about 3 %, on average), even when people ate very large amounts of soy protein (50 g, equivalent to about half an individual's usual protein intake). Moreover, soy protein had no significant effects on high-density lipoprotein cholesterol (HDL) cholesterol, triglycerides, lipoproteins, or blood pressure [168]. The 19 soy isoflavone studies evaluated in this review showed that supplementation with soy isoflavones had no effects on lipid risk factors or hot flushes in menopausal women, and the supplements had only equivocal effects on postmenopausal bone loss and unclear effects on cancer risk. There was little evidence that soy isoflavones alone are responsible for soy protein's cholesterol-lowering effects. The panel concluded that there was little evidence that soy protein had clinically important benefits compared to other proteins and did not recommend the use of isoflavone supplements in food or pills.

There is still much disagreement about the size of the effects of supplements containing soy or soy isoflavones on LDL. In a meta-analysis of 43 RCTs, median intakes of 30 g/day for 9.2 weeks, on average, of soy protein were associated with net decreases in serum lipoproteins of 5.5 % (95 % CI: −0.28, −0.18) in parallel studies and of 4.2 % (95 % CI: −0.22, −0.11) in crossover studies along with increases in serum HDL (3.2 %) in parallel studies [169]. In another meta-analysis of 30 RCTs with 2,913 participants to assess a United Kingdom health claim for foods containing soy, intakes of at least 25 g soy protein were associated with significant standard mean differences in mean LDL of 6.0 % or 0.23 mmol/L (95 % CI: −0.160, −0.306; $p < 0.0001$), total cholesterol of 3.7 % or 0.22 mmol/L (95 % CI: −0.142, −0.291; $p < 0.0001$), and the calculated average total cholesterol:HDL ratio was reduced by 10 %, although the results showed no dose-response effects at intakes of 15–40 g [170], which are the levels of isoflavones usually present in these foods. However, many different soy foods were included in the studies evaluated in this meta-analysis, and the quality of the included studies varied greatly. There is also continuing disagreement about whether the effects of soy on LDL and total cholesterol are due to soy isoflavones alone or to extracted soy isoflavones plus protein. A meta-analysis of ten systematic reviews and nine RCTs of the effects of consumption of an average of 70 mg/day soy isoflavones as aglycones without soy protein for up to 3 months found no measureable effects on either total (0.01 mmol/L, 95 % CI: −0.12, 0.14; $p = 0.86$) or LDL cholesterol levels (0.03 mmol/L; 95 % CI: −0.011, 0.16; $p = 0.71$) in menopausal women with normal cholesterol levels [171].

The Women's Isoflavone Soy Health trial (WISH), a double-blind RCT sponsored by NIH, included 350 postmenopausal women who did not have clinically evident diabetes or CVD at baseline [172]. They received either two daily doses of 25 g soy protein containing 91 mg aglycone isoflavone equivalents or placebo for 2.7 years. The researchers monitored their carotid artery intima-media thickness, a sign of subclinical atherosclerosis. Atherosclerosis progressed in both groups (4.77 μm/year, 95 % CI: 3.39, 6.16 in the treatment groups; and 5.68 μm; 95 % CI: 4.30, 7.06 in the placebo groups), and the rate of progression did not differ statistically between the two groups. However, in the subgroup of healthy younger women who had undergone menopause within the previous 5 years, those receiving isoflavone soy protein supplements had a lower progression rate than placebo participants and this difference was statistically significant (2.16 μm/year; 95 % CI: −1.10 versus 6.79 μm/year; 95 % CI: 3.56, 10.01; respectively).

An additional analysis of results from WISH revealed that the soy protein supplement had no effect on global cognition, a composite score of the weighted sums of 14 neuropsychological test scores, after more than 2 years [173]. Mean standardized improvements from baseline in global cognition score were 0.42 in the soy group and 0.31 in the placebo group, a difference of 0.11 points (95 % CI: −0.13, −0.35). Visual memory was better in the soy group (mean standardized difference: 0.33 points; 95 % CI: 0.06, 0.60), but three other cognitive factors and individuals test scores showed no changes. Furthermore, cognitive factor change scores did not improve significantly in younger postmenopausal women. The authors concluded that long-term supplementation with soy isoflavone supplements in doses comparable to those in traditional Asian diets had no effects on global cognition in healthy postmenopausal women, although the supplements might have improved visual memory.

The emerging evidence on soy protein and soy isoflavones demonstrates the importance for health care providers of keeping up with the literature on supplement safety and efficacy. For the same reason, health care providers need to continue to update their recommendations to patients because these recommendations might need to change over time.

Soy Protein and Soy Isoflavones: Osteoporosis

Osteoporosis is of great concern to many older women and to older men who have decreased bone density after the climacteric. A majority of the most effective treatments for decreased bone density in women have adverse side effects. Concerns have been raised that estrogen alone is associated with an increased stroke risk, and estrogen-progestin combinations are associated with a greater risk of both stroke and breast cancer [174, 175]. Bisphosphonates have been linked to osteonecrosis of the jaw and gastrointestinal problems, and other agents used to retard bone loss might have estrogen-related effects, including an increased risk of blood clots. Thus, there is much interest in the possible benefits of soy isoflavones and soy protein for bone health.

One meta-analysis of ten RCTs was based on data from 896 women who took 87 mg/day, on average, soy isoflavones for at least a year [176]. The results showed no effects on BMD at the lumbar spine, femoral neck, or total hip. A later and more complete systematic review included data on the effects of supplements containing soy isoflavone extracts or isolated soy protein on BMD and turnover markers in approximately twice as many menopausal women in Asia and Western countries [177]. This systematic review included three meta-analyses on the effects of soy isoflavones on lumbar spine, total hip, femoral neck, and trochanter BMD. Soy isoflavones improved lumbar spine BMD moderately but did not affect total hip, femoral neck, or trochanter BMD. A treatment period of 6 months appeared to be enough to exert beneficial effects at doses higher than 75 mg/day. Urine deoxypyridinoline, a bone resorption marker, decreased, but serum alkaline phosphatase and osteocalcin, two bone accretion markers, were not affected.

A more recent systematic review included 19 small RCTs in 1,442 women in Asia, Europe, and the United States who took supplements containing 22.7–126 mg soy isoflavones for 1 month to 2.5 years [178]. Bone-mineral density increased by 54 % (95 % CI: 0.13, 0.94; $p < 0.001$), and bone resorption, as measured by urine deoxypyridinoline, decreased by 23 % (95 % CI: −0.44, −0.02). However, serum alkaline phosphatase, a marker of bone formation, did not change. Also, there was substantial variation in results depending on the type of supplement, the dose of isoflavones, and the length of the intervention.

In contrast, an analysis of 12 RCTs in 1,433 women in Western countries who were consuming much lower total doses of soy isoflavones (52–120 mg/day for 24 weeks to 3 years) than the baseline levels of intake in the meta-analyses that included Asian women and in other older studies found few effects on bone loss [179]. The lack of effect might have been due to the lower isoflavone doses, the low baseline levels of isoflavone intakes, or other differences in the supplements that were used.

For women whose baseline levels of intake are already high, taking isoflavone supplements decreases bone loss at the lumbar spine (hip) to a moderate extent but not at other sites. However, the same isoflavone supplements might not benefit older American women whose baseline isoflavone levels are much lower. More studies are needed to verify the size of these effects in postmenopausal Americans women. Also, because some women eat soy foods and take supplements containing soy isoflavones and isolated soy proteins as well as anti-osteoporosis drugs, possible adverse interactions should be assessed. In a 2010 statement, the North American Menopause Society stated that data suggesting any benefit of dietary isoflavones in the prevention or treatment of postmenopausal osteoporosis, regardless of the isoflavone source, are relatively weak [180].

Soy Protein and Soy Isoflavones: Menopausal Symptoms

Hot flushes, also called hot flashes, are thermoregulatory disturbances, such as a sudden feeling of heat in the face, neck, and chest; night sweats; and other vasomotor symptoms that are common in perimenopausal and menopausal women. Recommendations regarding the use of hormone replacement therapy with estrogens alone or with progestins to relieve hot flushes, bone loss, or cardiovascular risk in menopausal women were revised and updated with newer long-term outcome data because of concerns that these treatments (especially estrogen-progestin therapy) could increase the risk of stroke, gallbladder disease, and breast cancer [181]. Health care providers counseled women to use hormone replacement therapy, if at all, at the lowest possible doses for only a short time. This advice led many women to seek alternative therapies for perimenopausal symptoms. These alternative therapies include dietary soy, isoflavone supplements, and red clover (*Trifolium pretense*, an isoflavone-rich medicinal herb) supplements as well other preparations that have been suggested to relieve these symptoms.

Soy isoflavones and soy protein have some effects on circulating estrogens and other hormones in pre- and postmenopausal women, but the clinical significance of these effects is equivocal. In a recent meta-analysis of 47 randomized or crossover studies, 35 studies in 1,165 postmenopausal women showed that taking supplements containing soy isoflavones and soy protein for 4–104 weeks had no statistically significant effects on estradiol, estrone, sex hormone-binding globulin, follicle-stimulating hormone, or luteinizing hormone levels [182]. The results did show a small, nonsignificant increase in total estradiol levels in women taking soy or isoflavones (approximately a 14 % SMD; $p = 0.07$, in 21 studies). Therefore, although isoflavone-rich soy products might increase estradiol levels in postmenopausal women, the clinical implications of the modest hormonal changes in follicle-stimulating hormone and luteinizing hormone remain to be determined.

The existing studies of the effects of isoflavones and soy products have used various doses and preparations (such as soy food supplements, soy extracts, or isoflavone concentrates of genistein or daidzein), and their duration of use and other factors have also varied, making firm conclusions about the efficacy of isoflavones and soy products to treat perimenopausal symptoms difficult [183]. One meta-analysis of 19 RCTs of soy isoflavones for at least 3 months in postmenopausal women found an overall SMD in favor of soy of −0.39 (95 % CI: −0.53, −0.25), but the data were heterogeneous, particularly for women taking extracts and supplements [184]. This study illustrates the difficulty of combining many different types of products with many different forms of isoflavones in a single analysis.

The largest and most recent review focused only on the efficacy of extracted or synthesized soybean isoflavones on hot flashes [185]. Ingestion of soy isoflavones (median dose 54 mg aglycone equivalents) for 6 weeks to 12 months reduced the frequency of hot flashes by 20.6 % (95 % CI: −28.38, −12.86) compared to placebo. The soybean isoflavones also reduced hot flash severity by 26.2 % (95 % CI: −42.23, −10.15). Moreover, at higher doses (above the median of 19 mg genistein), their potency for reducing hot flash frequency was greater. Therefore, these well-characterized soy isoflavone supplements seemed to be somewhat better than placebos in reducing the frequency and severity of hot flashes, but the clinical effects might not have been great enough to help some women.

Women undergoing treatment for breast cancer with anti-estrogenic therapies should consult their physicians before using concentrated isoflavone supplements, although there is little cause for concern about eating foods containing soy.

Black Cohosh (*Cimicifuga racemosa*)

Black cohosh has been used in Germany since the mid-1950s to manage menopausal symptoms [186]. The pharmacologically active ingredients in black cohosh are prepared from the plant's rhizome and root [186].

The mechanism of action of black cohosh has not been defined. Previously, experts thought that black cohosh might exert its beneficial effects through estrogen receptors to moderate menopausal symptoms and hot flashes. More recently, research has shown that black cohosh extracts possess serotonergic activity [187]. Much of the published evidence on the safety and efficacy of black cohosh is based on the use of a commercial extract, Remifemin, which has regulatory approval for use in Germany. Black cohosh has been used in clinical studies lasting up to 12 months [188, 189]. The quality of black cohosh products in American markets varies.

Although some of the data are contradictory, most research findings suggest that black cohosh extract has a modest effect on menopausal hot flashes, night sweats, anxiety, and insomnia. The Herbal Alternatives for Menopause Trial (HALT) included 351 pre- and postmenopausal women aged 45–55 years [190]. Participants in this 12-month, 5-arm trial were randomly assigned to treatment with: (1) black cohosh (160 mg/day); (2) multiple botanicals (including 200 mg/day black cohosh); (3) multiple botanicals plus counseling about dietary soy; (4) hormone therapy (0.625 mg conjugated equine estrogen daily); or (5) placebo. Hormone therapy significantly reduced vasomotor symptoms compared with the other four treatments, and no differences were detected between the other four treatment arms at any point in the trial. In general, women who had undergone menopause more recently seemed to have a better response to black cohosh than those who had undergone menopause earlier. Because HALT included a placebo group and an estrogen replacement group, 12-month follow-up data collection, and a 92 % trial completion rate, HALT provides strong evidence that black cohosh has, at best, limited efficacy for the treatment of menopausal symptoms.

There is some evidence that black cohosh preparations can improve menopausal vasomotor symptoms, but results vary from study to study [191]. Moreover, an NIH-sponsored RCT in 89 healthy pre- and postmenopausal women did not show that supplementation with black cohosh (128 mg/day standardized to 7.27 mg triterpene glycosides) or red clover (398 mg/day standardized to 120 mg isoflavones) for 12 months reduced the number of vasomotor symptoms compared to placebos [189]. Another RCT conducted in 92 healthy women aged 45–65 years who reported at least six vasomotor symptoms per 24 h in Australia also failed to show that taking a formula containing Chinese herbs and black cohosh (350 mg/day) for 16 weeks reduced vasomotor symptoms [192]. A Cochrane review included 16 RCTs that compared orally administered preparations of black cohosh (either *Cimicifuga racemosa* or *Actaea racemosa,* median dose 40 mg/day for 23 weeks, on average) or placebo for treating menopausal symptoms in 2,027 perimenopausal and postmenopausal women [193]. The authors found no significant effects on the frequency of hot flushes (mean difference: 0.07 flushes per day; 95 % CI: 0.43, 0.56) or on menopausal symptom scores (SMD: −0.10; 95 % CI: −0.32, 0.11). In addition, the herb (64 mg/day for up to 12 weeks) had little effect on anxiety compared to placebo in another study in 28 peri- or postmenopausal women [194].

At present, there is insufficient evidence to support the use of black cohosh to treat menopausal symptoms. However, black cohosh in chemically and biologically standardized extract form has a relatively good safety profile [189]. Because of case reports of liver toxicity associated with the herb and because some black cohosh preparations on the market are poorly characterized, health authorities from several countries require a cautionary label on black cohosh products. Women who have liver disorders or who develop symptoms of liver trouble (such as abdominal pain, dark urine, or jaundice) should discontinue use of the herb and consult a health care practitioner.

Saw Palmetto (*Serenoa repens*)

Saw palmetto has been popular for many years as an alternative therapy for treating the symptoms associated with benign prostatic hyperplasia (BPH), a nonmalignant enlargement of the prostate that can lead to obstruction and irritation in the lower urinary tract. The ripe fruit of saw palmetto is used in several forms, including ground and dried fruit or whole berries. Saw palmetto is available as a

liquid extract, tablets, capsules, and as an infusion or a tea. Modern saw palmetto preparations contain lipids extracted from the powdered berries. The primary ingredients include saturated and unsaturated fatty acids as well as free and conjugated plant sterols [195]. Many saw palmetto products are standardized based on their fatty acid content.

Saw palmetto has been shown to have anti-androgenic, anti-proliferative, and anti-inflammatory properties that seem to be responsible for relieving BPH symptoms [196]. Saw palmetto does not seem to affect overall prostate size, but experts believe that it shrinks the inner prostatic epithelium [196]. The fruit of saw palmetto has been shown in vitro to inhibit 5-alpha-reductase and aromatase and prevent the conversion of testosterone to dihydrotestosterone, which might play a role in the development of BPH [197].

In a number of double-blind RCTs, some lasting up to a year, saw palmetto improved urinary flow rate and most other measures of prostate disease compared to placebo [198]. However, in a well-designed clinical trial, 225 men with moderate-to-severe BPH had no improvement after taking 320 mg daily saw palmetto for 1 year compared to placebo [199]. To evaluate these findings further, NIH sponsored a large RCT of the effects of increasing doses of saw palmetto extract (one, two, or three doses of 320 mg/day for 24 weeks at each dose) in 369 men aged 45 years or older [200]. At baseline, the men had peak urine flow rates of 4 mL/s or more and a score on the American Urological Association's Symptom Index of between 8 and 24 for lower urinary tract symptoms. At 72 weeks, symptom scores decreased slightly from 14.4 to 12.2 in the treatment group (−2.20 points; 95 % CI: −3.04, −0.36), but symptom scores also declined in the placebo group, from 14.7 to 11.7 (−2.99 points; 95 % CI: −3.81, −2.17). The mean difference in symptom score change from baseline to 72 weeks between the saw palmetto extract and placebo groups was 0.79 points, but this difference favored the placebo.

The latest systematic review of saw palmetto for BPH, a Cochrane review that included the trials discussed above, evaluated data on 5,666 men who had symptomatic BPH for at least a month [198]. The 32 RCTs reviewed compared the effects of saw palmetto (100–960 mg/day for 29.2 weeks, on average) and placebo on outcomes such as urologic symptoms and urodynamic measurements. In the high-quality, longer-term trials, the herb reduced lower urinary tract symptoms to the same extent as placebo when measured using the Symptom Score Index (mean difference: 0.25 points; 95 % CI: −0.58, 1.07). However, the effects of saw palmetto and placebo on other measures, such as nocturia, peak urine flow, and prostate size were not significantly different. Therefore, at this time, there is not enough evidence to support the use of saw palmetto for reducing the size of an enlarged prostate.

Saw palmetto is well tolerated, is essentially nontoxic, and has no known drug interactions. Adverse effects such as abdominal pain, diarrhea, nausea, fatigue, headache, decreased libido, and rhinitis are rare and reversible upon cessation of use of the herb [201, 202]. An advantage of saw palmetto, unlike the standard therapy of Proscar, is that it does not appear to affect PSA readings, allowing clinicians to more accurately screen patients with BPH for prostate cancer.

Ginkgo biloba

Ginkgo biloba is one of the most popular medicines in Germany and France, where physicians prescribe it for memory lapses, dizziness, anxiety, headaches, tinnitus, and other problems. Ginkgo leaf and *Ginkgo biloba* extract (GBE) contain flavonoids, terpenoids, and organic acids. Each of these chemicals should exist in a specific amount in clinical-quality. Many of gingko's constituents have intrinsic pharmacological effects, and it is possible that the constituents work synergistically to produce more potent pharmacological effects than any individual constituent. The authors of two early independent meta-analyses concluded that 120–240 mg/day GBE for 3–12 months significantly improved objective measures of cognitive function compared to placebo [203, 204].

NIH sponsored a 5-year, multicenter RCT, the Ginkgo Evaluation of Memory (GEM) study, to evaluate the safety and efficacy to prevent dementia or Alzheimer disease of 240 mg daily *Ginkgo biloba* (EGb 761) for 6.1 years compared to placebo in 3,069 participants who were older than 75 years [205]. The primary outcome was the incidence of all-cause dementia; secondary outcomes included rates of cognitive and functional decline, cardiovascular and cerebrovascular events, and mortality. The overall dementia rate was 3.3 per 100 person-years in the gingko group and 2.9 per 100 person-years in the placebo group. Neither the HRs for *Gingko biloba* compared with placebo for all-cause dementia (1.12; 95 % CI: 0.94, 1.33) nor for Alzheimer disease (1.16; 95 % CI: 0.97, 1.39) was statistically significant. Gingko also had no significant effect on the rate of progression to dementia in participants with mild cognitive impairment (HR: 1.13; 95 % CI: 0.85, 1.50). Nearly a third of the GEM cohort reported use of some type of nonvitamin/nonmineral dietary supplement at entry into study [206]. Nearly 10 % of these participants were taking ginkgo and were unwilling to give up their current ginkgo supplements or would not accept assignment to placebo.

The GuidAge study, a 5-year, double-blind RCT of the efficacy of 240 mg/day of a standardized gingko extract, EGb 761, for the prevention of Alzheimer disease in 2,854 patients over age 70 with a memory complaint, was the largest study carried out in Europe on the prevention of Alzheimer disease [207]. Unfortunately, long-term use of the standardized GBE in that study did not reduce the risk of progression to Alzheimer disease compared with placebo. By 5 years, the rates of cases were 1.2/100 person-years for the ginkgo group and 1.4/100 person-years for the placebo group for probable Alzheimer disease (HR: 0.84; 95 % CI: 0.60, 1.18) [208]. The incidence of adverse events, stroke, and other hemorrhagic or CVD events was not different between the two groups.

A Cochrane review of 36 RCTs that evaluated the use of gingko (80–600 mg/day) for 3–52 weeks to treat dementia or cognitive decline showed only inconsistent and unreliable results [209]. Most of the studies used the same standardized gingko extract, EGb 761. Many of the studies were small, with possible publication bias, although few adverse events were observed. In a meta-analysis of 13 RCTs on the use of gingko to improve memory, executive function, and attention in 1,145 healthy adults, the use of *Ginkgo biloba* had no positive effects [210]. Another meta-analysis of six RCTs on the use of a standardized ginkgo preparation (120–240 mg/day) for at least 6 months to treat dementia in 1,838 adults found a small but significant SMD in favor of the herb compared to placebo in cognitive function (−0.89; 95 % CI: −1.82, 0.04) and change from baseline in cognitive score (−2.65; 95 % CI: −4.53, −0.76) [211]. A larger analysis of nine RCTs in 2,372 participants with vascular dementia, mixed dementia, or Alzheimer disease who received a standardized gingko extract (120–240 mg/day) for 12–52 weeks found that for all participants, cognition change scores favored the standardized gingko extract compared to placebo (SMD: 0.58; 95 % CI: −1.14, −0.01) [212]. However, differences were not significant for activities of daily living. A review of all the RCTs on treatment of memory disorder with gingko and/or drugs in patients with multiple sclerosis and mild memory impairment found that gingko was not associated with any serious adverse events, although the data on outcomes was not included in detail in the review [213]. Thus, at present, there is no evidence to support the use of ginkgo to treat memory disorders.

Gingko is generally safe, although it has the potential to cause bleeding, especially when used in combination with anticoagulants [15]. This adverse effect was not apparent in a study of ginkgo (100 mg/day) and CoQ10 (100 mg/day) in 24 patients (median age 64.5 years) on stable warfarin therapy; the mean dosage of warfarin did not change during either 4-week treatment period [214]. Similarly, in a double blind, crossover RCT in 50 healthy men aged 20–44 years, ginkgo (240 mg/day) combined with aspirin (500 mg/day) for 7 days did not alter bleeding times or other coagulation parameters beyond the effects of aspirin alone [215]. The authors of a meta-analysis of 18 RCTs in 1,895 adults (of which 87 % had dementia, peripheral artery disease, or diabetes mellitus; the remainder were healthy) concluded that the bleeding risk of standardized *Ginkgo biloba* extract therapy was no higher than that of placebo [216]. However, patients who are taking anticoagulants, have bleeding disorders, or are scheduled for surgery or dental extractions should be counseled not to use gingko until they consult a health care practitioner.

Non-nutrient, Non-botanical Supplements

Non-nutrient supplements include non-botanical products, such as melatonin and CoQ10, and many "condition-specific" supplements, such as glucosamine/chondroitin, that are marketed to prevent or cure many ills.

Glucosamine/Chondroitin

Glucosamine hydrochloride is an amino sugar compound in cartilage and other connective tissues. Chondroitin sulfate is a complex glucopolysaccharide that helps cartilage retain water. Both are marketed to elders with claims that these products help maintain healthy joints, protect tendons, and decrease inflammation. In 2004, the FDA denied a health claim that glucosamine, chondroitin, and glucosamine and chondroitin reduce the risk of osteoarthritis, joint degeneration, and cartilage deterioration.

A Cochrane review of 25 studies of the use of glucosamine (oral dose of 1,500 mg/day or parenteral dose of 800–2,800 mg/week) for 25.5 weeks, on average, to treat osteoarthritis in 4,963 patients failed to show any reductions in pain as measured by the Western Ontario and McMaster Universities Arthritis Index (WOMAC) [217]. Some brands appeared to be more efficacious than others, and one proprietary brand appeared to be more effective than placebo in treating pain and gait impairments.

In response to these and other findings, NIH funded the Glucosamine/Chondroitin Arthritis Intervention Trial (GAIT) to determine whether a combination of glucosamine (1,500 mg/day), chondroitin (1,200 mg/day), celecoxib (200 mg/day), a combination of all three treatments, or placebo for 24 months would help people with moderate-to-severe pain from knee osteoarthritis [218]. An analysis of 24 months of data on 662 patients enrolled in 9 of the 16 GAIT sites revealed that the odds of achieving a 20 % decrease in WOMAC pain subscale score was 1.21 for celecoxib, 1.16 for glucosamine, 0.83 for glucosamine and chondroitin sulfate, and 0.69 for chondroitin sulfate alone. The confidence intervals for all treatments overlapped substantially.

Many other studies have been carried out since GAIT. A Norwegian group, for example, studied the effects of 1,500 mg glucosamine for 6 months on pain-related disability in 125 adults with chronic low back pain and degenerative lumber osteoarthritis in an RCT [219]. The glucosamine treatment did not reduce pain-related disability at the end of the intervention period or 6 months later. A systematic evidence-based review of the use of glucosamine (1,500–1,800 mg/day), chondroitin (1,200 mg/day), and methylsulfonylmethane (another supplement) for 2–4 months to treat degenerative joint disease and spinal osteoarthritis found only two high-quality articles that included 124 adults [220]. The authors of both of these articles reported negative results.

A systematic review included ten large RCTs in 3,803 patients on the use of glucosamine (1,500 mg/day), chondroitin (800–1,200 mg/day), both glucosamine and chondroitin, or placebo for up to 3 years to treat osteoarthritis of the hip or knee that assessed differences in pain intensity on a 10 cm visual analogue scale [221]. The results were 0.4 cm for glucosamine (95 % CI: −0.7, −0.1), −0.3 cm for chondroitin (95 % CI: −0.7, 0.0), and 0.5 cm for the combination (95 % CI; −0.9, 0.0). None of these differences were considered to be clinically important. The differences were larger in industry-funded than in independently conducted trials. The authors concluded that none of these products reduced joint pain or narrowed joint space and that the treatment was not useful.

Although other studies have found that the use of glucosamine or chondroitin sulfate for longer than 3 years might delay radiological progression of osteoarthritis of the knee [222], their effects on pain have not been measured. And even if glucosamine or chondroitin are effective, their use has not been shown to be cost-effective [223].

A review of evidence by the Osteoarthritis Research Society International on therapies to treat hip and knee osteoarthritis identified 1 systematic review and 20 RCTs that evaluated the efficacy of glucosamine [224]. A meta-analysis of these RCTs found an effect size of 0.46 (95 % CI: 0.23, 0.69), but outcomes were heterogeneous and there was substantial evidence of publication bias. The review also identified five meta-analyses of chondroitin studies. The most recent, which included 20 trials in 3,846 patients, found an effect size of 0.75 (95 % CI: 0.50, 0.99), but these reports demonstrated publication bias and the results were also highly heterogeneous. Another expert group that reviewed different treatments for osteoarthritis of the knee recommended against using glucosamine or chondroitin [225].

In summary, the evidence supporting the use of glucosamine and chondroitin to prevent or treat joint pain and osteoarthritis is not compelling.

CoQ10

CoQ10, also known as ubiquinone, is involved in oxidative phosphorylation and generation of adenosine tri phosphate. In addition, CoQ10 is a free radical scavenger and membrane stabilizer. Japanese scientists first reported therapeutic properties of CoQ10 in the 1960s [196]. Some evidence suggested that CoQ10 might improve the efficiency of energy production in heart tissue and thus assist the heart during physical and/or oxidative stress. Typical doses of CoQ10 range from 100 to 200 mg in two to three divided doses a day [196].

CoQ10: Cardiovascular Health

Most of the consistent evidence for positive outcomes of CoQ10 therapy comes from people with congestive heart failure and not healthy people. Dozens of controlled trials have evaluated the effects of CoQ10 on CVD. Early studies summarized in the prior edition of this volume showed that CoQ10 has beneficial subjective (quality of life) and objective (increased left ventricular ejection fraction, improved stroke index scores, decreased hospitalizations) effects, but more recent studies have been less supportive [226].

The authors of a meta-analysis of nine RCTs in 824 patients of the use of CoQ10 (100–200 mg/day or 2 mg/kg) for 2–12 weeks to treat heart failure identified nonsignificant trends toward increased ejection fraction and reduced mortality [227]. However, the numbers of patients were insufficient to yield meaningful results. An updated meta-analysis that included 11 clinical trials in 319 patients of CoQ10 in doses ranging from 60 to 200 mg/day for 1–6 months found a net 3.7 % improvement in ejection fraction (95 % CI: 1.59, 5.77), and the effect was greater (6.74 %; 95 % CI: 2.63, 10.86) in patients who were not treated with angiotensin-converting enzyme inhibitors [228].

The most recent meta-analysis focused on 13 RCTs in 395 patients with heart failure in which the primary outcome was change in the ejection fraction or New York Heart Association functional class. CoQ10 supplementation (60–300 mg/day) for 4–28 weeks resulted in an improved pooled mean net change of 3.67 % (95 % CI: 1.60, 5.74) in ejection fraction and a decrease of −0.30 (95 % CI: −0.66, 0.06) in functional class [229]. Moreover, CoQ10 had positive effects in crossover trials, trials of short treatment duration (12 weeks), older studies (published before 1994), studies using a dose of 100 mg/day or less, and studies whose participants had less severe congestive heart failure at study entry. However the numbers of patients in the studies were small, although the results appear promising.

Reduced plasma or serum levels of CoQ10 have been documented in observational studies and a number of RCTs in patients on statin therapies. The largest trial included 1,049 patients with moderate hypercholesterolemia and showed reductions in plasma CoQ10 levels of about a third after 1 year of treatment with atorvastatin [230]. The decrease in blood CoQ10 levels with statin treatment might be related to reduced synthesis of CoQ10 as well as decreases in circulating levels of CoQ10 because LDL cholesterol

carries CoQ10 in the blood. Supplementation with CoQ10 (100 mg/day for 30 days) decreased muscle pain by 40 % ($p<0.001$) compared to vitamin E (400 IU/day) in 32 patients with statin-associated myopathy symptoms [231]. A recent systematic review of 18 studies on the role of CoQ10 in statin-associated myopathy confirmed that statin treatment (5–80 mg/day for 1–18 months) reduced circulating levels of CoQ10 and that CoQ10 supplementation could raise circulating levels of CoQ10 [232]. However, data on the effects of CoQ10 supplementation on myopathy symptoms remain scarce and contradictory. The review's authors concluded that the evidence is insufficient to prove that CoQ10 deficiency has a causal role in statin-associated myopathy and that more large, well-designed clinical trials were required to address this issue. In another study, 76 patients with myalgias presumed to be caused by statins were randomly assigned to therapy with 120 mg CoQ10 a day or placebo while continuing statin therapy [233]. CoQ10 did not reduce patient-reported pain to a greater extent than placebo.

At this time, therefore, routine use of CoQ10 to prevent myalgia due to statins is of questionable value.

CoQ10 has also been used to lower blood pressure. The authors of a Cochrane review of three RCTs evaluating the use of 100–120 mg/day CoQ10 for at least 3 weeks to reduce blood pressure in 96 patients with primary hypertension found that CoQ10 had no clear-cut effects [234]. Another meta-analysis of five RCTGs in 194 patients with and without CVD focused on CoQ10's effects on vascular endothelial function [235]. CoQ10 supplements (150–300 mg/day for 1–3 months) significantly improved flow-mediated dilation in a random effects model (SMD: 1.70; 95 % CI: 1.0, 2.4). However, endothelial function assessed by nitrate-mediated arterial dilatation did not improve when the authors used a fixed-effects model (SMD: −0.19; 95 % CI: −1.75, −1.38). An RCT that assessed the use of CoQ10 as adjunctive therapy in patients with hypertension and metabolic syndrome showed that it did not reduce systolic or diastolic blood pressure [236]. In an RCT of 56 patients with left ventricular systolic dysfunction and ischemic heart disease, CoQ10 supplementation (300 mg/day for 8 weeks) improved flow-mediated dilation by 1.51 % ($p=0.03$) compared to placebo [237]. Thus, the effects of CoQ10 supplements on CVD-related outcomes are not impressive at present.

In general, CoQ10 supplements appear to be safe. No significant side effects have been found, even in studies that lasted a year. CoQ10 chemically resembles vitamin K. Because vitamin K counters the anticoagulant effect of warfarin, anecdotal case reports have associated CoQ10 therapy with decreased international normalized ratio (INR), a measure of the time required for blood to clot compared to the average time in patients on warfarin therapy. In a randomized, double-blind, placebo-controlled, crossover trial, 100 mg CoQ10 daily for 4 weeks had no effect on INR in 21 patients on warfarin [214]. Patients taking both CoQ10 and warfarin should be aware that CoQ10 could decrease the effectiveness of warfarin and lower clotting time.

CoQ10: Neurological Health

There is great interest in investigating the potential usefulness of CoQ10 for treating neurodegenerative diseases.

CoQ10 has shown some promise for slowing the progression of Parkinson's disease. In an NIH-sponsored RCT, 80 people with early Parkinson's disease were given 300, 600, or 1,200 mg daily CoQ10 or placebo for 16 months [238]. The results suggested that CoQ10, especially at the highest dose, might have slowed disease progression. In a pilot trial, doses of up to 3,000 mg/day of CoQ10 were well tolerated [239]. In a more recent trial conducted in Germany, researchers randomly assigned 131 patients with mid-stage Parkinson disease who were taking medications for Parkinson disease to 300 mg of CoQ10 daily or placebo for 3 months [240]. The results did not show significant differences between the groups, although both the treatment and placebo groups had significant improvement in Unified Parkinson's Disease Rating Scale scores. The investigators concluded that the study did not support the hypothesis that restoring the impaired energy metabolism of dopaminergic neurons leads to beneficial effects in patients undergoing treatment for mid-stage Parkinson's disease.

A Cochrane review of four RCTs that assessed the safety and efficacy of CoQ10 in 452 patients with early-stage or mid-stage primary Parkinson's disease found that up to 1,200 mg/day for 16 months CoQ10 was well tolerated, with few adverse effects other than mild pharyngitis and diarrhea [241]. The treatment was associated with improvements in activities of daily living (weighted mean difference: −3.12; 95 % CI: −5.880, −0.36) and other tests.

In summary, the small neuroprotection trials of CoQ10 in Parkinson's disease conducted to date have been somewhat encouraging. However, further evidence is required before CoQ10 supplements can be recommended for routine use.

Guidelines for Safe Use of Dietary Supplements by Elders

Dietary supplements influence drug therapy within and outside of acute care facilities. Because so many elderly adults take medications and polypharmacy is very common, health care providers need to recognize the potential effects of dietary supplements on medical status and treatment. To that end, the Joint Commission has included vitamins, herbals, and "nutraceuticals" in their scope of medications addressed by safety standards. The Joint Commission expects healthcare facilities to establish standardized processes to compare current medication orders to medications usually taken and thus eliminate medication errors, such as omissions, drug interactions, duplications, and dosing discrepancies in diverse care settings (including admission, surgery, and discharge) and all transitions of care. For this reason, healthcare staff need to ask their patients about their use of dietary supplements. Registered dietitians, in particular, should become familiar with dietary supplements. Nurses also need to become familiar with dietary supplements because they do most admission assessment interviews. Shared accountability encourages processes that use input from all disciplines.

Some manufacturers use standardization to ensure the batch-to-batch consistency of their products. This process often involves the use of markers that help identify a consistent product and provide a measure of quality control. Because no legal or regulatory definition of standardization exists for dietary supplements, standardization statements on dietary supplement packages have no association with quality. Some hospitals have restricted or banned patient use of dietary supplements because of drug–nutrient interactions, inconsistent manufacturing standards, and concerns that admission assessments of such substances cannot be accurately conducted [242, 243].

Preventing Interactions with Dietary Supplements

The potential for drug/supplement interactions is particularly likely in the elderly due to their high use of medications. The Natural Medicines Comprehensive Database identifies more than 1,900 drug–supplement interactions [196]. Approximately 15 % of these interactions are likely to occur and be of high severity when they occur, including 74 % that are probable and of moderate severity and 11 % that are unlikely to occur and insignificant. Many of these interactions are documented only by a few case reports, underscoring the need for better adverse event reporting. Of these potential interactions, 25–45 % are pharmacokinetic (depending on their absorption, distribution, metabolism, and excretion patterns) and 45–55 % are pharmacodynamic (due to their metabolic effects). But most of these estimates are speculative because most of the interactions are not documented in an easily retrievable clinical format.

Botanical and herbal products, unlike most conventional drugs, consist of complex mixtures of bioactive entities that might or might not have therapeutic activity. The active ingredients are frequently not known and complete characterization of all the chemical constituents is lacking, as

Table 23.1 Distinctions between herbal and botanical supplements and drugs

Criterion	Drugs	Herbal and botanical supplements
History of use	Typically a short tradition of use	Typically a long tradition of use for the whole plant but not necessarily for extracts or other preparations
Ingredient characteristics	Active ingredient known	Active ingredient often not known, and marker compounds often used as standards
	Pure compound available	Pure compounds not available; many compounds often present
	Composition constant	Composition variable due to season, temperature, and other harvest conditions
Mechanism of action	Often known	Often unknown
Safety	Side effects often known	Side effects often not studied and adverse effects might have been evaluated for some but not all marketed forms
	Frequently a narrow therapeutic window	Usually a wide therapeutic window
	Frequent adverse effects	Rare or unknown and poorly characterized adverse effects
Regulatory oversight in the United States	Requires prior approval from Food and Drug Administration for marketing	Does not require premarket approval from Food and Drug Administration for marketing

described in Table 23.1. As with conventional drugs, many herbal products are therapeutic at one dose and toxic at another, particularly if they are highly concentrated. Concurrent use of herbs can mimic, magnify, or oppose the effects of drugs. The importance of unrecognized interactions between herbs and conventional drugs is particularly important in cardiology because many cardiovascular drugs, such as warfarin and digoxin, have narrow therapeutic windows.

Additional references for herb/botanical-drug interactions are listed in Table 23.2. Some herbal products affect clinical laboratory test results by direct interference, most commonly with immunoassays; exert physiologic effects through toxicity or enzyme induction; or produce interference by contaminants.

Needs Assessment for Dietary Supplements

Given the prevalence of inadequate dietary intakes of many vitamins and minerals as well as the potential for inappropriate supplement use among older adults, health care providers should routinely screen elderly clients for both the need to use dietary supplements and the risk of excessive supplement intake. The following questions can identify conditions, symptoms, or situations that suggest a need to offer counseling on the use of fortified foods and/or dietary supplements in addition to advising older adults to make appropriate dietary changes.

1. Has the older client been diagnosed with physical conditions or does he/she display symptoms that could indicate a need for fortified foods and/or dietary supplements? Examples of conditions that could indicate a need for dietary supplements and supplements that might benefit patients with these conditions are as follows:

    - Osteoporosis: calcium, vitamin D, and magnesium
    - Alcohol abuse: B-vitamins and magnesium
    - Gastrointestinal abnormalities, including acid reflux, diarrhea, fat malabsorption, and atrophic gastritis: vitamin B_{12}, fat-soluble vitamins (vitamins A, D, E, and K), and magnesium

Table 23.2 References on dietary supplements and herb–drug interactions

	Title	Additional information
Monographs	American Herbal Pharmacopoeia® monographs	Available from: American Herbal Pharmacopoeia PO Box 66809 Scotts Valley, CA 95067 www.herbal-ahp.org ahp@herbal-ahp.net Phone: 831-461-6318
	Blumenthal M, Goldberg A, Brinkmann J, editors. *Herbal Medicine*: *Expanded Commission E Monographs*. Austin (TX): Integrative Medicine Communications; 2000.	Available to American Botanical Council members from: American Botanical Council 6200 Manor Road Austin, TX 78723 www.herbalgram.org abc@herbalgram.org Phone: 512-926-4900 Also available from online booksellers
	World Health Organization. *WHO Monographs on Selected Medicinal Plants. Vol. 1*. Geneva: World Health Organization; 1999. (28 monographs)	Provide scientific information on the safety, efficacy, and quality control of widely used medicinal plants; available at: Volume 1: http://apps.who.int/medicinedocs/pdf/s2200e/s2200e.pdf
	World Health Organization. *WHO Monographs on Selected Medicinal Plants. Vol. 2*. Ravello-Salerno (Italy): World Health Organization; 1999. (30 monographs)	Volume 2: http://apps.who.int/medicinedocs/pdf/s4927e/s4927e.pdf
	World Health Organization. *WHO Monographs on Selected Medicinal Plants. Vol. 3*. Ottawa (Canada): World Health Organization; 2001. (31 monographs)	Volume 3: http://apps.who.int/medicinedocs/documents/s14213e/s14213e.pdf
	World Health Organization. *WHO Monographs on Selected Medicinal Plants. Vol. 4*. Salerno-Paestum (Italy): World Health Organization; 2005. (28 monographs)	Volume 4: http://apps.who.int/medicinedocs/documents/s17534en/s17534en.pdf
Books	Barrett M, editor. *The Handbook of Clinically Tested Herbal Remedies*. New York: Routledge; 2013.	
	Bone K, Milles S. *Principles and Practice of Phytotherapy: Modern Herbal Medicine*. 2nd ed. London: Churchill Livingstone; 2013.	
	Coates PM, Betz JM, Blackman MR, Cragg GM, Levine M, Moss J, White JD, editors. *Encyclopedia of Dietary Supplements*. 2nd ed. New York: Informa Healthcare; 2010.	
	Fugh-Berman A. *The 5-Minute Herb and Dietary Supplement Consult*. Philadelphia: Lippincott Williams & Wilkins; 2003.	
	Gardner Z, McGuffin M, editors. *American Herbal Products Association's Botanical Safety Handbook*. 2nd ed. Boca Raton (FL): CRC Press; 2013.	
	Hendler S, Rorvik D. *PDR® for Nutritional Supplements*. 2nd ed. Montvale (NJ): PDR Network; 2008.	

	Natural Standard. *Natural Standard Herb & Supplement Guide: An Evidence-Based Reference*, 1st ed. Mosby, St. Louis (MO); 2010.	
	Otten JJ, Hellwig JP, Meyers LD, editors. *Dietary Reference Intakes: The Essential Guide to Nutrient Requirements*. Washington: National Academies Press; 2006.	
	Pharmaceutical Press Editorial. *Herbal Medicines*. 4th ed. London: The Pharmaceutical Press; 2013.	
	Schulz V,Hänsel R, Blumenthal M, Tyler VE. *Rational Phytotherapy: A Reference Guide for Physicians and Pharmacists*. 5th ed. New York: Springer-Verlag; 2004.	
	Thomson Healthcare. *PDR® for Herbal Medicines*. 4th ed. Montvale (NJ): Thomson Reuters; 2007.	
Databases	Integrative Medicine Service, Memorial Sloan-Kettering Cancer Center. About Herbs, Botanicals & Other Products. Available from: www.mskcc.org/cancer-care/integrative-medicine/about-herbs-botanicals-other-products.	Evidence-based information about herbs, botanicals, and dietary supplements
	ConsumerLab. Available at: www.consumerlab.com.	Evaluations of the composition, potency, purity, bioavailability, and consistency of commercially available dietary supplements; annual subscriptions available for a fee
	Office of Dietary Supplements and National Library of Medicine, National Institutes of Health. Dietary Supplement Label Database. Available at: www.dsld.nlm.nih.gov/dsld/	Data on information from labels of some dietary supplements marketed in the United States
	Health Canada. Natural Health Products Ingredients Database. Available at: webprod.hc-sc.gc.ca/nhpid-bdipsn/	Information on acceptable medicinal and nonmedicinal ingredients used in natural health products in Canada
	MedLine Plus, National Library of Medicine. Herbal Medicine. Available at: http://www.nlm.nih.gov/medlineplus/herbalmedicine.html	Up-to-date, high-quality health care information on herbs and herbal medicine
	MedLine Plus, National Library of Medicine. Dietary Supplements. Available at: http://www.nlm.nih.gov/medlineplus/dietarysupplements.html.	Links to information sources, including the latest research, on dietary supplements
	Natural Medicines Comprehensive Database. Available to subscribers at: www.naturaldatabase.com	Searchable database of monographs with extensive information pm common uses, evidence of efficacy and safety, mechanisms, interactions, and dosages of dietary supplements that is extensively referenced and updated daily; requires a subscription fee
	Natural Standard. Food, Herbs & Supplements. Available at: http://www.naturalstandard.com/databases/herbssupplements/all/a/.	Searchable database of information on herbs and supplements, including quality of evidence; requires a subscription fee
	National Center for Complementary and Alternative Medicine, National Institutes of Health. Herbs at a Glance. Available at: nccam.nih.gov/health/herbsataglance.htm	Brief fact sheets with basic information about specific herbs and botanicals, including common names, scientific evidence, potential side effects, and information resources

(continued)

Table 23.2 (continued)

	Title	Additional information
	Office of Dietary Supplements. PubMed Dietary Supplement Subset. Available at: ods.od.nih.gov/Research/PubMed_Dietary_Supplement_Subset.aspx.	Filter designed to limit search results of the PubMed database to citations from a broad spectrum of dietary supplement literature, including publications on vitamin, mineral, phytochemical, ergogenic, botanical, and herbal supplements in human nutrition and animal models; includes links to many full-text articles on journal websites and other related Web resources
Mobile applications	Office of Dietary Supplements. MyDS. Available at: http://ods.od.nih.gov/HealthInformation/mobile/AboutMyDS.aspx	A free mobile application that helps consumers track the vitamins, minerals, herbs, and other supplements they take and provides access to reliable, science-based information on dietary supplements
	European Scientific Operative on Phytotherapy. ESCOP Herb Reference iPhone® App. Available at: http://www.escop.com	Lists more than 100 herbs and their uses for a range of health conditions

- Renal insufficiency: vitamin D
- Cardiovascular disease: vitamin E and folic acid
- Nutritional anemia: iron, vitamin B_{12}, and folic acid
- Weight loss, anorexia, nausea, or other symptom indicating inadequate intake: general MVM supplement or medical nutritional supplement

2. Does the older client have eating or supplement use behaviors that place him/her at high risk of nutritional deficiency or excess? These behaviors could include the following:

- Eats fewer than two meals per day
- Drinks more than one (women) or two (men) alcoholic beverages per day
- Eats less than two servings of vegetables per day
- Eats less than two servings of fruits per day
- Takes many dietary supplements every day
- Takes doses of vitamin and mineral supplements that greatly exceed the RDA (unless a physician has recommended these doses), especially if intakes are greater than the UL
- Does not know the doses of supplements that he or she takes
- Consumes a high volume of grapefruit juice that could interact with medications
- Uses proton-pump inhibitors, which could cause significant magnesium depletion and the patient therefore require periodic checks of serum magnesium levels

3. Do body composition changes or physical limitations suggest that the patient might have nutrient deficiencies? These changes and limitations include the following:

- Has a body mass index of less than 21
- Has unintentionally lost or gained 10 lb in the last 6 months
- Has difficulty chewing or swallowing
- Has physical disabilities that limit his or her ability to shop for and/or prepare food

4. Does the patient have lifestyle habits or conditions that could impair normal nutrient intakes? These lifestyle habits or conditions include the following:

- Is housebound
- Has clinical evidence of depressive illness
- Needs assistance with self-care
- Demonstrates mental or cognitive impairment

5. Does the client have a disease or medical condition that contraindicates the use of dietary supplements? For example, does the patient have medical problem(s), such as impaired renal function, that limit excretion of supplements such as magnesium? Does the patient take any medications that could adversely interact with dietary supplements?

Every day, clinicians must interpret the evidence, both established and emerging, to provide the best care for their patients. Recommendations occur on many levels [226]. Level I recommendations are influenced by the physician's personal experience with the disease and capacity to deal with risk. When making such decisions, physicians might ask themselves, "Would I have this done for myself or for someone else in my immediate family?" A clinician making Level II recommendations for a patient is also influenced by prior experience, but the strength of the scientific evidence might play greater role. Lastly, a Level III recommendation can be viewed as an across-the-board public health recommendation for a population. Such recommendations must be based on rigorous assessments of the scientific evidence. As the data on dietary supplements become more robust and more evidence becomes available, clinicians will feel more confident in making recommendations about the use of dietary supplements for health maintenance and risk reduction at both the individual and group levels.

Dietary Supplement Databases and Other Resources

In addition to the print resources listed in Table 23.2, the Office of Dietary Supplements (ODS), in collaboration with the National Library of Medicine of NIH recently developed a dietary supplement label database that is available at http://dsld.nlm.nih.gov. Other useful information on dietary supplements is available on the ODS website, at http://www.ods.od.nih.gov, and the National Center for Complementary and Alternative Medicine's website, at http://www.nccam.nih.gov. The FDA website, http://www.fda.gov/Food/DietarySupplements, provides up-to date information on dietary supplement recalls and health claims.

Conclusion: Continuing Concerns

Older people, particularly those in fragile health, need to describe and discuss their use of dietary supplements with their health care providers. Providers and patients must talk frankly with each other about these products. Open discussions about the reasons elders use dietary supplements sometimes help health care providers identify health problems, such as memory difficulties, that otherwise might go undetected. These discussions also permit providers and patients to work together to choose appropriate supplements when supplements are necessary, avoid adverse interactions with the many medications that patients take, and avoid falling prey to misleading and deceptive advertising. Dietary supplements are often costly and can be difficult for elders on fixed incomes to afford. In addition, because elders often suffer from many chronic diseases that require multiple medications, they have a higher risk than younger people of adverse reactions. For all of these reasons, frank and forthright discussions about the safety and efficacy of dietary supplements should be a part of interactions between older patients and health care providers.

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Index

A
Abusabha, R., 9
Acid–base balance, diet
  acidic environment
    bone, negative effects, 280
    muscles, negative effects, 280
  for bone development and preservation, 274
  metabolic acidosis, 280
  NAE values, 280–281
  potassium bicarbonate, 281
ACSM Position Stand: Exercise and Physical Activity for Older Adults, 365–366
Activity of daily living (ADL), 44, 288
Administration on Aging (AoA), 368
Adverse Event Reporting (AER), 379, 408
Aerobic exercise, 106, 119, 316, 319, 360, 364–366
Agency for Healthcare Research and Quality (AHRQ) review, 22–24, 389–390, 396–397
Age-Related Eye Disease Study (AREDS), 64, 65, 67, 70–72, 385–386
Age-related macular degeneration (AMD)
  abnormal blood vessels, 58
  blindness, 58
  and cataracts, 58–60
  components, 58
  early and intermediate stages, 58
  for eye health, 341, 379, 385
  and lens opacities, 385
  lutein and zeaxanthin, 65–66
  modifiable risk factors, 58
  nutrient supplement effects
    AREDS study, 70–71
    epidemiologic studies, 71
    lutein and zeaxanthin, 72
    vitamin C, 71
    vitamin E, 71
    zinc, 72
  omega-3 fatty acids, 66–68
  prevalence, 58
  restore vision, 60
  retina (macula), 59
  retinal pigment epithelium (RPE), 59
  vitamin C, 64, 65
  vitamin E, 64, 65
  zinc, 67–68
Aging
  AD, 133
  anti-aging effects (*see* Calorie restriction (CR))
  biomarkers, 131, 321–322
  cognitive function, 126–127
  high-risk nutrients (*see* Nutrient intake)
  knowledge and procedural memory, 125
  mediterranean diet, 136
  monounsaturated and polyunsaturated fatty acids, 135
  and polyphenols, 133
  successful agers, 13
  usual, 13
  vitamin D, 131, 277
Aglycone isoflavone equivalents, 398
Allman, R., 239
Alpha-Tocopherol and Beta-Carotene trial, 71
Alzheimer's disease (AD)
  aging, 133
  APOE ε4, 129
  B-complex vitamins, 128, 388–389
  dementia patients, 192, 288, 306–307
  FAST, 306
  mediterranean diet, 137
  omega-3 fatty acids, 339, 397–398
  polyphenols, 132
  primary neurological symptom, 136
  vitamin D, 131, 391
  vitamin E supplements, 345
Amella, E., 9
Amella, E.J., 287–299
American Association of Clinical Endocrinologists (AACE), 186
American College of Sports Medicine (ACSM), 104, 365–367
American Diabetes Association (ADA), 181, 183–187, 194
American Geriatric Society (AGS), 183
Amyotrophic lateral sclerosis (ALS), 307

C.W. Bales et al. (eds.), *Handbook of Clinical Nutrition and Aging*, Nutrition and Health,
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Analytic framework. *See also* Systematic reviews
dietary reference intakes, 22, 23
organizational structure, 22
vitamin D and calcium, 23, 24
Annweiler, C., 131, 132
Anthony, P.S., 239
Anthropometrics, 40–41, 228, 238, 290
Apolipoprotein E (APOE) ε4 genotype, 129
Arnarsson, A., 63
Arthritis, 167, 204
Artificial nutrition/hydration (ANH)
terminal cancer, 305–306
terminal dementia
alternative approaches, 307
comfort feeding only, 307
costs and benefits, 306–307
Aselage, M.B., 287–299
Atrophic gastritis, 343
Auditory Consonant Trigram (ACT), 328

B
Baldwin, C., 254
Bales, C.W., 287–299
Banks, M., 168
Barrett, M., 410
Bartholomew, L.K., 6
Basal metabolic rate (BMR), 220, 221
Baumgartner, R.N., 101, 103
B-complex vitamins
cognition, 388–389
CVD, 387
mortality, 386–387
risks of excess amounts, 387–388
Beatty, S., 66
Beddhu, S., 261–268
Behavioral Risk Factor Surveillance System (BRFSS), 364, 366
Behavior modification, obesity, 172–173
Benign prostatic hyperplasia (BPH), 402–403
Bennett, D.A., 239
Benton Visual Retention Test (BVRT), 328
Berg, A.C., 354–372
Bergenstal, R.M., 184
Bergstrom, N., 239
Berlowitz, D.R., 239
Bernstein, M., 8
Bernstein, P.S., 66
Betz, J.M., 410
Bioavailability, 28, 130
Bioequivalence, 29
Blackman, M.R., 410
Blanc, S., 316
Blood glucose, DM
cognitive impairment, 192
food and insulin intake, 191
ICU, 186
management, 182
and metabolic abnormalities, 181
metabolic syndrome, 188
micro and macrovascular disease, 182
non-Hispanic whites, 180
nutrition care plans, 187
postprandial, 183
SMBG, 189
type 1 diabetes, 189
Blood nutrient status, 90–91
Blueberries, 133
Blue Mountains Eye Study, 63, 386
Blumenthal, M., 410, 411
BMD. *See* Bone mineral density (BMD)
Body mass index (BMI)
frailty, 169
overweight and obesity, 165, 166, 223, 263–264
periodontitis, 86
recommendations, older adults, 42
unintentional weight loss, 41, 238
uremia, 265
Body Shape Questionnaire (BSQ), 327
Bolland, M.J., 276
Bone, K., 410
Bone mass, 274, 277–279
Bone mineral density (BMD)
age-related bone loss, 274
calcium and vitamin D, combinations, 384
fractures and bone mass, vitamin D, 278
increased body weight, 169
osteoporosis, nutritional concerns, 274, 400
PA/EX effects, 362
protein intakes, 337
weight loss in older adults, 170, 171
Bone, R.A., 66
Botanicals. *See* Herbals and botanicals
Bouchard, D.R., 99–108
Bourdel-Marchasson, I., 239
Bozzetti, F., 257
Brady, A.O., 354–372
Brandeis, 239
Breslow, R.A., 239, 240
Bridge to heart transplantation (BTT), 218
Brief Inventory for Mental State (BIMS), 293
Brinkmann, J., 410
Briscoe, V.J., 195
Brown, B., 129
Brown, L., 64
Bruera, E., 255
B-type natriuretic peptide (BNP), 221
Buse, J.B., 184
Buys, D.R., 147–157
B vitamins
Alzheimer's disease, 128
and APOE ε4 genotype, 129
and cognitive function, 128
deficiencies, 127
homocysteine, 127–128
MTHFR genotype, 129–130
one-carbon metabolism cycle, 127
SAM, 127
supplementation, 128
vitamin B_6, 341–342
vitamin B_{12}, 342–343

C
Cachexia
cancer, 305–306
cardiac (*see* Cardiac cachexia)
cytokine-induced, 247
inflammatory-mediated, 245, 247
interventions, 247
Calcium
minerals, 346
osteoporosis
intake requirements, 275
physiology, 274–275
recommendations, 276
safety, 276
phosphorus, 267–268
and vitamin D, combinations
bone mineral density, 384
dietary reference intakes (DRIs), 383
fractures, 384
mortality and other outcomes, 384–385
osteoporosis, 383–384
CALERIE (Comprehensive Assessment of the Long-term Effect of Reducing Intake of Energy), 318–321, 323, 326–328
Calorie restriction (CR)
cardiovascular disease, 316–317
centenarians from Okinawa, 317–318
increased longevity in humans, 328–329
insulin resistance, 316–317
and lifespan, 315–316
physiological effects
body composition, 321
cardiovascular and diabetes risk factors, 322–323
DHEA-S, 324
leptin, 324
longevity, biomarkers, 321–322
metabolic adaptation and oxidative stress, 323
physical activity, 324–326
somatotropic axis, 324
thyroid function, 323
psychological and behavioral effects
cognitive function and performance, 328
eating disorder symptoms, 327
hunger, subjective feelings, 327
outcomes, 326
QOL and mood, 327–328
rate of living and oxidative stress, 316
RCT, nonobese humans, 318
type 2 diabetes mellitus, 316–317
unexpected CR, Biosphere 2, 318, 319
Vallejo study, 318
Calorie Restriction with Optimal Nutrition (CRON) diet, 328
Cancer
cachexia, 305–306
exercise, benefits, 361
head and neck, 258
incurable, enteral nutrition, 254–255
MVM supplements, 382
obesity, 167
omega-3 fatty acids, 397
oral (*see* Oral cancer (OC))
PA/EX, effects, 361
physical activity, 361
preoperative, 257
prevention, vitamin E, 393
prostate, 385
selenium, 394–395
terminal, ANH, 305–306
treatable, malnourished cancer patients, 256–257
vitamin D, 391
Cardiac cachexia
BNP, 221
characterization, 220
definition, 220
endotoxin, 221
ghrelin, 221
leptin, 221
metabolic disturbances, 220
starvation, 220
TNF-α, 220–221
Cardiac event prevention
AHA diet and lifestyle recommendations, 205
alcohol, 210
comorbidities, 204–205
description, 203–204
and dietary intake, 205–209
dietary patterns, 210–212
dyslipidemia, 205
heart-healthy diet, 213
hypertension, 205
lifestyle behavioral counseling, 205
nutrition counseling, 205
physical changes, 204
PROSPER study, 205
socio-economic change, 204
sodium, 210
stanols and sterols, 209
statin therapy, 205
Cardiac function
abnormalities, 216
oral administration, 226
and oxygen consumption, 222
and symptoms, 225
Cardiovascular disease (CVD)
B-complex vitamins, 387
CR, anti-aging effects, 316–317
diabetes-related comorbidities, 190, 192
dynapenic obesity, 104
and MetS, 188
omega-3 fatty acids, 395–397
PA/EX, effects, 359–360
potassium, 394
soy protein and soy isoflavones, 398–400
type 2 diabetes, 180, 316–317
vitamin C supplementation, 225
vitamin D, 130

Caregiving team, interdependent roles
consultant therapists
occupational therapy, 292
physical therapy, 292
SLP, 291
social worker, 291
dietitians and dietary managers, 290–291
family caregivers, 292
interdisciplinary team approach, 292
nursing, 291
physician/nurse practitioner/physician assistant, 290
Carotenoids in Age-Related Eye Disease Study (CAREDS), 65, 66
Cataract
cortical, 59
definition, 59
human eye, 58, 59
lens, 58, 59
lutein and zeaxanthin, 62–64
nuclear, 59
nutrient supplement effects
LINXIAN trial, 70
REACT, 70
vitamin C, 69
vitamin E, 69–70
omega-3 fatty acids, 63
PSC, 59
vitamin C, 60, 61
vitamin E, 60–63
Certified nursing assistants (CNAs), 289, 291, 295
Chasen-Taber, L., 64, 69
Chen, X., 261–268
Chernoff, R.S., 240
Chocolate, 134, 135, 379
Christen, W.G., 64, 71
Chronic kidney disease (CKD)
calcium-phosphorus, 267
diet and obesity, role
insulin resistance and risk, 263–264
protein intake and kidney function, 262–263
salt intake, hypertension and risk, 262
dietary recommendations, 268
nutritional status, role, 262
parathyroid hormone, 267
uremia, nutritional issues
malnutrition, pathophysiology, 265–267
obesity paradox, 265
vascular calcification, 267–268
Chung, M., 23, 24
Chylack, L.T. Jr., 61
Clark, B.C., 102
Clark, N., 195
Coates, P.M., 375–414
Coenzyme Q10 (CoQ10)
for anti-aging, 378
cardiovascular health, 406–407
neurological health, 407–408
Cognitive function
B vitamins, 127–130
cross-sectional studies, 126
epidemiological studies, 126
FFQ, 126
mediterranean diet, 136–137
Mini-Mental State Examination, 127
monounsaturated and polyunsaturated fatty acids, 135–136
number of domains, 126
nutrient intake, 126
polyphenols, 132–135
prospective studies, 126
RCTs, 126–127
score ranges, 127
vitamin D, 130–132
Conners' Continuous Performance Test-II (CPT-II), 328
Costello, R., 375–414
Cragg, G.M., 410
Cresci, G., 259
CR mimetics, 326, 329
CRONIES, 323–324, 328–329
Cumming, R.G., 63
CVD. *See* Cardiovascular disease (CVD)
Cytokines
in apoptosis, 219
induced cachexia, 247
inflammatory, 221, 246–247
mediated anorexia and weight loss, 246
pressure ulcers, 246–247

D

Daly, J.M., 257
D'Anci, K.E., 125–138
Dawson-Hughes, B., 273–281
de Koning, L., 205
Delcourt, C., 63, 64
Delmi, M., 239
Dementia
caregiving team, interdependent roles
consultant therapists, 291–292
dietitians and dietary managers, 290–291
family caregivers, 292
interdisciplinary team approach, 292
nursing, 291
physician/nurse practitioner/physician assistant, 290
mealtime difficulties, assessment
causes, 289–290
compromised meal behaviors, 293
health status, 293–295
neurologic/cognitive, 293
personal factors, 295–296
physical and social environment, 296–297
nutritional care, PWD
careful hand feeding, PEG feeding, 298
PEG feeding, risks/benefits, 297–298
Dental caries
artificial sweeteners, 84
characterized, 84
cheese consumption, 84
chewing sugar-free gum, 84

demineralization/remineralization process, 84
diet, 84
fluorides, 84
oral conditions, 82
saliva, 84
sugar intake, 84
Depression
and cognition, 363
and dementia, 180
DM, 191–192
GDS, 294
QOL, 194
symptoms, 326
weight loss in LTC, 295
Desneves, K.J., 241
DETERMINE checklist, 38, 39, 48
Devore, E.E., 133
Dherani, M., 61
Dhesi, J.K., 132
Diabetes Control and Complications Trial (DCCT) assay, 181–183, 189
Diabetes mellitus (DM)
acute illness, 186
ADA, 183
AGS, 183
balancing diet and medication, 185
blood glucose, 182
blood pressure reduction, 183
cardiovascular morbidity and mortality, 183
cognitive dysfunction, 192–193
comorbidities, 190
DCCT, 182–183
depression, 191–192
diagnosis, 181
dietary habits, 191
dietary intake, 193–194
enteral and parenteral nutrition, 186, 187
glycemic goals, 183
health consequences, 180
hospitalization, 186–187
imparting dietary information, 196
long-term care facilities, 188
macronutrient recommendations, 184–185
management of hyperglycemia, 183, 184
nutritional recommendations, 184
overweight and obesity, 185–186
quality of life, 194–196
self-management behaviors, 190–191
treatment, 181
type 1 diabetes, 181–182
type 2 diabetes, 182
UKPDS, 183
underweight and malnutrition, 186
Diabetes prevention program (DPP), 188, 196
Diabetes self-management education and training (DSME/T), 190, 192
Diamant, M., 184
Diastolic heart failure, 217, 218, 224
Diet
eating and healthful, 4
healthy and nutrient-dense, 5
low quality diets types, 12
multivitamins, 31
older adults, 6, 10
and related behaviors, 13
restrictive, 4
Dietary Approaches to Stop Hypertension (DASH) Sodium Study, 172, 206, 208, 210, 262
Dietary counseling, 91, 218, 257–258
Dietary fats
benefits *vs.* risks of eating fish, 207
omega-3 and omega-6 fats, 207
saturated and *trans*-fats, 206–207
Dietary fiber, 28, 90, 208, 336, 338, 340, 347
Dietary intake
and blood levels, nutrients and eye disease, 60–68
DM
and attitudes, 193
and self-care, ethnic/cultural issues, 193–194
and heart disease management
added sugars, 209
dairy products, 208
dietary fats, 206–207
fruits and vegetables, 206
whole grains and starches, 208
nutrition assessment, 44
Dietary patterns
OC, 88–89
preventive cardiology
caloric intakes, 211–212
low-carbohydrate diet, 210
randomized clinical trial, 210
weight loss, 210
Dietary reference intakes (DRIs), 23, 31, 224–226, 383–384, 389
Dietary Supplement and Nonprescription Drug Consumer Protection Act, 379
Dietary Supplement Health and Education Act (DSHEA), 379
Dietary supplements
bicarbonate supplements, 106
cardiovascular/heart heath condition-specific supplement, 379
combination and condition-specific products, 378
CoQ10, 378
definition, DSHEA, 379
food-based interventions, 29
glucosamine/chondroitin products, 379
guidelines for safe use
assessment, 409, 413
databases and other resources, 414
preventing interactions, 408–409
health claims
FDA website, 380
Nutrition Labeling and Education Act, 380
health concerns and nutrient, 32

Dietary supplements (*cont.*)
and herb–drug interactions, 410–412
hormones, 106
marketplace, 376
multivitamins, 378
non-nutrient supplements, effectiveness and safety
herbals and botanicals, 308–404
non-nutrient, non-botanical supplements, 405–408
nutrient and herbal, 28
nutrient-containing supplements, 377–378
nutrient supplements, effectiveness and safety
calcium and vitamin D combinations, 383–385
minerals, 393–395
omega-3 and-6 fatty acids, 395–398
vitamins, 381–393
omega-3 fatty acid, 106
protein supplements, 105–106
regulation, 379–380
types, 376–377
use, Older Americans, 377
Diet therapy
education distribution, 196–197
older adult weight-loss therapy, 174
weight management intervention, 172
DiMaria-Ghalili, R.A., 9, 35–48
Diuretic-induced hyponatremia, 224
DM. *See* Diabetes mellitus (DM)
Docosahexaenoic acid (DHA), 24, 29, 58, 86, 378, 386, 395
Dual-energy X-ray absorptiometry (DEXA), 103, 104
Dwyer, J.T., 375–414
Dynapenia
consequences
functional limitation and physical disability, 102
metabolic health, 103
mortality, 103
description, 102
obesity, 103–104, 106–107
prevalence, 102
prevention and treatment
resistance training, 104–105
whole-body vibration, 105
Dyslipidemia
added sugars, 209
dietary behaviors, 204
and hypertension, 205
low-density lipoprotein cholesterol levels, 205
MetS and T2DM, 360

E
Eat Better Move More, 372
Eating Inventory, 327
Ecological model
aging, 4
nutrition interventions, 8
and social support models, 7
Edentulism
and obesity, 90
tooth loss, 82–83
weight loss, 90
Edinburgh Feeding Evaluation in Dementia Scale (EdFED), 293
Eicosapentaenoic acid (EPA), 24, 29, 58, 67, 135, 386, 395
Electrolytes, 224, 227, 228, 230, 304
End-stage renal disease (ESRD), 262, 264
Enteral nutrition
ALS, 307
diabetes mellitus, 186–187
at the end of life, 291, 308–309
head and neck cancer patients, 257
immunonutrition, 259
in incurable cancer patients, 254–255, 306
medical treatment, 305, 310
nutritional counseling, 258
tube feedings, 240, 304
Esmarck, B., 105
Estimated average requirement (EAR), 24, 275
Evans, E.M., 354–372
Evidence-based programs
Administration on Aging (AoA), 368
National Council on Aging (NCOA), 368, 372
National Institute on Aging (NIA), 368
physical activity and nutrition programs, 368–371
SilverSneakers program, 372
Title IIID of the Older Americans Act (OAA), 368
Walk With Ease Program, 372
Evidence tables, 25–26
Exercise (EX)
advantages, 118
aerobic, 106, 170
basal muscle protein synthesis rates, 118
benefits
cancer, 361
cardiovascular disease, 359–360
cognition and depression, 363
dyslipidemia, 360
MetS, 360
mortality and QOL, 363–364
obesity, 358–359
osteoporosis, 361–363
physical functional capacity, 361–363
T2DM, 360
BMD, 171
capacity, 173
definition, 356
and diet, synergistic effect, 356–357
endurance exercise, 119
fast twitch/type II muscle fibers, 118
intracellular stress, 118
low-intensity activities, 119
motor unit denervation, 118
and nutrition, 120
for older adults, 357
physical activity, 172
prevention *vs.* management of disease, 357
resistance, 119, 170
specialist, 173
and weight loss therapy, 170, 173
Exercise and Physical Activity: Your Everyday Guide, 366

Eye disease
AMD (*see* Age-related macular degeneration (AMD))
AREDS, 385
cataract (*see* Cataract)
treatment guidelines, 72–74

F
Falls
balance activities, 365
magnesium intake recommendation, 347
malnutrition, 36, 154
proteins, 337
unintentional weight loss, 41
vitamin D supplementation, 277–278, 280, 281, 389–390
Fan, S.T., 256–257
Fat-free mass (FFM), 101, 103, 164, 165, 168–170, 323
Fatty acids
monounsaturated, 59, 135–136
n-3, 336
omega-3, 24, 58, 63, 66–67, 72, 86, 206–207, 336, 339–340, 378, 386, 395–397
omega-6, 378, 395–397
polyunsaturated, 59, 135–136, 222
triglyceride and ethyl esters, 29
Federal Food, Drug, and Cosmetic Act, 379
Feeding
assistance, PWD, 289
behavior, changes, 45
careful hand, 297–298
comfort feeding only, 304, 307
difficulties, 131
direct hand, 291, 298, 299
enteral, 240, 257
hand over hand, 298, 299
hand under hand, 298, 299
hypercaloric, 245, 247
non-oral, 304
PEG, 245, 297–298
recreational, 304, 307
resistive or aversive, 288, 293
self-feeding, 293, 297
tube, 187, 242, 245, 291, 304–307
Feldman, J.J., 13
Ferrannini, E., 184
Ferrell, 239
Ferrigno, L., 61, 63
Fitness
cardiorespiratory, 359–360, 363
centers, 372, 378
definition, WHO, 356
muscular, 362
physical, health-related, 356–357, 362
Flavanols, 134, 135
Florez, H., 195
Folic acid
B vitamins, 341–342
CVD, 387
deficiencies, 150, 226
folate, 29
homocysteine levels, 388
mortality, 386–387
risks of excess amounts, 387–388
Food assistance
food insecurity, 148
older adults, 155–156
Food insecurity
distribution
geographic variation, 153
individual and household characteristics, 151–152
middle and older adults, 152–153
health implications
diabetes, 153
malnutrition, 154–155
older adults, 154
poor physical and mental health status, 153
risk factors, 153
interventions, 155–156
linchpin of healthful living, 148
and malnutrition, 336
overnutrition and obesity, 151
in US
CFSM, 148, 149
communities, 149
FSS, 148
high food security, 148
households, 148–149
low food security, 148
LSRO, 148
marginal food security, 148
USDA, 148
very low food security, 148
WHO definition, 148
Food intake
and diets, 148
FFQ, 126
healthcare services, 6
interpersonal and individual factors, 5
neighborhood environment, 6
policy-related factors, 6
social factors, 5
Foods
bolus, swallowing, 92
carbohydrates, 84
carcinogenesis, 87
dietary patterns, 88–89
dry and sticky, 92
hard, 90
high-fat, 89
and hydration at end of life, 308
insecurity, 147–157
intakes of dairy, 85
lactic acid, 85
lutein/zeaxanthin, 73
and nutrients, 88, 338
physical characteristics, 84
plaque, 84
softer, 91
vitamin C, 73
vitamin E, 73

Food Safety Modernization Act, 380
Fractures. *See also* Osteoporosis
and bone mass, vitamin D
BMD, 278
hip fracture risk, 279
multiple-dose anti-fracture efficacy trial, 279
subject-level meta-analysis, 278–279
calcium intake requirements, 275, 346, 383–384, 389–390
femoral neck, 239, 244, 246
hip, 156, 169, 240, 273–275, 278, 337
vitamin D, 277–280, 344
Frailty
BMI, 169
bone fractures, 361
physical activity, 172
quality of life, 170–171
sarcopenia, 114, 168, 182
sarcopenic-obese, 168
unintentional weight loss, 41
Fruits
citrus, 134
polyphenol-rich foods, 136
randomized controlled trials, 133
total fruit, 134
and vegetables, 87, 132, 133, 137, 206
Fugh-Berman, A., 410
Functional capacity
factors influencing, 361–363
loss, older adults, 361–362
and osteoporosis, 362

G
Gale, C.R., 64
Gardner, Z., 410
Geriatric Depression Scale (GDS), 294
Giles, G.E., 125–138
Gilmore, L.A., 314–329
Ginkgo biloba extract (GBE), 133, 403–404
Ginkgo Evaluation of Memory (GEM) study, 404
Glomerular filtration rate (GFR), 263
Glucosamine/Chondroitin Arthritis Intervention Trial (GAIT), 405
Goldberg, A., 410
Golden, S.D., 9
Goodwin, J.S., 128
Gorse, 239
Grapes, 133, 138
Green tea, 134
Gritz, D.C., 69
Growth hormone (GH), 106, 114, 118, 165, 221, 324
Guralnik, J.M., 239

H
Haas, L.B., 195
Halfdanarson, T.R., 258
Halter, J.B., 195
Hankinson, S.E., 61, 62, 64, 69, 70
Hänsel, R., 411
Harris-Benedict equation, 241–242
Harris, T.B., 13
Hartgrink, H.H., 239
Health behavior change
and adherence, 13
and education, 8
inform and guide interventions, 7
theories and models, 7
Health claims
FDA website, 380
Nutrition Labeling and Education Act, 380
Health promotion
information technology, 12–13
interventions, 9
older adults, 9
Healthy Moves for Aging Well, 368
Heart failure
age-related changes, 216
age-specific nutritional issues, 227–228
caloric intake, fat and protein, 221–222
cardiac cachexia, 220–221
cardinal symptoms, 217
description, 216
device-specific nutritional therapies, 228
etiology, 216–217
medication effects, 227
metabolic syndrome, 219–220
nutrients (*see* Nutrient(s))
and obesity, 222–223
pathophysiology, 217
prognosis, 217–218
recommendations
caffeine, 230
fluid intake, 229
nutritional guidelines, 228, 229
sodium restriction, 228
well-balanced diet rich, 230
treatment
ACE inhibitors, 218
ARBs, 218
diuretics, 218
LVADs, 218–219
metoprolol and carvedilol, 218
nonpharmacological measures, 218
pharmacotherapy, 218, 219
spironolactone reduces mortality, 218
Heart failure with preserved ejection fraction (HFPEF), 217–218
Heart failure with reduced ejection fraction (HFREF), 217–218
Heart Outcomes Prevention Evaluation (HOPE) trial, 225–226, 392
Hellwig, J.P., 411
Hemodialysis, 265–267
Henderson, C.T., 240
Hendler, S., 410
Herbal Alternatives for Menopause Trial (HALT), 402

Herbals and botanicals
black cohosh *(Cimicifuga racemosa),* 401–402
Ginkgo biloba, 403–404
herb–drug interactions, 410–412
saw palmetto *(Serenoa repens),* 402–403
soy protein and soy isoflavones
CVD, 398–400
menopausal symptoms, 401
osteoporosis, 400
supplements and drugs, 409
Holley, C.L., 215–231
Hormones, 41, 106, 108, 114, 187, 321, 323, 361–362, 401
Hot flushes (Hot flashes), 399, 401
Houwing, R.H., 239
Humans
CR (*see* Calorie restriction (CR))
longevity, 316, 328–329
nonobese, RCT, 318
obese, 322–323
protein-calorie undernutrition, 237
vitamin D deficiency, 277
Hunger
CR, 327
food insecurity, 148
and malnutrition, 149
older adults, 150
U.S. Household Food Security Scale, 149
Hunt, C.D., 275
Hypertension
added sugars, 209
cardiovascular disease, 359–360
cardiovascular risk factors, 205
CHD, 259
CKD, 262
CoQ10, 407
dietary behaviors, 204
and dyslipidemias, 205
heart failure and obesity, 222
and hypercholesterolemia, 392
salt intake and CKD, 262
Hypoglycemia, DM
blood glucose-lowering agents, 189
DCCT, 189
drugs, 189
malnourished, 189
management of diabetes, 188
self-monitoring and dietary treatment, 189
unawareness and treatment, 189–190
Hypomagnesemia, 224

I
Immunonutrition, 259
Inman, 239
Instrumental activities of daily living (IADLs), 4, 44, 156, 190, 293, 389
Insulin-like growth factor-1 (IGF-1), 114–118, 317, 324
Intervention
emerging, 12–13
heart failure interventions and age, 227–228
inflammatory-mediated cachexia, 247
nutrition (*see* Nutrition interventions)
nutritional, 239–241
persons with diabetes, 186–188
weight management intervention, 172
Inzucchi, S.E., 184

J
Jacobs, D.R. Jr., 208
Jacques, P.F., 61, 62, 69
Jalal, D., 61
Janssen, I., 99–108
Jatoi, A., 253–259
Johnson, D., 10
Johnson, E., 275
Johnson, E.J., 57–74
Johnson, M.A., 354–372
Joshipura, K.J., 81–93

K
Kahn, R.L., 13
Kalmijn, S., 126
Kanarek, R.B., 125–138
Keller, H.H., 291
Key questions
components, 25
limitations, 31
nutrients, 29
systematic reviews, 23
vitamin D and calcium, 23
King, A.C., 3–14
Kirkman, S.M., 195
Klein, S., 168
Knekt, P., 63
Knight, H.M., 179–197
Krall, E.A., 85
Kraus, W.E., 203–213
Kristal, A., 8

L
LaRowe, T.L., 66
Lee, J.S., 154
Lee, S.K., 241
Left ventricular assist devices (LVADs), 218, 219, 228
Leigh, B., 241
Leske, M.C., 60–63, 69, 70
Levine, M., 410
Licensed Practical Nurses (LPNs), 291
Lichtenstein, A.H., 21–32
Lindquist, L.W., 91
Lipid-modified diet, 205
Locher, J.L., 147–157
Longevity
biomarkers, 321–322
CR, 322
DHEA-S, 324
in humans, 328–329

Long-term care (LTC). *See* Dementia
Lutein and zeaxanthin
AMD, 65–66
cataracts, 62–64
content of foods, 72, 73
dietary intakes, 386
Lyle, B.J., 64

M
Macready, A.L., 127
Macronutrients
dietary fiber, 340
omega-3 fatty acids, 339–340
protein, 337–338
Macular degeneration. *See* Age-related macular degeneration (AMD)
Malnutrition
adult, 46–47
ASPEN, 46
definition, 46
ESPEN, 46
and health, 154–155
and hunger, 149
inflammation, 46
older adults, 150
and underweight, 186
in uremia, 265–267
Manini, T.M., 102
Mares-Perlman, J.A., 60–66
McCann, R.M., 255
McCay, C.M., 315
McGeer, A.J., 254
McGuffin, M., 410
Mealtime difficulties, dementia
causes, PWD, 289–290
compromised meal behaviors, 293
health status
meal intake and bowel movement review, 294–295
psychosocial factors, 295
vital signs/lab work and weight patterns, review, 294
impact, 288
neurologic/cognitive, 293
personal factors
emotional factors, 295
functional performance, 296
physiological determinants of intake, 295
physical and social environment
dining ambience, 297
light level, noise level, and/or temperature, 296
recommendations, 296
staff stability and staff mix, 297
precipitators, 289
Measured resting energy expenditure (mREE), 241
Medical nutrition therapy (MNT), 12, 187
Mediterranean diet
AD, 137
and cognitive aging, 136
components, 137
food groups, 136
healthy eating index, 137
Mini-Mental State Examination, 137
monounsaturated fats and fish, 137
polyphenol, 136
vascular disease, 137
Mente, A., 205
Merchant, A.T., 86
Merkel, J., 375–414
Messier, V., 103
Meta-analysis
calcium balance, 280
omega-3 fatty acids, 66–67
RCTs, 382
subject-level, 279
systematic reviews, 27
vitamin D supplements, 391
Metabolic acidosis, 265–267, 280
Metabolic syndrome (MetS)
and CVD, 188
description, 188
DPP, 188
heart failure, 219–220
insulin resistance, 188
NCEP-ATP III, 188
T2DM and dyslipidemia, 360
type 2 diabetes, 188
Metabolism
calcium, 85, 344, 346
carbohydrate, 221, 227
energy, 323, 325, 342, 407
lipid, 227, 346, 356
muscle, 117, 120
protein, 114, 220–222, 346
MetS. *See* Metabolic syndrome (MetS)
Meyers, L.D., 411
Miller, M.D., 101
Milles, S., 410
Minerals
bone mineral density, 171
calcium, 346
heart failure, 225
magnesium, 346–347
potassium
CVD, 394
2010 Dietary Guidelines for Americans, 393
high risk nutrients, 347
pressure ulcers, 244–245
selenium
cancer, 394–395
excessive amounts, 395
and vitamins, 244–245
Mini-Mental State Examination scores (MMSE), 127, 132, 134, 135, 137, 293, 398
Minimum Data Set (MDS), 38, 292, 293
Mini-nutrition assessment-short form (MNA-SF), 39
Moayyeri, A., 274
Modification of Diet in Renal Diseases (MDRD) Study, 263
Moeller, S.M., 66

Mohan, M., 61
Mokshagundam, S.P.L., 179–197
Monounsaturated fatty acids (MUFA), 135–136, 187
Moolten, 239
Moreland, J.D., 102
Moss, J., 410
MTHFR genotype, 129–130
Multifactorial Assessment of Eating Disorder Symptoms (MAEDS), 327
Multivitamin/multimineral (MVM) supplements
  cancer, 382
  chronic disease prevention, 381
  cognition, 382
  CoQ10, 378
  dietary intakes, 383
  infection, 382
  mortality, 382
  nutrients in diet, 381
  products, 377
Muscle mass
  and IGF-1/Akt-1 signaling, 116
  and muscle strength, 99–108
  older adults, 114–117
  sarcopenia, 114, 115
  signaling hormones, 114, 115
  skeletal muscle, 114
  STARS/SRF signaling, 116–117
Muscle metabolism
  muscle mass, regulation (*see* Muscle mass)
  and nutrition, 117–118
  strength (*see* Strength and function, muscle)

N
Nadalin, G., 69, 70
Nass, R.M., 106
National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III), 188
National Council on Aging (NCOA), 368
National Health and Nutrition Examination Survey (NHANES), 262, 337–338, 376
National Health Interview Survey, 377
National Institute on Aging (NIA), 368
Nauck, M., 184
Need-Driven Dementia Compromised (NDB) Model, 290
Net acid excretion (NAE) values, 280–281
Newsome, D.A., 67, 71
Nixon, D.W., 254
Norris, J.R., 241
Nourmohammadi, I., 63
Nutrient(s)
  antioxidant, 60, 70, 72, 74
  bioavailability, 28
  bioequivalence, 29
  biological stores, 29
  and eye disease, 60–68
  heart failure
    carnitine, 226
    coenzyme Q_{10}, 226
    creatine phosphate, 226
    electrolytes, 224
    minerals, 225
    multinutrient therapy, 227
    propionyl L-carnitine, 226
    vitamins, 225–226
    water and sodium, 223–224
  and oral health, 81–93
  status, 28
Nutrient intake
  food groups, 338
  macronutrients
    dietary fiber, 340
    omega-3 fatty acids, 339–340
    protein, 337–338
  minerals
    calcium, 346
    magnesium, 346–347
    potassium, 347
  NHANES, 338
  vitamins
    B vitamins, 341–343
    vitamin A and carotenoids, 340–341
    vitamin D, 343–345
    vitamin E, 345
Nutrition
  assessment (*see* Nutrition assessment)
  heart failure
    caloric intake, fat and protein, 221–222
    cardiac cachexia, 220–221
    metabolic syndrome, 219–220
    and obesity, 222–223
  malnutrition, 36
  and muscle metabolism
    amino acids and BCAA, 117
    anabolic resistance, 117
    inflammation and oxidative stress, 118
    mTOR, 117
  nutritional status, 36
  osteoporosis, nutritional concerns (*see* Osteoporosis)
  overnutrition, 36
  screening (*see* Nutrition screening)
  systematic reviews, 21–32
Nutritional supplements, pressure ulcers
  amino acids, 243–244
  energy, 241–242
  mode of delivery, 245
  protein, 242–243
  vitamins and minerals, 244–245
Nutrition assessment
  anthropometrics, 40–41
  body composition, 41–42
  comorbid conditions, 45–46
  description, 40
  dietary intake, 44
  functional status, 44
  health professions, 47–48
  medications, 44, 45
  physical exam, 42–43
  psychosocial and economic factors, 44–45
  visceral proteins, 43

Nutrition interventions. *See also* Older adults
aging, 4
emerging intervention, 12–13
evaluation and assessment, 10–11
financial resources, 12
food assistance programs, 12
health-promoting information technology, 12–13
MNT, 12
obesity, 14
persons with diabetes
acute illness, 186
enteral and parenteral nutrition, 187
hospitalization, 186–187
long-term care, 188
racial and ethnic minorities, 11
in rural areas, 12
Nutrition Labeling and Education Act, 380
Nutrition screening
and assessment, 36, 37
definition, 36
DETERMINE checklist, 39
health professions, 47–48
MNA-SF, 39
programs, 39
regulations
community, 38
homecare, 38
hospital/acute care settings, 36
long-term care, 36, 38
primary care, 38
Nutrition support
in advanced, incurable cancer patients
acknowledging exceptional circumstances, 255–256
alternative palliative strategies, 255
enteral nutrition, 254–255
parenteral nutrition, 254
decision-making
families and surrogate decision maker, 309
legal, religious, and ethical precedents, 304–305
and treatment goals, 308
definitions, 304
at end of life
ANH, advanced illness, 305–308
enteral/parental nutrition and hydration, 308–309
food and hydration, 308
solid tumor cancer patients
head and neck cancer patients, 258
immunonutrition, 259
nasogastric *vs.* PEG, 257
nutritional counseling, 258
treatable cancers, 256–257

O
Obesity
adverse effects
arthritis, 167
cancer, 167
comorbid disease, 166
functional impairment and QOL, 168–169
metabolic abnormalities, 166–167
mortality, 166
pulmonary abnormalities, 167
urinary incontinence, 167
and diet, CKD
insulin resistance and risk, 263–264
protein intake and kidney function, 262–263
salt intake, hypertension and risk, 262
dynapenia
aerobic exercise, 106
caloric restriction, 107
consequences, 104
definition and prevalence, 103–104
and heart failure, 222–223
in older adults
aging, 164
beneficial effects, 169
body fat, 164
definition, 163
fat-free mass (FFM), 164
fat mass (FM), 164
NHANES, 164
and overnutrition, 151
and overweight, 165, 166, 185–186
paradox in uremia, 265
pharmacotherapy, 173
prevalence of obesity, 164
and undernutrition, 149
weight loss, 170–171, 173
weight management intervention, 163, 172–173
PA/EX, effects, 358–359
sarcopenia
aerobic exercise, 106
caloric restriction, 107
consequences, 103
definition and prevalence, 103
Office of Dietary Supplements (ODS), 410–412, 414
Older adults
DM (*see* Diabetes mellitus (DM))
exercise, 118–120
food assistance, 155–156
with heart failure (*see* Heart failure)
high-risk nutrients (*see* Nutrient intake)
hypoglycemia, 188–190
muscle metabolism, 114–118
nutrition interventions
community-based and institutional, 9
components and delivery channels, 7–8
ecological perspective, 8
food intake, 5–6
framework, 6–7
interpersonal and intrapersonal, 8–9
multilevel and policy, 9–10
nutritional status, 4–5
planning and design, 6
obesity (*see* Obesity)
oral health (*see* Oral health)
PA/EX (*see* Exercise (EX); Physical activity (PA))
systematic reviews, 31–32

weight-loss therapy
bariatric surgery, 175
behavior therapy, 174
diet therapy, 174
exercise therapy, 174
initial assessment, 174
Ollberding, N., 8
Omega-3 fatty acids
AMD
AREDS, 67
Beaver Dam Eye Study, 67
Blue Mountain Eye Study, 67
Dietary Ancillary Study of the Eye Disease Case-Control Study, 67
and late ARM, 67, 68
meta-analysis, 66
cancers, 397
cataracts, 63
cognition, 397–398
CVD, 395–397
fish oils, 72, 74
Omega-6 fatty acids, 395–398
Oral cancer (OC)
anti-oxidants and micronutrients, 87–88
dietary patterns, 88–89
disparities, 83
eating and swallowing, 92
fiber and whole grains, 88
fruits and vegetables, 87
and pharyngeal, 83
problem management, 92
squamous cell carcinoma, 83
tobacco and alcohol use, 86
Oral health
dental caries, 81, 82
nutritional status
chronic periodontitis, 85–86
dental caries, 84
dentate, blood, 90–91
OC (*see* Oral cancer (OC))
plaque and calculus formation, 83–84
tooth loss, 89–90
tooth replacement strategies, 91
xerostomia, 92
periodontal disease, 82
periodontitis, 81
quality of life, 81
root caries, 82
tooth loss, 82–83
Osteoarthritis (OA), 167, 405–406
Osteoporosis
acid–base balance, diet, 280–281
BMD assessments, 274
calcium
intake requirements, 275
physiology, 274–275
recommendations, 276
safety, 276
supplements, 383–384
definition, 273
heritability of bone loss, 274
and physical functional capacity, 361–363
vitamin D
bone mass and fractures, 278–279
muscle performance, balance, and falls, 277–278
physiology and interactions, aging process, 277
recommendations, 280
supplements, 383–384
Otten, J.J., 411

P

Paddon-Jones, D., 113–120
Palacios, C., 81–93
Palliative treatment, 308
Parathyroid hormone (PTH), 267, 274
Parenteral nutrition
in advanced, incurable cancer patients, 254
diabetes mellitus, 186
palliative effects, 255–256
treatable cancers, 256–257
Parkinson's disease, 308, 344, 407–408
Patel, Krishna A., 253–259
Peneau, S., 133
Pennings, B., 106
Percutaneous endoscopic gastrostomy (PEG)
careful hand feeding, 298
placement, 307–308
pressure ulcer, 245
risks/benefits, 297–298
Periodontal disease, 82, 85, 86, 91–93
Periodontitis
bacterial plaque, 85
BMI, 86
dairy foods, 85
diet and nutrients, 85
genetic risk factors, 85
immune-modulating nutrients, 86
NHANES III, 85, 86
and obesity, 86
omega 3 fatty acids, 86
PPD, 86
and tooth loss, 85
VDR polymorphisms, 85
vitamin C, 86
vitamin D, 85, 86
waist circumference (WC), 86
Persons with dementia (PWD). *See also* Dementia
careful hand feeding, PEG feeding, 298
mealtime difficulty, 289–290
PEG feeding, risks/benefits, 297–298
Pharmacotherapy
left ventricular systolic dysfunction, 219
obesity in older adults, 173
osteoporosis, 276
systolic heart failure, 218
Physical activity (PA)
benefits
cancer, 361
cardiovascular disease, 359–360

Physical activity (PA) (*cont.*)
cognition and depression, 363
dyslipidemia, 360
MetS, 360
mortality and QOL, 363–364
obesity, 358–359
osteoporosis, 361–363
physical functional capacity, 361–363
T2DM, 360
CR, 324–326
definition, 356
environmental barriers, 367
evidence-based programs, 368, 372
Exercise is Medicine, 367
for older adults, 357
PAR-Q, 367
2008 Physical Activity Guidelines for Americans, 364–365
prevalence, 364
prevention *vs.* management of disease, 357
self-esteem and self-efficacy, 368
2008 Physical Activity Guidelines for Americans
aerobic exercise, 365
balance exercises, 365
DHHS PA guidelines, 364
muscle-strengthening activities, 365
warm-up, cool-down, and flexibility exercises, 365
Physical activity readiness questionnaire (PAR-Q), 367
Physical function
dynapenia, 102
functional capacity, 361–363
and quality of life, 170–171
sarcopenia, 101
Pinchcofsky-Devin, G.D., 239
Plaque and calculus formation, 83–84
Podrabsky, M., 205
Polyphenols
berries, 133
chocolate, 134
description, 132
executive function, 135
flavanoid intake, 134
fruits and vegetables, 132, 133
grapes, 133
green tea, 134
language and verbal abilities, 134–135
n–3 PUFA, 138
plant food consumption and performance, 132
polyphenol-rich foods, 133
questionable dementia, 132
total polyphenol intake, 134–135
Polyunsaturated fatty acids (PUFA), 135–138, 222
Posterior subcapsular cataract (PSC), 59, 60, 62, 63, 70
Potassium bicarbonate, 281
Preoperative cancer patients, 257
Pressure ulcers
cachexia, 245
cytokines, 246–247
epidemiological associations, 238, 239
healing, trials, 240–241
inflammatory-mediated cachexia, interventions, 247
nutritional supplements
amino acids, 243–244
energy, 241–242
mode of delivery, 245
protein, 242–243
vitamins and minerals, 244–245
prevention
enteral tube feedings, 240
nutritional interventions, 238, 239
oral nutrition supplements, effects, 238–240
serum proteins, measures, 245–246
and undernutrition, 237–238
weight loss and undernutrition, 245
Pressure Ulcer Scale for Healing (PUSH) score, 242–244
Prostate cancer, 341, 345–346, 382, 385, 393–394, 403
Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, 388
Prostate-specific antigen (PSA), 385
Protein
high-risk nutrients, 337–338
intake
with CKD, 263
and nutritional status, uremia, 265–266
with renal function, 262–263
metabolism
exercise, 18–20
nutrition (*see* Nutrition)
PLP, 341
Pruitt, J.D., 203–213
Przybelski, R., 132
Public Health Security and Bioterrorism Preparedness and Response Act of 2002, 379

Q

Quality of life (QOL)
DM
and diabetes diet, 194–195
and weight loss, 195–196
and functional impairment, 168–169
malnutrition, 36
and mood, 327–328
and mortality, 363–364
and patient definitions, 193
and physical function, 170–171
physical functioning and vitality, 328

R

Rautiainen, S., 69
Ravasco, P., 258
Ravussin, E., 314–329
Recommended dietary allowance (RDA), 275, 337
Redman, L.M., 314–329
Registered Dietitian (RD), 290–291
Remifemin, 402
Remig, V., 205
Renal disease, 262–263
Resistance exercise

and aerobic exercise, 360, 363
blood flow, 105
muscle mass and strength in older populations, 119
muscle strengthening activities, 104–105
physical activity, 104
protein supplements, 105
treatment strategy, sarcopenia and dynapenia, 108
Resting energy expenditure (REE), 241, 316, 358
Resting metabolic rate (RMR), 164, 241, 319, 323–324, 337
Retina
AMD, 58
human eye, 59
and lens, 58
lutein and zeaxanthin, 65
oxidative stress, 59
photoreceptors, 60
RPE, 59
Rey Auditory and Verbal Learning Test (RAVLT), 328
Rich, M.W., 215–231
Ritchie, C.S., 303–310
Robertson, J.M., 69, 70
Root caries, 82, 84
Rorvik, D., 410
Rosenberg, I., 99
Rose, S.B., 287–299
Rouhiainen, P., 63
Rowe, J.W., 13
Russell, A.P., 113–120

S
Sahyoun, N.R., 8
Sanders, T.A.B., 65, 307
Sarcopenia
adults at risk, 113
age-related skeletal muscle loss, 99, 100
body composition, 170
combat, 114
consequences
functional limitation and physical disability, 101
metabolic health, 102
mortality, 101
definition and prevalence, 100–101, 114
FFM, 168
and frailty, 182
muscle size, 100
obesity, 103, 106–107
physical frailty, 114
prevalence, 168
prevention and treatment
resistance training, 104–105
strategies, 114
whole-body vibration, 105
progression, 114
in uremia, 266
Schulz V, 411
Schweitzer, D., 66
Sebring, N.G., 91
Seddon, J.M., 65, 66, 71
Selenium and Vitamin E Cancer Prevention Trial (SELECT), 393
Self-monitoring of blood glucose levels (SMBG), 189, 190
Selman, C., 316
Senechal, M., 104, 107
Shah, K., 163–175
Shea, B., 275
Sheats, J.L., 3–14
Siener, C., 168
SilverSneakers program, 372
Silver tsunami, 4
Simon, J.A., 61
Sinacore, D.R., 168
Skeletal muscle (SM)
aging human, 116
molecular signaling pathways, 115
muscle protein synthesis and muscle protein, 114
resistance training + protein supplements, 105
sarcopenia, 100–102
size and strength, 104
Snellen, E.L., 66
Sodium
DASH-sodium trial, 210, 262
food preparation, 12
lowering blood pressure, 210
restriction, 223–224
and water, 223–224
Speech language pathologist (SLP), 291
Stanford Chronic Disease Self-Management Program, 372
Stanols, 209
Starches, 89, 208
Stein, M.S., 132
Sterols, 209, 403
Stetson, B., 179–197
Strength and function, muscle
and aerobic, 364
and functional capacity, 114
and muscle mass (*see* Muscle mass)
vitamin D supplementation, 390
Sugars
and calories content, 12
and carbohydrates, 83, 84
classification, 209
controlling, sugar consumption, 209
empty calories, 336
food and beverages, 209
glucosamine/chondroitin, 405
Sunshine vitamin, 130
Symons, T.B., 105
Systematic reviews
analytic framework, 22–24
extract and summarize data, 25–26
field of medicine, 22
field of nutrition, 22
hypovitaminosis D, 131
impartial and complete assessment, 22
inclusion/exclusion criteria, 24
internet-mediated interventions, 196
literature selection, 25, 26

Systematic reviews (*cont.*)
meta-analysis, 27
nutrition
availability, biological stores, 29
baseline exposure, 27–28
bioavailability, 28
bioequivalence, 29
DHA, 29
dose–response relationships, 30
EPA, 29
food-based interventions, 29
nutrient status, 28
older adults, 31–32
research (key) questions, 23
review team, 22
RTCs, 127, 381, 382, 385, 389
search terms, 25
Systolic heart failure, 217, 218, 222, 229

T
Tan, A.G., 61
Tan, J.S.L., 66
Tavani, A., 61, 62, 69
Taylor, H.R., 71
Taylor, T.V., 241
Tea
black/oolong, 134
green, 134
sweeten coffee and breakfast cereal, 209
Technology-based interventions, 12–13
Teikari, J.M., 71
Terminal illness
cancer, 305–306
dementia
alternative approaches, 307
costs and benefits, 306–307
terminal stages, neurological diseases, 307–308
ter Riet, G., 241
Theory
free radical theory of aging, 316
health behavior change, 7
intervention methods and practical strategies, 7
planned behavior, 7
rate of living theory, 316, 323
social cognitive theory, 7
Thiamine, 225, 227
Thomas, D.R., 237–248
Tooth loss
health surveys in US, 82
non-Hispanic black and white adults, 82
oral health
body weight status, 90
nutritional status, 89–90
public health problems, 83
Tooth replacement strategies, 91
Total daily energy expenditure (TDEE), 325
Trumbore, L.S., 239
Tucker, K.L., 128, 335–348
Tyler, V.E., 411
Type 1 diabetes, 181–182, 185, 189
Type 2 diabetes mellitus (T2DM)
calorie restriction, 316–317
cardiovascular disease, 316–317
characterization, 182
dynapenic obesity, 104
insulin resistance, 316–317
mechanism of insulin resistance, 182
metabolic syndrome, 188
overweight and obesity, 185

U
Ubiquinone. *See* Coenzyme Q10 (CoQ10)
Undernutrition
biochemical and anthropometric variables, 238
categories, 245
hunger, 150
malnutrition and health, 154–155
and obesity, 149
older adults, 150–151
and overnutrition, 156
and pressure ulcers, 245
protein-calorie undernutrition, 231
serum albumin, 242
and weight loss, 245
Unintentional weight loss
AD, 45
adverse effects, 41
comorbid conditions, 45–46
intentional *vs.,* 41
and malnutrition, 36, 44, 305
and nutritional status, 36
pressure ulcers, 238
undernutrition, 150–151
United Kingdom Prospective Diabetes Study (UKPDS), 183
Uremia
malnutrition, pathophysiology
inflammation and nutritional status, 267
metabolic acidosis and nutritional status, 266–267
protein intake and nutritional status, 265–266
obesity paradox, 265
sarcopenia, 265
US Department of Health and Human Services (DHHS), 364

V
Vader, J.M., 215–231
Valero, M.P., 61
van Anholt, R.D., 241
Van Belle, T.L., 182
Villareal, D.T., 163–175
Vision loss
AMD (*see* Age-related macular degeneration (AMD))
cataract (*see* Cataract)
lens implantation, 57
Visser, M., 102
Visual Analogue Scales (VAS), 327

Vitale, S., 61, 63, 69
Vitamin A and carotenoids, 340–341
Vitamin C
  AMD, 64, 65
  cataracts
    antioxidant status, 60, 61
    epidemiologic studies, 60, 61
    NHANES II, 60
    plasma ascorbic acid concentrations and prevalence, 60
  content of foods, 72, 73
  fruits and vegetables, 87
  recommended daily allowance (RDA), 244
Vitamin D
  administration, 131
  age-related diseases, 130
  aging population, 343–345
  Alzheimer's disease, 131
  antioxidant and anti-inflammatory properties, 131
  bioavailability, 130
  bone health, 389–391
  building and maintaining strong bones, 130
  and calcium
    BMD, 384
    fractures, 384
    homeostasis, 226
    mortality and outcomes, 384–385
    osteoporosis, 383–384
  cancer, 391
  in children, 130
  chronic diseases, 391–392
  cognition and dementia, 391
  dietary supplements, 130
  intranasal insulin, 132
  low serum levels, 131
  MCI, 131
  and mental functioning, 132
  nervous system, 130, 131
  neurotransmitters, 131
  neurotrophic factors, 131
  oral administration, 132
  osteoporosis
    bone mass and fractures, 278–279
    muscle performance/balance/falls, 277–278
    physiology and interactions, aging process, 277
    recommendations, 280
  RCT, 132
  serum level of 25(OH)D, 130, 131
  type 1 diabetes, 181–182
  type 2 diabetes, 182
  VDR, 130–131
Vitamin D receptor (VDR), 85, 130, 131, 275, 277
Vitamin E
  aging population, 345
  AMD, 64, 65
  anti-oxidant properties, 225
  cancer prevention, 393
  cardiovascular health, 392–393
  cataracts
    epidemiologic studies, 60, 62
    high and low vitamin E intake, 61–62
    lower prevalence, 60–61
    plasma vitamin E, 62, 63
  content of foods, 72, 73
  fruits and vegetables, 87
Vitamins
  B-complex vitamins
    cognition, 388–389
    CVD, 387
    mortality, 386–387
    risks of excess amounts, 387–388
  combinations
    eye health, 385–386
    MVMs, 381–383
    prostate cancer, 385
  folic acid, 226
  high-dose niacin, 226
  homocysteine, 226
  HOPE-TOO, 225–226
  low beta-carotene intake, 226
  vitamin A and carotenoids, 340–341
  vitamin B_6, 226, 341–342
  vitamin B_{12}, 226, 342–343
  vitamin B_1 (thiamine) deficiency, 225
  vitamin C supplementation, 225
  vitamin D
    aging population, 343–345
    bone health, 389–391
    cancer, 391
    cognition and dementia, 391
    other chronic diseases, 391–392
  vitamin E
    aging population, 345
    cancer prevention, 393
    cardiovascular health, 392–393
Vogiatzoglou, A., 128
Vu, H.T.V., 64

W
Waist circumference (WC), 11, 86, 165–167, 188, 208
Walford, Dr.R., 318
Walk With Ease Program, 372
Weight loss
  aerobic exercise, 106
  anorexia/cachexia syndrome, 245
  anthropometrics, 40–41
  caloric restriction, 107
  CMS, 38
  comorbid conditions, 45, 46
  and cytokine-mediated anorexia, 246
  definition, MDS, 292
  geriatric patients, 38, 44
  health status, 293–294
  heart failure, 221
  intentional *vs.* unintentional, 41
  measurement, 42
  MNA-SF, 39
  obesity
    BMD, 171
    body composition, 170
    medical complications, 170

Weight loss (*cont.*)
mortality, 171
physical function and QOL, 170–171
physiological determinants of intake, 295
and QoL in older adults with diabetes, 195–196
surgery, 173
unintentional (*see* Unintentional weight loss)
Weight management intervention
behavior modification, 172–173
diet therapy, 172
physical activity, 172
Western Ontario and McMaster Universities Arthritis Index (WOMAC), 405
West, S., 65
White, J.D., 410
Whole-body vibration apparatus, 105
Whole grains
dietary fiber, 340
and starches, 208
Williamson, D.A., 327
Winter, S.J., 3–14
Wolff's law, 362
Women's Health Initiative (WHI), 276
Women's Isoflavone Soy Health trial (WISH), 399
Wound healing, pressure ulcers, 240–241

X
Xerostomia, 89, 92, 93

Y
Yamada, Y., 316
Yukawa, M., 35–48, 303–310

Z
Zinc
AMD, 67–68
eye health, 385
supplementation, 72
urinary excretion, 225