Nutrition and Health
Series Editors: Adrianne Bendich · Connie W. Bales

Ted Wilson
Norman J. Temple
George A. Bray *Editors*

Nutrition Guide for Physicians and Related Healthcare Professions

Third Edition

Humana Press

Nutrition and Health

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

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Ted Wilson • Norman J. Temple • George A. Bray
Editors

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Editors
Ted Wilson
Department of Biology
Winona State University
Winona, MN, USA

George A. Bray
Pennington Biomedical Research Center
Baton Rouge, LA, USA

Norman J. Temple
Athabasca University Centre for Science
Athabasca, AB, Canada

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To my Dad, my boy Jack, brown trout, and the Big Horn River in Montana

Ted Wilson

To Evie, my adorable granddaughter

Norman Temple

To my wife, Mitzi, who has been a loving companion for over 40 years.

George Bray

Preface

It has often been pointed out that there is a near absence of nutrition education during medical school [1]. If this deficiency is corrected during postgraduate medical training, it often owes more to accident than design, or to the personal interests of individual physicians. As a result most physicians have gaping holes in their knowledge of nutrition [2, 3]. This book is intended to help correct this deficiency.

A great many advances in our understanding of nutrition took place during the twentieth century. In the first half of the century the focus was largely on vitamins and minerals. Since the 1970s there has been a flood of research studies on the role of diet in such chronic diseases as heart disease and cancer. Today, we have a vastly greater understanding of the role of diet in causing various chronic diseases of lifestyle. This evidence convincingly demonstrates that nutrition serves as an essential weapon for physicians in the battle against disease and for the enhancement of human health. We know, for example, that the risk of developing cancer, heart disease, obesity, and type 2 diabetes is affected by such foods as whole grain cereals, fruits, vegetables, the kinds of meats that are eaten, and the beverages consumed.

We can point to a great many examples of how dietary change can have a profound effect on health, especially for the risk of chronic diseases. Here is one example. Poland went through a severe economic and political crisis during the 1980s and into the 1990s. One of the results of this was a sharp decrease in the availability of meat and other foods of animal origin. At the same time there was an increase in consumption of fruits and vegetables and a decrease in smoking. This was followed by a 40% drop in mortality from coronary disease during the period 1990–2002 [4]. Nevertheless, there are still many gaps in our knowledge in the area of nutrition and health. For example, we cannot properly explain why taking a vitamin supplement pill seldom delivers the expected health benefits.

To paraphrase Churchill, advances in the field of nutrition science in recent years represent "not the beginning of the end but, perhaps, the end of the beginning." In the opinion of the editors, we are ready to help physicians and other healthcare professionals move their patients from the hors d'oeuvres to the main course.

Cultural change at a global, national, and regional level means that our nutrition habits and our interpretation of them will change as time marches on. As George Bernard Shaw said: "Everything I eat has been proved by some doctor or other to be a deadly poison, and everything I don't eat has been proved to be indispensable for life. But I go marching on." His comments are a reflection of the continued confusion in the public and among health professionals about what to eat and how much to eat. A simple walk through the self-help section of a book store will confirm the existence of many differing opinions of what "preventative nutrition" is all about, some verging on quackery and others built upon solid facts. Physicians and other healthcare professionals need the best possible interpretation of nutrition so that they are empowered to provide accurate advice to their clients.

In the words of Confucius: "The essence of knowledge is that, having acquired it, one must apply it." But, ironically, despite overwhelming evidence that nutrition has such enormous potential to improve human well-being – at modest cost – there is still a chasm between nutrition knowledge and its full exploitation for human betterment. There is also an important chasm between evaluating the

strength of the supporting science and understanding its true meaning. Once the true meaning of nutrition is understood, the next hurdle is to bring dietary change to the public and the healthcare professionals who provide healthcare to the public.

As gatekeepers to the nutritional health of their patients, it is important that healthcare professionals have access to up-to-date nutrition resources – such as this handbook – as well as the nutrition expertise of registered dietitians. *Nutrition Guide for Physicians and Related Healthcare Professionals* endeavors to address the needs of those who would most benefit from up-to-date information on recent advances in the field of nutrition. Accordingly, our book contains chapters by experts in a diverse range of nutritional areas. Our aim is to present a succinct overview of recent thinking and discoveries that have the greatest capacity to aid physicians and other healthcare professionals in improving the nutritional health of their clients.

The structure of the book is as follows:

- After the Introduction (Part 1) the following seven chapters (Part 2) address the nutrient requirements and special nutrition-related issues for people across all stages of the lifespan – from pregnancy and infancy through the adolescent years to the older adult years.
- Chapters 9, 10, 11, 12, 13 and 14 (Part 3) summarize the role of nutrition in the prevention and management of chronic conditions frequently seen in clinical practice, including obesity, diabetes, bone disorders, coronary heart disease, hypertension, and cancer.
- This is followed by Chapters 15, 16, 17 and 18 (Part 4) that describe different dietary patterns (the Mediterranean diet, the DASH diet, the vegetarian diet, and the ketogenic diet).
- Chapters 19, 20, 21, 22, 23, 24, 25 and 26 (Part 5) describe nutrition challenges specific to surgery and several different acute diseases and disorders (gastrointestinal disorders, food allergy and intolerance, diseases of the liver and pancreas, kidney disease, eating disorders, bariatric surgery, sarcopenia, and drug interactions with food).
- After this comes Chapters 27, 28, 29, 30, 31, 32, 33, 34, 35 and 36 (Part 6) which look at different aspects of the diet (coffee, tea, dietary fat, dietary sugars, energy drinks, alcohol, dietary fiber, vitamins, minerals, and the gut microbiome).
- Chapters 37, 38, 39, 40 and 41 (Part 7) examine a range of factors that influence dietary health decisions (creating nutritional behavior change, methods for assessing nutritional status, Dietary Reference Intakes, an overview of the diet and food guides, food labels, and sources of nutrients).
- Chapters 42 and 43 (Part 8) look at dietary supplements (including the problem of dishonest marketing) and false and misleading information in the area of nutrition.
- Chapter 44 (Part 9) shares final thoughts about why clinical nutrition has been, is, and will continue to be ever evolving.

Some readers may disagree with particular opinions presented by the authors, but in nutrition differences of opinion are often unavoidable because nutrition is an ever-changing science that lives and breathes debate and controversy. Readers are also reminded that nutrition is a fast evolving science. Many ideas regarding nutrition that are widely accepted today may be discredited in coming years. The following two quotes illustrate our changing understanding of what constitutes nutritional and medical wisdom.

The role of nutrition for creating optimal health has remained well known for millennia. An ancient Chinese proverb says: “He that takes medicine and neglects diet, wastes the skills of the physician” and the Greek physician Hippocrates noted: “Let food be thy medicine, and let medicine be thy food”. If we had the wisdom to know “what” to eat.

It was not so long ago that vegetarians were seen as annoyingly esoteric. Here is what George Orwell had to say on this in *The Road to Wigan Pier*, written in 1936:

> I have here a prospectus [from a socialist summer school] which… asks me to say 'whether my diet is ordinary or vegetarian'. They take it for granted, you see, that it is necessary to ask this question. This kind of thing is by itself sufficient to alienate plenty of decent people. And their instinct is perfectly sound, for the food-crank is by definition a person willing to cut himself off from human society in hopes of adding five years on to the life of his carcass; this is, a person out of touch with the common humanity.

Drummond and Wilbraham published a seminal book entitled *The Englishman's Food* in 1939. Jack Drummond was a major nutrition authority in the 1920s and 1930s. It would be foolhardy to believe that we can be any more accurate today in our predictions than they were over 70 years ago.

> So much precise research has been done in the laboratory and so many precise surveys have been made that we know all we need to know about the food requirements of the people….The position is perfectly clear-cut [with respect to Britain]. The role of nutrition for creating optimal health has remained well known for millennia. An ancient Chinese proverb says: "He that takes medicine and neglects diet, wastes the skills of the physician" and the Greek physician Hippocrates noted: "Let food be thy medicine, and let medicine be thy food". If we had the wisdom to know "what" to eat.

Winona, MN, USA — Ted Wilson
Athabasca, AB, Canada — Norman J. Temple
Baton Rouge, LA, USA — George A. Bray

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Series Editor Pages

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) comprehensive tables and figures, (6) identification of paradigm shifts and the consequences, (7) virtually no overlap of information between chapters, but targeted, inter-chapter 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 and 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.

As we are all aware, 2020 and 2021 have been the years of COVID**.** For all of us.

It has taken much greater effort to do everything that we could normally accomplish in the required time. We have often failed to meet anything but first, family-related priority deadlines and have not accepted any requests for book chapters, etc. *Nutrition Guide for Physicians and Related Healthcare Professionals, Third Edition*, edited by Ted Wilson, Norman J. Temple, and George A. Bray is not only a very welcome addition to the Nutrition and Health Series**,** but it is simply extraordinary that the editors were able to enlist over 100 authors to contribute the new, updated and excellent 44 chapters for this highly anticipated third edition during these two COVID years. Moreover, many of the most COVID-relevant chapters include addenda, and in total, more than 50 COVID-specific references have been added to the 1000+ references in this valuable text.

The present volume represents a critical updating of the chapters and topics that were so well received when the first edition was published in 2010 and the second edition in 2010. This timely volume also includes current topics that have moved to the forefront of clinical nutrition importance including, where relevant, the findings from peer-reviewed journals concerning COVID and nutrition. This volume will remain an important resource for physicians in many clinical fields who see patients of all ages, nutritionists and dietitians, research and public health scientists, and related health professionals who interact with clients, patients, and/or family members. This volume provides timely objective, relevant information for professors and lecturers, advanced undergraduates and graduates, researchers and clinical investigators who require extensive, up-to-date literature reviews, instructive

tables and figures, and excellent references on all aspects of the role of nutrition in human health and disease. This volume is especially relevant as the number of research papers and meta-analyses in the clinical nutrition arena increases every year and clients and patients are very much interested in dietary components for disease prevention. Nutrition research is presented to the lay public daily on numerous websites and podcasts, and the COVID pandemic has heightened the awareness of the public to the critical link of obesity and the adverse effects of COVID infection, as but one example. Certainly, the obesity epidemic has been associated with significantly increased infection morbidity and mortality in all age groups and racial and ethnic groups as well. The major obesity comorbidities, such as the metabolic syndrome, Type 2 diabetes, hypertension, and hyperlipidemia, often seen in seniors and even in young children, clearly further increase COVID infection risks. The editors have made great efforts to provide health professionals with the most up-to-date and comprehensive volume that highlights the key references and discussions concerning COVID and nutrition that were available. As many of the chapters had been completed before the most recent research papers were published, the new information related to COVID has been added, with references, at the end of the relevant chapters.

The editors have combined their broad backgrounds in research as well as clinical practice to help the reader better understand the relevant science without the details of complex discussions of in vitro and laboratory animal studies. **Ted Wilson, Ph.D.,** is Professor of Biology at Winona State University in Winona, Minnesota. His research examines how diet affects human nutritional physiology and whether food/dietary supplement health claims can be supported by measurable physiological changes. He has studied many foods, dietary supplements, and disease conditions including pistachios, low-carbohydrate diets, walnuts, cranberries, cranberry juice, apple juice, grape juice, wine, resveratrol, creatine phosphate, soy phytoestrogens, eggplants, coffee, tea, energy drinks, heart failure prognosis, diabetes, and obesity. Diet-induced changes have included physiological evaluations of plasma lipid profile, antioxidants, vasodilation, nitric oxide, platelet aggregation, and glycemic and insulinemic responses using in vivo and in vitro models. He also enjoys teaching courses in Nutrition, Physiology, Cardiovascular Physiology, Cell Signal Transduction, and Cell Biology. **Norman J. Temple, Ph.D.,** is Professor of Nutrition at Athabasca University in Alberta, Canada. He has published 95 papers, mainly in the area of nutrition in relation to health. He has also published 14 books. Together with Denis Burkitt he coedited *Western Diseases: Their Dietary Prevention and Reversibility* (1994). This continued and extended Burkitt's pioneering work on the role of dietary fiber in chronic diseases of lifestyle. Since 2001, he has coedited six volumes in the Nutrition and Health Series including *Nutritional Health: Strategies for Disease Prevention* edited by Ted Wilson and Norman J. Temple; *Beverage Impacts on Health and Nutrition* edited by Ted Wilson and Norman J. Temple; *Nutritional Health: Strategies for Disease Prevention, Second Edition*, edited by Norman J. Temple, Ted Wilson, and David R. Jacobs; *Nutrition Guide for Physicians* edited by Ted Wilson, Norman J. Temple, George A. Bray, and Marie Boyle Struble and published in 2010; *Nutritional Health: Strategies for Disease Prevention, Third Edition*, edited by Norman J. Temple, Ted Wilson, and David R. Jacobs and published in 2012; and *Beverage Impacts on Health and Nutrition, Second Edition*, edited by Ted Wilson and Norman J. Temple. He conducts collaborative research in Cape Town on the role of the changing diet in South Africa on the pattern of diseases in that country, such as obesity, diabetes, and heart disease. **George A. Bray, M.D., M.A.C.P., M.A.C.E.,** is Boyd Professor Emeritus at the Pennington Biomedical Research Center of Louisiana State University in Baton Rouge, Louisiana, and Professor of Medicine Emeritus at the Louisiana State University Medical Center in New Orleans. After graduating from Brown University summa cum laude, he entered Harvard Medical School graduating magna cum laude. His postdoctoral training included an internship at the Johns Hopkins Hospital, Baltimore, MD, a fellowship at the NIH, residency at the University of Rochester, and a fellowship at the National Institute for Medical Research in London and at the Tufts-New England Medical Center in Boston. He served as Director of the Clinical Research Center at the

Harbor UCLA Medical Center in Torrance, CA. He organized the First Fogarty International Center Conference on Obesity in 1973 and the Second International Congress on Obesity in Washington DC in 1977. In 1989 he became the first Executive Director of the Pennington Biomedical Research Center in Baton Rouge, a post he held until 1999. He is a Master of the American College of Physicians, Master of the American College of Endocrinology, and Master of the American Board of Obesity Medicine. Bray founded the North American Association for the Study of Obesity in 1982 (now the Obesity Society), and he was the founding editor of its journal, *Obesity Research*, as well as co-founder of the *International Journal of Obesity* and the first editor of *Endocrine Practice*, the official journal of the American Association of Clinical Endocrinology. Dr. Bray has received many awards during his medical career including the Johns Hopkins Society of Scholars, Honorary Fellow of the American Dietetic Association, the Bristol–Myers Squibb Mead-Johnson Award in Nutrition, the Joseph Goldberger Award from the American Medical Association, the McCollum Award from the American Society of Clinical Nutrition, the Osborne–Mendel Award from the American Society of Nutrition, the TOPS Award, the Weight Watchers Award, the Stunkard Lifetime Achievement Award, the Presidential Medal from the Obesity Society, and in 2019 the W.O. Atwater Award from the USDA and American Society for Nutrition. During his 50 academic years Bray authored or coauthored more than 2,000 publications, ranging from peer-reviewed articles and reviews to books, book chapters, and abstracts reflected in his Hirsch (H) Index of 134. Dr. Bray is the coeditor of the three editions of *Nutrition Guide for Physicians and Related Healthcare Professionals*, and has had a long interest in the history of medicine and has written articles and a book on the history of obesity.

This text is organized so that each chapter includes clear definitions of medical terms and distinctions are made concerning commonly asked patient questions such as what are the differences between the types of fats and their negative and positive health aspects. An excellent explanation concerning the possible reason for disparity between study findings is provided in the positing of insightful questions such as: Were all serum measurements made within hours or weeks following dietary changes? Definitions are provided for the numerous types of vegetable-based diets that are often discussed with health professionals.

Unique to this volume are the in-depth chapters that explain the development of the dietary recommendations and how these are translated into information on food labels. Chapters concerning the growing interest in organic foods and food safety are included. There is an extensive analysis of the recommendations by nations on the contents of a healthy diet and suggestions for physicians and other health professionals in helping patients reach the goal of understanding the value of consuming a healthy diet. A separate chapter reviews the importance of certain dietary supplements as well as separate chapters that review the essential vitamins and essential minerals. This volume includes 44 review chapters that contain Key Points and Key Words as well as over 1,200 targeted references, over 80 useful tables and figures, and a listing of recommended readings. In addition the volume contains an extensive index and helpful Appendices. The volume chapters are organized in nine parts that enhance the reader's ability to identify the areas most relevant for their needs. All chapters are available online and are downloadable as is the entire volume.

Part One: Introduction

The editors have provided readers with a broad overview of their objectives and vision for this important volume and provide their perspectives concerning the importance of assessing the nutritional status of patients during the COVID pandemic.

Part Two: Nutritional Considerations Across the Lifespan

The seven chapters provide readers with the basics of nutritional requirements during pregnancy, lactation, weaning and early infant transition to solid foods, childhood nutrition, adolescent nutrition, unique needs of the menstruating female, and a new chapter concerned with dietary factors that are particularly important during the menopausal transition, and there is a separate chapter that examines the critical role of nutrition in supporting healthy aging. The chapters describe investigations into the mechanisms and factors affecting nutrient metabolism and the changes that occur at each life stage. Chapter 2 begins with a description of the preparations for pregnancy and reviews the periconceptional need for folic acid and other micronutrients as well as the importance of weight control. Descriptions of the nutritional and immunological value of breast milk are included in Chap. 3 as is a discussion of the importance of protein, essential micronutrients, and balanced consumption of the other macro- and micronutrients during childhood growth and during pregnancy, and as of March 2021, breast feeding continues to be recommended for COVID-infected mothers. Reviews of the major clinical studies and national guidelines for each age and life stage are included. The chapter on adolescence and young adults examines the development of eating disorders including obesity, anorexia, bulimia, and binge eating. Chapter 7 reviews the unique nutritional needs in older adults. The significant impacts of COVID on this population, including a sensitive analysis of the devastating effects of COVID in the nursing home patient population that often includes the oldest patients, as well as home-bound seniors living alone and whose diets are often compromised, are reviewed and relevant references are included. Healthy eating is particularly relevant to menopausal women described in Chap. 8. The effects of stress levels on weight maintenance in this population as well as the biological and mental effects of growing older are discussed. The findings of increased weight gain and additional stress associated with reduced access to fresh fruits and vegetables (as examples) and many types of exercise programs during the COVID pandemic are examined in the chapter's addendum.

Part Three: Nutrition for the Prevention and Management of Chronic Conditions

Part Three contains six chapters that examine the critical issues of weight management and consequences including eating disorders, obesity, and diabetes. Chapters examine the effects of obesity and its comorbidities including insulin resistance, cardiovascular complications, lipid disorders, hypertension, and hormonal imbalances. Chapter 9 includes in-depth discussions of classification of obesity stages, adverse health effects, and types of treatments including diets, drugs, and surgeries. The tables are especially informative. At the end of Chap. 9, there are statistics related to the serious adverse effects of obesity on the morbidity of COVID infection and related, significantly increased risk of mortality as BMI increases in this population. Chapter 10 provides a detailed review of the many aspects of medical nutrition therapy that are critical to maintaining the health of diabetics and includes the recent findings of increased morbidity risk from COVID in both Type 1 and Type 2 diabetes patients. Practice guidelines and tools for obesity management including up-to-date information surgical obesity treatments and their implications for improving human health and reducing obesity-related diseases are tabulated for the reader in the next chapter. The chapter on bone health reviews the critical nutrients necessary to build and maintain strong bones throughout the lifespan. The chapters on coronary heart disease and blood pressure contain valuable information about salt intake, plant stanols and sterols, homocysteine, and antioxidants and review the major clinical trials that showed the power of diet to beneficially affect cardiovascular outcomes: the DASH study (which is examined in depth in a separate chapter) and the Trial of Hypertension Prevention are but two examples. The

new chapter concerning diet, physical activity, and cancer prevention integrates our current knowledge of the intertwined effects of these factors on reducing the risk of major cancers.

Part Four: Dietary Patterns

There are four new chapters in this part that are included as the role of whole diets and dietary patterns is becoming a focus of not only clinical nutrition but public health nutrition research. Separate chapters review the details of and research findings associated with the Mediterranean Diet, the DASH diet, vegetarian and flexitarian diets, and ketogenic diets. These chapters are of particular value to healthcare providers, especially dieticians, as many clients are confused by the details of these plans and how they may benefit from these programs. Detailed tables in these chapters provide further guidance.

Part Five: Nutritional Requirements Following Surgery and Acute Disease

There are eight chapters in this part and the first chapter reviews the often increased nutrient requirements seen in mainly adult patients dealing with inflammatory and/or infectious diseases in the gastrointestinal tract, including malabsorption diseases, GERD, ulcers, constipation, diarrhea, and diverticulosis. Many GI tract issues in children and young adults are linked to food allergies or food intolerance and these topics are examined in the next chapter. The following chapter looks at nutritional needs in patients with diseases of the liver and the pancreas; discussions of cirrhosis, nonalcoholic fatty liver disease, and acute as well as chronic diseases including cancers of these organ systems are included. Chapter 22 reviews the anatomy and physiology of renal function, and its critical role in fluid balance. Because of the interplay of cardiovascular disease, diabetes, and often resultant kidney disease, the chapter emphasizes the value of a specialist medical nutrition dietician for patients with kidney diseases and comments on the increased risk of kidney disease development in COVID patients as well as renal patients being at increased risk for serious adverse effects if they are infected with COVID. The new chapter, Chap. 23 is new to this volume and importantly examines the effects of many of the most common eating disorders on the patient's nutritional status and provides guidance on medical nutrition diet modification programs as well as cognitive behavioral therapy and pharmaceutical drug use. The addendum alerts us to the finding of increased risk of eating disorders during the COVID pandemic and potentially, its aftermath. Another new chapter provides the latest data concerning the effects of bariatric surgery on the nutritional status of the patient before, immediately after, and following recovery. The specific essential nutrient requirements that are altered by certain types of this surgery are clearly reviewed. The third new chapter in this part examines the critical importance of protein in the diet of the elderly who are losing muscle mass (sarcopenia) and the equal importance of targeted exercise programs. As all of these patient populations often use one or more prescription drugs/day, the last chapter in this part reviews the most common drug-nutrient/food interactions and includes two comprehensive tables of drug–nutrient interactions.

Part Six: Food and Nutrient Health Effects

The ten chapters in this part review the major areas of patient questions concerning foods and beverages they consume as well as food components, including fat, fiber, vitamins and minerals. Six of the ten chapters in this part are new, including the first two chapters; the first chapter examines the data on coffee consumption and potential health benefits and the second chapter looks at the research to

determine the health benefits associated with consuming either black or green tea. Fats are reviewed in the next chapter including all of the types of dietary fats that are found in both meat and vegetable-based diets. As with fats, sugar sources often confuse patients and the advent of many artificial sweeteners adds to further confusion. This chapter discusses these topics as well as the health effects of added versus naturally occurring sugars within whole foods. Fiber also has its own chapter and examines their many sources, functions, and the types including those found in supplements. Energy drinks are a relatively new and growing category of high caffeine-containing beverages and a new chapter is devoted to this topic that includes relevant safety issues. Chapter 32 reviews the types of alcoholic beverages, measures of alcoholic beverage consumption, and the potential health benefits and risks and discusses the increase in alcohol consumption during the lockdowns associated with the COVID pandemic. The benefits and risks associated with vegetarian as well as vegan diets are reviewed. The last chapter in this part looks at the questions of food safety and quality and emphasizes the importance of understanding the meaning of organic when used to describe different types of foods. The separate chapters on vitamins and minerals (Chaps. 34 and 35) are comprehensive and provide helpful references including addendums concerning recent evidence of roles related to COVID. The last chapter, which is new to this volume, provides a broad overview of the role of the gut microbiome in overall health. The terms prebiotics and probiotics are defined and their usefulness is described as well as the value of providing microbes to the gut from foods/supplements. There are several comprehensive tables found in these chapters including the in-depth tables concerning vitamins and minerals.

Part Seven: Influencing Dietary Health Decisions

The five chapters in this part provide guidance to the health professional on diverse topics that affect client/patient health. The first chapter provides an in-depth examination of the value of behavioral change programs especially during weight reduction. The second chapter explains the methods used to assess nutritional intakes to help in defining the nutritional status of the patient. With the advent of COVID, nutritional assessments could no longer be performed face-to-face; recent suggestions for using telemedicine for assessments are cited in the addendum of Chap. 38. It is equally important that the health provider have a nutrition-based standard to share with the client that indicates the best dietary intake recommendations. The next chapter describes the US Dietary Reference Intakes and how these apply to the client/patient. The chapter provides clear guidance and also includes helpful references. Of great importance to the consumer, there is an informative chapter devoted to explaining each part of the food label and its new updated format, discusses the front of the label as well as the back including the nutrition facts box, and also reviews the health claims that are approved for use on the front label. The last chapter provides an historical view of the development of recommendations from single nutrients to the importance of whole foods and building diets around foods and not their components.

Part Eight: Opinions Concerning Supplements

The last two chapters provide the opinions of Dr. Temple and present the reader with examples of how to identify non-FDA approved claims as well as non-FDA approved ingredients mainly found in pill form and often sold in health food stores, health provider offices, and sold by mail.

Appendices

The volume includes two helpful appendices that include a table of aids for calculating nutritionally related concentrations and a list of books and websites that contain reliable nutrition and diet information.

Conclusions

Drs Wilson, Temple, and Bray are internationally recognized leaders in the fields of human nutrition including obesity research and clinical outcomes. These editors are proven excellent communicators, and they have worked tirelessly to develop this volume that is destined to become the benchmark in the field because of its extensive compilation of relevant topics covering the most important aspects of clinical nutrition. The titles of the chapters speak to their importance to clients, patients, as well as consumers interested in how nutrition affects their health. As well, the volume includes the latest research on the complex interactions between diet, health, and disease and includes recent findings linking many of the chapter topics with risk of contracting COVID as well as descriptions of the nutritional effects seen in COVID patients. The editors have chosen 70 of the most well-recognized and respected authors from around the world to contribute the 44 informative chapters in the volume. Hallmarks of all of the chapters include complete definitions of terms with the abbreviations fully defined for the reader and consistent use of terms between chapters. Key features of this comprehensive volume include the informative Key Points and Key Words that are at the beginning of each chapter and suggested readings as well as bibliography at the end of each chapter. The editors have added useful appendices including a detailed table of major conversions used in nutrient calculations. The volume also contains more than 80 detailed tables and figures, an extensive, detailed index, and more than 1,200 up-to-date references that provide the reader with excellent sources of worthwhile information about the role of diet, nutrition and exercise, food intake, nutritional value of foods, human physiology, and pathophysiology of the diet-related morbidities and comorbidities.

In conclusion, *Nutrition Guide for Physicians, Third Edition*, edited by Ted Wilson, Ph.D., Norman J. Temple, Ph.D., and George A. Bray, M.D., provides health professionals in many areas of research and practice with the most up-to-date, organized volume on well-accepted, data-driven nutrition topics that are often discussed by patients with their health provider. This volume serves the reader as the benchmark in this complex area of interrelationships between food and body weight, diet and health, and the role of national organizations in setting recommendations on dietary intakes. Moreover, the interactions between obesity, genetic factors, and the numerous comorbidities are clearly delineated so that practitioners can better understand the complexities of these interactions. Wherever possible, relevant information concerning COVID infection and the nutritional implications for the patient have been included. The editors are applauded for their efforts to develop this volume during this time of COVID with their firm conviction that "nutrition serves as an essential weapon for all doctors in the battle against disease and for the enhancement of human health." This excellent text is a very welcome addition to the Nutrition and Health Series.

Adrianne Bendich, Ph.D., FACN, FASN

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We, the editors, Ted Wilson, Norman J. Temple, and George A. Bray, wish to thank our series editor, Dr. Adrianne Bendich. We appreciate her enthusiastic support going back to the first edition of the present book that was published in 2010, as well as our five other books. Thanks for your strong support and for the countless times you have shared your insights with us. We also applaud her outstanding work in supporting the dozens of other books in the *Nutrition and Health Series*.

We also thank Stephanie Frost, Daniel Dominguez, Samantha Lonuzzi, and Jessica Gonzalez, our developmental editors at Springer in New York, who helped with the morass of details needed to get this book published. We value their skilled work.

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About the Volume Editors

Ted Wilson, Ph.D., is Professor of Biology at Winona State University in Winona, Minnesota. His research examines how diet affects human nutritional physiology and whether food/dietary supplement health claims can be supported by measurable physiological changes. He has studied many foods, dietary supplements, and disease conditions including pistachios, low-carbohydrate diets, cranberries, cranberry juice, apple juice, grape juice, wine, resveratrol, creatine phosphate, soy phytoestrogens, eggplants, coffee, tea, energy drinks, heart failure prognosis, diabetes, and obesity. Diet-induced changes have included physiological evaluations of plasma lipid profile, antioxidants, vasodilation, nitric oxide, platelet aggregation, and glycemic and insulinemic responses using in vivo and in vitro models. With Dr. N. Temple he edited the first and second edition of *Beverages in Nutrition and Health* (Humana Press, 2004 and 2016), *Nutritional Health: Strategies for Disease Prevention* (Humana Press, 2001 first, 2006 second, and 2012 third editions), and *Nutrition Guide for Physicians*, first and second editions (Humana/Springer Press Inc., 2010). He also enjoys teaching courses in Nutrition, Physiology, Cardiovascular Physiology, Cell Signal Transduction, and Cell Biology. When not in the laboratory he enjoys family time, the outdoors, and farming.

Norman J. Temple, Ph.D., is Professor of Nutrition at Athabasca University in Alberta, Canada. He has published 95 papers, mainly in the area of nutrition in relation to health. He has also published 14 books. Together with Denis Burkitt he coedited *Western Diseases: Their Dietary Prevention and Reversibility* (1994). This continued and extended Burkitt's pioneering work on the role of dietary fiber in chronic diseases of lifestyle. He coedited *Nutritional Health: Strategies for Disease Prevention* (2012; third edition), *Beverage Impacts on Health and Nutrition* (2016; second edition), *Community Nutrition for Developing Countries* (2016), and *Excessive Medical Spending: Facing the Challenge* (2007). He conducts collaborative research in Cape Town on the role of the changing diet in South Africa on the pattern of diseases in that country, such as obesity, diabetes, and heart disease.

George A. Bray, M.D., M.A.C.P., M.A.C.E., is Boyd Professor Emeritus at the Pennington Biomedical Research Center of Louisiana State University in Baton Rouge, Louisiana, and Professor of Medicine Emeritus at the Louisiana State University Medical Center in New Orleans. After graduating from Brown University summa cum laude in 1953, Bray entered Harvard Medical School graduating magna cum laude in 1957. His postdoctoral training included an internship at the Johns Hopkins Hospital, Baltimore, MD, a fellowship at the NIH, residence at the University of Rochester, and a fellowship at the National Institute for Medical Research in London and at the Tufts-New England Medical Center in Boston. In 1970, he became Director of the Clinical Research Center at the Harbor UCLA Medical Center in Torrance, CA. He organized the First Fogarty International Center Conference on Obesity in 1973 and the Second International Congress on Obesity in Washington, DC, in 1977. In 1989 he became the first Executive Director of the Pennington Biomedical Research Center in Baton Rouge, a post he held until 1999. He is a Master of the American College of Physicians, Master of the American College of Endocrinology, and Master of the American Board of Obesity Medicine. Bray founded the North American Association for the Study of Obesity in 1982 (now the Obesity Society), and he was the founding editor of its journal, *Obesity Research*, as well as co-founder of the *International Journal of Obesity* and the first editor of *Endocrine Practice*, the official journal of the American College of Endocrinologists. Dr. Bray has received many awards during his medical career including the Johns Hopkins Society of Scholars, Honorary Fellow of the American Dietetic Association, the Bristol–Myers Squibb Mead-Johnson Award in Nutrition, the Joseph Goldberger Award from the American Medical Association, the McCollum Award from the American Society of Clinical Nutrition, the Osborne–Mendel Award from the American Society of Nutrition, the TOPS Award, the Weight Watchers Award, the Stunkard Lifetime Achievement Award, the Presidential Medal from the Obesity Society, and in 2019 the W.O. Atwater Award from the USDA and American Society for Nutrition. During his 50 academic years Bray authored or coauthored more than 2000 publications, ranging from peer-reviewed articles and reviews to books, book chapters, and abstracts reflected in his Hirsch (H) Index of 134. Bray has had a long interest in the history of medicine and has written articles and a book on the history of obesity.

About the Series Editor

Adrianne Bendich, Ph.D., FASN, FACN, has served as the Nutrition and Health **Series Editor** for more than 25 years and has provided leadership and guidance to more than 200 editors that have developed more than 90 well-respected and highly recommended volumes in the Series.

In addition to *Nutrition Guide for Physicians and Related Healthcare Professionals 3rd Edition* **edited by Ted Wilson, Norman J. Temple, and George A. Bray, the 40 newest editions published from 2012 to 2020 include:**

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3. **Vitamin E in Human Health** edited by Peter Weber, Marc Birringer, Jeffrey B. Blumberg, Manfred Eggersdorfer, Jan Frank, 2019
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Earlier books included *Alcohol, Nutrition and Health Consequences* **edited by Dr. Ronald Ross Watson, Dr. Victor R. Preedy, and Dr. Sherma Zibadi;** *Nutritional Health, Strategies for Disease Prevention, Third Edition* **edited by Norman J. Temple, Ted Wilson, and David R. Jacobs, Jr.;** *Chocolate in Health and Nutrition* **edited by Dr. Ronald Ross Watson, Dr. Victor R. Preedy, and Dr. Sherma Zibadi;** *Iron Physiology and Pathophysiology in Humans* **edited by Dr. Gregory J. Anderson and Dr. Gordon D. McLaren;** *Vitamin D, Second Edition* **edited by Dr. Michael Holick;** *Dietary Components and Immune Function* **edited by Dr. Ronald Ross Watson, Dr. Sherma Zibadi and Dr. Victor R. Preedy;** *Bioactive Compounds and Cancer* **edited by Dr. John A. Milner and Dr. Donato F. Romagnolo;** *Modern Dietary Fat Intakes in Disease Promotion* **edited by Dr. Fabien De Meester, Dr. Sherma Zibadi, and Dr. Ronald Ross Watson;** *Iron Deficiency and Overload* **edited by Dr. Shlomo Yehuda and Dr. David Mostofsky;** *Nutrition Guide for Physician***s edited by Dr. Edward Wilson, Dr. George A. Bray, Dr. Norman Temple, and Dr. Mary Struble;** *Nutrition and Metabolism* **edited by Dr. Christos Mantzoros and** *Fluid and Electrolytes in Pediatrics* **edited by Leonard Feld and Dr. Frederick Kaskel. Recent volumes include:** *Handbook of Drug-Nutrient Interactions* **edited by Dr. Joseph Boullata and Dr. Vincent Armenti;** *Probiotics in Pediatric Medicine* **edited by Dr. Sonia Michail and Dr. Philip Sherman;** *Handbook of Nutrition and Pregnancy* **edited by Dr. Carol Lammi-Keefe, Dr. Sarah Couch, and Dr. Elliot Philipson;** *Nutrition and Rheumatic Disease* **edited by Dr. Laura Coleman;** *Nutrition and Kidney Disease* **edited by Dr. Laura Byham-Grey, Dr. Jerrilynn Burrowes, and Dr. Glenn Chertow;** *Nutrition and Health in Developing Countries* **edited by Dr. Richard Semba and Dr. Martin Bloem;** *Calcium in Human Health* **edited by Dr. Robert Heaney and Dr. Connie Weaver; and** *Nutrition and Bone Health* **edited by Dr. Michael Holick and Dr. Bess Dawson-Hughes.**

Dr. Bendich served as President of Consultants in Consumer Healthcare LLC, and has edited ten books including *Preventive Nutrition: The Comprehensive Guide for Health Professionals, Fifth Edition***, co-edited with Dr. Richard Deckelbaum (www.springer.com/series/7659). Dr. Bendich serves on the Editorial Boards of the** *Journal of Nutrition in Gerontology and Geriatrics* **and** *Antioxidants* **and has served as Associate Editor for** *Nutrition* **the International Journal, served on the Editorial Board of the** *Journal of Women's Health and Gender-Based Medicine***, and served on the Board of Directors of the American College of Nutrition.**

Dr. Bendich was Director of Medical Affairs at GlaxoSmithKline (GSK) Consumer Healthcare and provided medical leadership for many well-known brands including TUMS and Os-Cal. Dr. Bendich had primary responsibility for GSK's support for the Women's Health Initiative (WHI) intervention study. Prior to joining GSK, Dr. Bendich was at Roche Vitamins Inc. and was involved with the groundbreaking clinical studies showing that folic acid-containing multivitamins significantly reduced major classes of birth defects. Dr. Bendich has coauthored over 100 major clinical research studies in the area of preventive nutrition. She is recognized as a leading authority on antioxidants, nutrition and immunity and pregnancy outcomes, vitamin safety, and the cost-effectiveness of vitamin/mineral supplementation.

Dr. Bendich received the Roche Research Award, is a *Tribute to Women and Industry* **Awardee, and was a recipient of the Burroughs Wellcome Visiting Professorship in Basic Medical Sciences. Dr. Bendich was given the Council for Responsible Nutrition (CRN) Apple Award in recognition of her many contributions to the scientific understanding of dietary supplements. In 2012, she was recognized for her contributions to the field of clinical nutrition by the American Society for Nutrition and was elected a Fellow of ASN (FASN). Dr. Bendich served as Adjunct Professor at Rutgers University. She is listed in Who's Who in American Women.**

Connie W. Bales, Ph.D., R.D., is Professor of Medicine in the Division of Geriatrics, Department of Medicine, at the Duke School of Medicine and Senior Fellow in the Center for the Study of Aging and Human Development at Duke University Medical Center. She is also Associate Director for Education/Evaluation of the Geriatrics Research, Education, and Clinical Center at the Durham VA Medical Center. Dr. Bales is a well-recognized expert in the field of nutrition, chronic disease, function, and aging. Over the past two decades her laboratory at Duke has explored many different aspects of diet and activity as determinants of health during the latter half of the adult life course. Her current research focuses primarily on the impact of protein enhanced meals on muscle quality, function, and other health indicators during obesity reduction in older adults with functional limitations. Dr. Bales has served on NIH and USDA grant review panels and is a member of the American Society for Nutrition's Medical Nutrition Council. Dr. Bales has edited three editions of the *Handbook of Clinical Nutrition in Aging* and is Editor-in-Chief of the *Journal of Nutrition in Gerontology and Geriatrics*.

Contributors

Kelly C. Allison Center for Weight and Eating Disorders, Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

Katherine M. Appleton Research Centre for Behaviour Change, Bournemouth University, Poole, UK

Jamy D. Ard Wake Forest School of Medicine, Winston Salem, NC, USA

Connie W. Bales Center for the Study of Aging, Duke University School of Medicine, Durham, NC, USA

Department of Medicine, Duke University School of Medicine, Durham, NC, USA

Geriatric Research, Education, and Clinical Center, Durham VA Medical Center, Durham, NC, USA

Lindsay M. Boland Department of Nutrition, Brigham and Women's Hospital, Boston, MA, USA

Michael S. Borack Center for the Study of Aging, Duke University School of Medicine, Durham, NC, USA

Erin A. Bouquet Division of Gastroenterology, Hepatology and Nutrition, Vanderbilt University Medical Center, Nashville, TN, USA

Department of Internal Medicine, Vanderbilt University Medical Center, Nashville, TN, USA

George A. Bray Pennington Biomedical Research Center, Baton Rouge, LA, USA

Maija Broox Bruzas Center for Weight and Eating Disorders, Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

Chenxi Cai School of Public Health, Xiamen University, Xiamen, China

Michael Camilleri Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN, USA

Catherine M. Champagne Pennington Biomedical Research Center, Baton Rouge, LA, USA

Charles B. Chen Department of Pediatric Gastroenterology, University of Missouri Women's and Children's Hospital, Columbia, MO, USA

Gail A. M. Cresci Department of Pediatric Gastroenterology, Cleveland Clinic Children's Hospital, Cleveland, OH, USA

Department of Inflammation & Immunity, Lerner Research Institute, Cleveland Clinic, Cleveland, OH, USA

Center for Human Nutrition, Digestive Disease and Surgery Institute, Cleveland Clinic, Cleveland, OH, USA

Karen M. Davison Nutrition Informatics Lab, Kwantlen Polytechnic University, Richmond, BC, Canada

Junia Nogueira de Brito Division of Epidemiology and Community Health, University of Minnesota School of Public Health, Minneapolis, MN, USA

Desiree de Waal University of Vermont Medical Center, Department of Nephrology, South Burlington, VT, USA

William J. Evans Department of Nutritional Sciences and Toxicology, University of California, Berkeley, CA, USA

Barbara A. Fielding Department of Nutritional Sciences, University of Surrey, Guildford, UK

Emily W. Flanagan Pennington Biomedical Research Center, Baton Rouge, LA, USA

James K. Friel Department of Food and Human Nutritional Sciences, University of Manitoba, Winnipeg, MB, Canada

Karen M. Gibson Department of Nutrition and Dietetics, Viterbo University, La Crosse, WI, USA

Linda A. Gilmore UT Southwestern Medical Center, Department of Clinical Nutrition, Dallas, TX, USA

Laura A. Graeff-Armas University of Nebraska Medical Center, Omaha, NE, USA

Valentina Guercio Didcot, Oxfordshire, UK

TanYa M. Gwathmey Wake Forest School of Medicine, Winston Salem, NC, USA

Samar Hafida Joslin Diabetes Center, Boston, MA, USA

Harvard Medical School, Boston, MA, USA

Corrine Hanson University of Nebraska Medical Center, Omaha, NE, USA

Janetta Harbron Health through Physical Activity, Lifestyle and Sport Research Centre (HPALS), Division of Physiological Sciences, Department of Human Biology, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa

Ryan T. Hurt Division of General Internal Medicine, Mayo Clinic, Rochester, MN, USA

Mamoru Isemura Tea Science Center, University of Shizuoka, Shizuoka, Japan

Garvan C. Kane Division of Cardiovascular Disease, Department of Internal Medicine, Mayo Clinic, Rochester, MN, USA

Penny M. Kris-Etherton Department of Nutritional Sciences, The Pennsylvania State University, University Park, PA, USA

Christopher Larson Department of Minimally Invasive Bariatric Surgery, Gundersen Health System, La Crosse, WI, USA

Temitope O. Lawal Department of Pharmacy Practice, University of Illinois at Chicago, Chicago, IL, USA

Department of Pharmaceutical Microbiology, University of Ibadan, Ibadan, Nigeria

Pao-Hwa Lin Duke University Medical Center, Department of Medicine; Division of Nephrology, Durham, NC, USA

Andy Liu Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN, USA

Gail B. Mahady Department of Pharmacy Practice, University of Illinois at Chicago, Chicago, IL, USA

Division of Cardiovascular Disease, Department of Internal Medicine, Mayo Clinic, Rochester, MN, USA

Margaret A. Maher Department of Biology and Nutrition Minor, University of Wisconsin – La Crosse, La Crosse, WI, USA

Chetan Mandelia Division of Pediatric Gastroenterology, East Carolina University Brody School of Medicine, Greenville, NC, USA

Kara L. Marlatt Pennington Biomedical Research Center, Baton Rouge, LA, USA

Claire McEvoy Centre for Public Health, Queen's University Belfast, Belfast, UK

Michelle C. McKinley Centre for Public Health, Queen's University Belfast, Belfast, UK

Kelsey McLimans Department of Nutrition and Dietetics, Viterbo University, La Crosse, WI, USA

Johnson W. McRorie Jr Procter & Gamble and Personal Healthcare, Mason, OH, USA

Roeland J. W. Middelbeek Joslin Diabetes Center, Boston, MA, USA

Harvard Medical School, Boston, MA, USA

Derek Miketinas Texas Woman's University, Department of Nutrition and Food Sciences, Houston, TX, USA

J. Bernadette Moore School of Food Science & Nutrition, University of Leeds, Leeds, UK

Maria Morgan-Bathke Department of Nutrition and Dietetics, Viterbo University, La Crosse, WI, USA

Rachel A. Murphy Cancer Control Research, BC Cancer, and the School of Population and Public Health, University of British Columbia, Vancouver, BC, Canada

Yoriyuki Nakamura Tea Science Center, University of Shizuoka, Shizuoka, Japan

Blair J. O'Neill Mazankowski Alberta Heart Institute, Department of Medicine, Division of Cardiology, University of Alberta, Edmonton, AB, Canada

Roman Perri Division of Gastroenterology, Hepatology and Nutrition, Vanderbilt University Medical Center, Nashville, TN, USA

Department of Internal Medicine, Vanderbilt University Medical Center, Nashville, TN, USA

Monira Pervin Tea Science Center, University of Shizuoka, Shizuoka, Japan

Kristina S. Petersen Department of Nutritional Sciences, Texas Tech University, Lubbock, TX, USA

Kathryn N. Porter Starr Center for the Study of Aging, Duke University School of Medicine, Durham, NC, USA

Department of Medicine, Duke University School of Medicine, Durham, NC, USA

Geriatric Research, Education, and Clinical Center, Durham VA Medical Center, Durham, NC, USA

Kathrina Prelack Clinical Nutrition Department, Shriners Hospitals for Children, Boston, MA, USA

Simmons University, Boston, MA, USA

Wafaa A. Qasem Department of Human Nutritional Sciences, University of Manitoba, Winnipeg, MB, Canada

Paolo Raggi Mazankowski Alberta Heart Institute, Department of Medicine, Division of Cardiology, University of Alberta, Edmonton, AB, Canada

Frances R. Ragsdale Department of Biology, Winona State University, Winona, MN, USA

Nishikant Raut Department of Pharmacy Practice, University of Illinois at Chicago, Chicago, IL, USA

Leanne M. Redman Pennington Biomedical Research Center, Baton Rouge, LA, USA

Jamie C. Rincker Center for the Study of Aging, Duke University School of Medicine, Durham, NC, USA

Kieko Saito Tea Science Center, University of Shizuoka, Shizuoka, Japan

Philip A. Sapp Department of Nutritional Sciences, The Pennsylvania State University, University Park, PA, USA

Désirée Schliemann Centre for Public Health, Queen's University Belfast, Belfast, UK

Cara Schrager Joslin Diabetes Center, Boston, MA, USA

Jennifer Shiel Clinical Nutrition Department, Shriners Hospitals for Children, Boston, MA, USA

Kyle J. Sloan Procter & Gamble and Personal Healthcare, Mason, OH, USA

Jamie S. Stang Division of Epidemiology and Community Health, University of Minnesota School of Public Health, Minneapolis, MN, USA

Laura P. Svetkey Duke University Medical School; Department of Medicine; Division of Nephrology, Durham, NC, USA

Jessica R. Szczepanski Department of Health Sciences, Northern Arizona University, Flagstaff, AZ, USA

Elad Tako Department of Food Science, Cornell University, Ithaca, NY, USA

Norman J. Temple Centre for Science, Athabasca University, Athabasca, AB, Canada

Crystal Tyson Duke University Medical Center, Department of Medicine; Division of Nephrology, Durham, NC, USA

Keiko Unno Tea Science Center, University of Shizuoka, Shizuoka, Japan

Emmy van den Heuvel Research Centre for Behaviour Change, Bournemouth University, Poole, UK

Laboratory of Behavioural Gastronomy, Maastricht University, Maastricht, Netherlands

Sheila M. Wicks Department of Clinical and Molecular Medicine, Rush University, Chicago, IL, USA

Ted Wilson Department of Biology, Winona State University, Winona, MN, USA

Robert R. Wolfe Donald W. Reynolds Institute on Aging, University of Arkansas for Medical Sciences, Little Rock, AR, USA

Division of Geriatrics, Duke University Medical Center, Durham, NC, USA

Jayne V. Woodside Centre for Public Health, Queen's University Belfast, Belfast, UK

Part I

Introduction

Nutrition Guide for Physicians and Related Healthcare Professionals

1

George A. Bray, Norman J. Temple, and Ted Wilson

Keywords

Nutrition education · Healthcare professionals · Advances in nutrition

Nutrition has been a central element in the prevention and treatment of disease since time immemorial. It was a cornerstone of medicine in the days of Hippocrates and Galen more than 2000 years ago and has continued to be a part of the treatment portfolio of every medical tradition since. Patients ask questions that are sometimes outside the clinical specialty of the healthcare provider, and in this regard there is pressure to be omnipotent. In spite of this long history of nutrition as a central component of medical practice and care of sick patients, many healthcare professionals need a ready source of reliable information about how to apply nutrition to the care of their patients and clients today. The content of this book is designed to meet the need that a healthcare professional has to provide the answer to basic, and the oftentimes "not"-so-basic, questions about how nutrition and clinical practice intersect.

Nutrition is important to all living creatures. It describes the foods that are needed for human beings and other animals to grow and develop and to be healthy. It starts with the knowledge of the nutrients that are provided by the foods we eat. These include both macronutrients and micronutrients. The role of the macronutrients, proteins, fats, and carbohydrates is the development of cardiovascular disease and obesity as well as in their prevention. Keto diets, low-glycemic diets, and low-fat diets have all found their champions, and this book provides evidence to evaluate them. Micronutrients in food are another important element in maintaining food health. This book will focus on both micronutrients and macronutrients in relation to disease and its prevention but also discuss how our understanding of nutrition continues to evolve.

G. A. Bray (✉)
Pennington Biomedical Research Center, Baton Rouge, LA, USA
e-mail: George.Bray@pbrc.edu

N. J. Temple
Centre for Science, Athabasca University, Athabasca, AB, Canada
e-mail: normant@athabascau.ca

T. Wilson
Department of Biology, Winona State University, Winona, MN, USA
e-mail: twilson@winona.edu

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Nutrition and Health, https://doi.org/10.1007/978-3-030-82515-7_1

In a perfect world, good nutrition prevents the need for healthcare, but our limited access to nutritional information during professional education diminishes the potential of nutrition to improve our health. Nutritional knowledge of physicians and healthcare professionals may be inadequate for at least two reasons. The first is that the core of material taught in many professional schools, including medical schools and nursing schools, is limited. There are several reasons for this. Many physicians such as pathologists, radiologists, laboratory scientists and surgeons have little or no need for detailed nutrition in order to practice their specialties, and given the limited time in the medical curriculum, nutrition often gets short shrift.

Observations of the limited availability of nutrition education in the medical curriculum have been documented many times and are legion. The need for nutrition is mainly for physicians and nurses working one on one with patients who ask questions in the clinical setting. For these individuals, a source of reliable information about nutrition is most important, and it is presumed that they will get this information in their postdoctoral training. Yet most primary care training programs only have a limited amount of time for providing nutrition education. A healthcare provider does not need a PhD or MD to answer all questions; they just need a good working knowledge and a good source of basic information needed to answer the oft-asked questions.

A second reason that there is a need for a book like this one is that there are continuing advances in the field that make updating an individual's knowledge of nutrition an ongoing responsibility. There are, of course, continuing education courses that provide updates on the latest knowledge in nutritional science and nutritional practice. But these programs may not always deal with the issues that are of concern for a particular practitioner or for a particular patient. The utility of this book is that it provides information about the best studies that have documented the value of nutritional interventions that may be of value to individual patients—several cases in point. The value of diet in reducing blood pressure was clearly demonstrated in a study called the Dietary Approaches to Stop Hypertension (DASH Trial), and the DASH diet which arose from this trial is described in detail in this book. A second obvious example is the Mediterranean diet which has clear value for improvement of cardiovascular health and general well-being. The Mediterranean diet, too, is described in this volume. The US Food and Drug guidelines indicate that medications for treatment of obesity should be used with a comprehensive lifestyle program that involves diet which is also described in this volume.

The genetic composition of *Homo sapiens sapiens* has not changed very much in the last 40,000 years. However, the foods we can choose to eat, the way we eat, and the reasons we eat have experienced revolutionary changes in the last 40 years, which is arguably about half of the duration of our life cycle. As we know, many of the nutritional decisions made in early childhood do not impact us for decades to come (i.e., future obesity and CVD risk), while other nutritional outcomes are relatively immediate (i.e., DASH and blood pressure). Understanding nutritional changes through the life cycle is critical for improving our understanding of how diets and nutrition can be modified to improve health outcomes. This book is designed for pediatricians, internists, family physicians, physician assistants, and nurse practitioners who work with newborns, with children, with adults, and with the older members of society. We hope that those who use the *Nutrition Guide for Physicians and Related Healthcare Professionals* will find that it fills all of these needs.

The purpose of this book is to provide clinicians with the guidance they need for basic and long-standing problems related to clinical nutrition. COVID-19 in the year of this book's publication has created a myriad of problems on many levels of nutrition. We know that COVID-19 results in losses in olfactory and gustatory senses in approximately 41% of patients [1], and the lack of taste and smell leads to poor nutrition; this was just the tip of the Covid-nutrition iceberg. We know that the COVID-19 lockdown changed food delivery globally [2] in a manner that led to food insecurity for some, nutritional deficiencies for others, and potentially new food delivery systems for nearly everyone. Within a few months of the pandemic, it became almost common knowledge that those who are diabetic, obese, or elderly experience a greater risk of mortality if they contract COVID-19 [3–5].

At the time this was written (March 22, 2021), over 127 million doses of COVID-19 vaccine had been administered in the USA [6]. This number of immunizations will be far greater when this addendum is read by you, the reader, as we target heard immunity in our nation and world. It is the view of many that unlike smallpox and polio even intense global immunization may never lead to completely eradicate COVID-19. It is possible that future COVID-19 infections may become something akin to a common cold [7], and it is also the voice of optimism that the day-to-day clinical impact of COVID-19 in future nutrition in the healthcare setting will be greatly diminished.

The editors of this book believe that our return to a post COVID-19 pandemic period of normalcy will make the content of this book ever more important. It will become ever more important because our resources this last year have gone to understanding and interpreting COVID-19, not the basic nutrition that is the foundation of our health and the focus of many problems that were left, by choice or necessity, clinically unmanaged in this last year of the pandemic.

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Part II

Nutrition Considerations Across the Lifespan

Pregnancy: Preparation for the Next Generation

2

Michelle C. McKinley and Jayne V. Woodside

Keywords

Pregnancy · Nutrient requirements · Weight gain · High-risk pregnancies · Food safety · Breastfeeding

Key Points

- Good nutrition practices should begin in the preconception period.
- A healthy weight should be achieved before conception, if possible, and appropriate weight gain during pregnancy should be based on prepregnancy body mass index (BMI).
- Most nutrient requirements during pregnancy can be met through consumption of a wide variety of nutritious foods. However, all women of childbearing age should take a folic acid supplement before and during pregnancy, and some high-risk women can benefit from iron and/or calcium supplements during pregnancy as well.
- Nutrition remains an important concern during the postpartum period, especially for women who choose to breastfeed their infants and to promote postpartum weight loss.
- Referrals for specialized advice or additional support should be made for women with high-risk pregnancies, inappropriate gestational weight gain, hyperemesis gravidarum (excessive nausea and vomiting), multiple gestations, chronically poor diet/dietary restriction/disordered eating, chronic diseases such as hypertension and diabetes, and women with concerns about breastfeeding.

Introduction

Nutrition is a modifiable factor that has a notable impact on healthy pregnancy outcomes. Some effects of good nutrition during pregnancy can be appreciated immediately, such as reduced risk of maternal anemia and improved maternal glucose control. Others are evident upon the birth of the infant, such as healthy birth weight and absence of congenital defects. Still other benefits of a healthy diet during pregnancy may not be apparent for years to come.

Evidence continues to emerge supporting the fetal origins hypothesis which theorizes that in utero conditions have profound and long-lasting effects on fetal DNA and the subsequent health of offspring [1]. Furthermore, dietary habits during pregnancy have been associated with health status

M. C. McKinley (✉) · J. V. Woodside
Centre for Public Health, Queen's University Belfast, Belfast, UK
e-mail: m.mckinley@qub.ac.uk

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indicators in children such as evidence from the Project Viva [2] and Generation R [3] studies showing that a higher intake of sugar-sweetened beverages during pregnancy is associated with greater adiposity in children after adjustment for confounding factors.

Good nutrition practices should be part of a continuum of care beginning with preconception counseling and continuing throughout pregnancy, lactation, and the postpartum period.

Nutrition in the Preconception Period

Recent data indicate that 45% of live births were the result of unintended pregnancies [4]. In this light, it is clear that issues pertaining to childbirth readiness should be discussed with all women of childbearing age at primary care visits.

Achieving and/or maintaining a healthy body weight is a goal that should be considered well in advance of pregnancy. The Institute of Medicine recommends that women with obesity lose weight before pregnancy to improve menstrual functioning, ovulation, and metabolic profile and reduce infertility. In addition, overweight women should receive preconception counseling to improve diet quality, increase physical activity, and normalize weight. Women who enter pregnancy with a BMI in the overweight or obese range have an increased risk of fetal death, stillbirth, and neonatal, perinatal, and infant death, as well as gestational diabetes, preeclampsia, and other complications of pregnancy. However, weight loss during pregnancy is not recommended [5].

Eating habits can be difficult to change, but women often have increased motivation to make positive lifestyle changes before conception. Some key advice to promote optimal preconception nutrition includes:

- Following the recommendations of the USDA Dietary Guidelines for Americans (www.choosemyplate.gov; provides advice on planning meals during pregnancy [6]).
- Consuming a wide variety of foods from the five food groups.
- Following a regular eating pattern such as eating three meals and two to three snacks per day.
- Choosing minimally processed foods rather than foods with added salt, sugar, and fat.
- Achieving a healthy weight.
- Taking 400 μg of folic acid every day.
- Limiting caffeine to less than 200 mg/day.
- Avoiding alcohol.

In addition, the physician should screen for conditions, habits, and practices that might interfere with good nutrition, such as lactose intolerance, iron deficiency anemia, diets that restrict or eliminate food groups (such as vegan diets), pica, use of megadose vitamin and mineral supplements, use of herbal supplements, history of bariatric surgery, and extreme weight loss/fad diets/disordered eating. It may be warranted to refer women who fall into these categories to a registered dietitian nutritionist (RDN) for specialized support.

Women with preexisting disease conditions with a nutrition component should be referred to a RDN for medical nutrition therapy. These include diabetes, hypertension, HIV/AIDS, and phenylketonuria. Gestational diabetes is a condition that sometimes develops as a result of pregnancy and is discussed later in this chapter.

Folic acid has been proven to reduce the risk of neural tube defects when taken in the periconception period. Since the neural tube is formed and closes within the first month of pregnancy, and many women are not aware that they are pregnant until after this critical period, folic acid supplementation is most effective at preventing defects when taken before conception. The current recommendation is that all women of childbearing age take a supplement every day containing 400 μg folic acid [7] in addition to consuming foods that are good sources of folic acid, including leafy green vegetables, citrus fruits, and fortified cereals. Women in the lowest socioeconomic brackets deserve special

consideration as they tend to have the highest risk for neural tube defects [8] and may be least likely to use supplements [9]. Women who have previously had a pregnancy affected by a neural tube defect should take a 4000 μg folic acid supplement daily for at least 1 month before conception and for the first 3 months of pregnancy [7].

Nutrition During Pregnancy

The goal of nutrition during pregnancy is twofold, namely, to reduce adverse outcomes in the mother and in the fetus. Maternal outcomes that can be affected by nutritional status include risk for maternal anemia, gestational diabetes, preeclampsia, postpartum infections, and complications of labor and delivery. For the infant, low birth weight (<2500 g), small for gestational age, prematurity, fetal death, infant death, macrosomia, and some congenital defects are all poor birth outcomes that can be affected by nutrition status.

Weight Gain in Pregnancy

Weight gain guidelines for pregnant women are dictated primarily by the woman's prepregnancy BMI (see Table 2.1) [5]. These recommended weight gain ranges apply to all women irrespective of height and racial or ethnic group.

In addition to total weight gain, the pattern of weight gain is also important, and the IOM has indicated appropriate rates of weight gain during the second and third trimesters as summarized in Table 2.1. Any sudden and drastic gain in weight should be investigated carefully as this may indicate fluid retention and possible hypertension.

Energy and Macronutrient Needs During Pregnancy

Calorie needs during pregnancy are not increased in the first trimester, but are increased by 340 and 450 kcal/day in the second and third trimesters, respectively. Individuals who engage in little physical activity may need less, and the converse is true for individuals who are very active. The best way to assess whether caloric intake is sufficient is by monitoring weight gain.

Protein needs are increased modestly from 0.8 g of protein/kg/day for the nonpregnant state to 1.1 g of protein/kg/day during pregnancy. Protein-rich foods include lean meat, poultry, fish (some fish should be limited or avoided during pregnancy as described below), eggs, beans, nuts, and peanut butter. Protein supplements, such as high-protein drinks, are not recommended.

Approximately 175 g/day of carbohydrate is required during pregnancy. Again, this amount is adequately provided by a healthy diet, and most women have no difficulty achieving this. Carbohydrate is necessary to provide energy to the fetal brain and to spare protein for tissue growth. Some women who have adopted very-low-carbohydrate diets should be counseled on the importance of including

Table 2.1 Recommended total weight gain and rate of weight gain in pregnancy based upon prepregnancy BMI

Prepregnancy body mass index (BMI)	Suggested total weight gain (lb [kg])	Rates of weight gain in the second and third trimesters (lb/week [kg/week])[a]
<18.5 (underweight)	28–40 [12.7–18.2]	1 [0.45]
18.5–24.9 (healthy weight)	25–35 [11.4–15.9]	1 [0.45]
25.0–29.9 (overweight)	15–25 [6.8–11.4]	0.6 [0.27]
≥30 (obese)	11–20 [5.0–9.1]	0.5 [0.23]

[a]Assumes a weight gain of 1.1–4.4 lb. (0.5–2 kg) in the first trimester
Source of information: Ref. [5]

complex carbohydrates in their meals and snacks as the safety of low-carbohydrate diets during pregnancy has not been established.

Essential fatty acids (n-3 and n-6 fatty acids) are required for the proper development of the fetal central nervous system. Good sources of these fats include vegetable oils, seeds, nuts, and fish. Several research studies have shown a clear positive association between fish intake during pregnancy and indicators of neural development of the child, including cognition and visual acuity [10, 11]; however, evidence from randomized controlled trials (RCTs) is inconclusive [12].

Although fish are the richest source of n-3 fatty acids, intake of some fish should be limited, and some fish should be avoided, during pregnancy due to concerns about mercury, as discussed below under "Food Safety During Pregnancy."

Fluid needs during pregnancy are generally accommodated for in response to increased levels of thirst. Water, milk, and other unsweetened beverages are the best choices for hydration.

Vitamin and Mineral Needs During Pregnancy

The requirements for many vitamins and minerals are increased during pregnancy. A carefully chosen diet of nutrient-dense foods is sufficient to cover most vitamin and mineral needs. However, there are some nutrients that remain a concern during pregnancy. See Table 2.2 for recommended intakes for selected nutrients [13, 14]. Additional information on vitamins and minerals is provided in the tables in Chaps. 34 and 35.

The importance of taking a folic acid preconception in order to prevent neural tube defects such as spina bifida has been discussed earlier in this chapter. The RDA for folate in pregnancy is 600 μg/day. It may be hard for women to get the recommended amount from food alone, and so all women should continue to take a daily 400 μg folic acid supplement during pregnancy alongside consuming a diet rich in folate.

Vitamin D plays an essential role in fetal growth and deposition of calcium in the skeleton and teeth. Primary sources of vitamin D include exposure to the sun and milk fortified with vitamin D. Women who have dark skin, use sunscreen, avoid sun exposure, live in northern latitudes, or avoid milk may have low blood levels of the vitamin. In such cases, increased intakes of fortified dairy products and supplementation at levels consistent with the RDA (Table 2.2) are the preferred strategy. However, in cases of actual deficiency, supplementation at higher doses may be necessary to prevent osteomalacia in the mother or rickets in her offspring.

Table 2.2 Recommended dietary allowance (RDA) and adequate intake (AI) for selected nutrients in pregnancy

Life stage	RDA folate (μg/day)	RDA vitamin D (μg/day)	RDA vitamin A (μg/day)	RDA vitamin B_{12} (μg/day)	RDA iron (mg/day)	RDA calcium (mg/day)
Pregnancy, 14–18 years	600	15	750	2.6	27	1300
Pregnancy, 19–30 years	600	15	770	2.6	27	1000
Pregnancy, 31–50 years	600	15	770	2.6	27	1000
Lactation, 14–18 years	500	15	1200	2.8	10	1300
Lactation, 19–30 years	500	15	1300	2.8	9	1000
Lactation, 31–50 years	500	15	1300	2.8	9	1000

Source of information: Refs. [13, 14]

Excess intake of vitamin A is a concern during pregnancy as it is a known teratogen and may cause birth defects. In addition to avoiding supplements with more than 1500 μg (5000 IU) of retinol or retinoic acid, women should be warned against the use of oral acne medications, such as Accutane, which is derived from vitamin A. Beta-carotene, the precursor form of vitamin A found in plant foods, is nontoxic.

Although the requirement for vitamin B_{12} is increased during pregnancy, needs are easily met by a mixed diet that includes foods of animal origin. Vegan diets may be deficient in vitamin B_{12}, and, therefore, women who consume no animal products must use a supplement or choose foods that are fortified with the vitamin.

Calcium metabolism changes dramatically during pregnancy. Absorption, bone turnover, and excretion all increase, and the fetus and placenta accumulate calcium. By these mechanisms, calcium balance is adequately maintained without increasing dietary intake over prepregnancy requirements. Women with chronically low intakes of calcium should be encouraged to increase their intake of dairy foods and/or other foods that are good sources of calcium, including fortified foods (such as cereals, juices, and soymilk), dark green leafy vegetables, and legumes. The calcium in dairy foods is the most bioavailable, and calcium requirements can be met through 3–4 servings of dairy foods a day. Women with calcium intake below 500 mg/day may need supplements to ensure maternal and fetal bone requirements are met [17].

Iron requirements are increased during pregnancy to support increases in maternal and fetal hemoglobin production. Although the maternal body compensates with increased absorption, fetal needs appear to take precedence over maternal needs, often leading to iron deficiency and/or iron deficiency anemia. Iron deficiency anemia during pregnancy is linked to increased risk for preterm birth, low birth weight, fatigue, and reduced resistance to infection in the mother and lower intelligence quotients and abnormal behavior scores in children born to anemic mothers.

Because plasma volume increases at a more rapid pace than red blood cell production, hemodilution is common in pregnancy. Therefore, the cutoff values used for screening for anemia are different for pregnancy. Hemoglobin values less than 11 g/dL (110 g/L) in the first trimester and less than 10.5 g/dL (105 g/L) in the second and third trimesters indicate anemia.

Iron requirements are increased by a greater percentage during pregnancy than are calorie needs. These increased needs are hard to meet through diet alone. For this reason, many healthcare practitioners routinely prescribe supplements with 30 mg of iron for all pregnant women beginning at the second trimester. Others, however, prefer to screen for anemia before recommending a supplement. Women diagnosed with anemia may be prescribed larger dose supplements, with 60–180 mg iron. However, high doses of iron are associated with adverse gastrointestinal effects, including nausea, cramps, and constipation. A balance between increased dietary intake from food and a tolerable level of supplemental iron must be sought.

It was formally believed that low-sodium diets help prevent water retention, edema, and hypertension. It is now known that adequate sodium plays an important role in fluid balance during pregnancy, and women should not be advised to restrict their sodium intake.

Substances to Limit or Avoid in Pregnancy

Women who are pregnant or who could become pregnant should abstain from drinking alcohol to prevent the array of birth defects associated with fetal alcohol spectrum. Women should be counseled to quit smoking before becoming pregnant, but quitting at any time during pregnancy will confer benefits. Moreover, as second-hand smoke can harm the infant after birth, infants should not be exposed to cigarette smoke. Caffeine consumption should be limited to less than 200 mg/day or about

two 6 oz. cups of coffee or four cups of tea. Energy drinks contain varying amounts of sugar, caffeine, and legal stimulants or herbal ingredients. Their safety during pregnancy has not been studied, and it is advisable for pregnant women to avoid consumption [15]. Artificial sweeteners such as aspartame, sucralose, and saccharine are safe to use in moderation. The safety of many herbal supplements and remedies has not been tested, and practitioners should question their patients about their use of these products.

Food Safety During Pregnancy

There are some basic steps that can greatly reduce the risk of foodborne illness during pregnancy: washing hands often before and during food preparation and before eating; keeping raw foods separate from cooked and ready-to-eat foods; cooking foods to proper temperatures; and promptly refrigerating leftover foods and cold foods brought home from the grocery store. Women should be cautioned against eating raw or undercooked meat and eggs, including raw cookie dough, Caesar dressing, soft cooked eggs, and rare hamburgers.

The bacteria *Listeria monocytogenes* can cause miscarriage, premature labor, and infant death. It is unique because it can grow at refrigerated temperatures. For this reason, pregnant women should avoid eating unpasteurized dairy products, including unpasteurized cheese, deli meats, deli salads, smoked seafood, and pâtés. Processed and cured meats like hot dogs must be heated until steaming.

The bacteria *Toxoplasma gondii* is commonly known to infect cat litter but can also be present in raw and undercooked meats and on the surface of fruits and vegetables. Avoiding touching cat litter, thoroughly cooking meats, and rinsing fruits and vegetables before eating can reduce the risk of exposure.

The mercury content of fish is also a concern for pregnant women [16, 17]. Advice for women who are pregnant and breastfeeding is to eat 2–3 servings a week (8–12 oz) of a variety of fish. Best choices that are lowest in mercury include salmon, shrimp, pollock, tuna (light canned), tilapia, catfish, and cod. Some fish should be limited to no more than one serving a week (max 6 ounces) (termed "good" choices) such as halibut, snapper, and monkfish. Pregnant women should avoid eating shark, swordfish, king mackerel, marlin, orange roughy, tuna (bigeye), and tilefish from the Gulf of Mexico. Full details of the "best" and "good" choices and fish to avoid can be found in the American College of Obstetricians and Gynecologists practice advisory on seafood consumption during pregnancy [17].

Translating Nutrition Guidelines into Practical Advice About Food

Women do not eat grams of macronutrients or milligrams of minerals; they eat foods from different food groups on their own or as part of a meal. Practical advice for women, therefore, needs to be food-based rather than nutrient-based. Most nutrient needs will be met by a carefully selected, varied, nutrient-dense diet. Food guidelines for pregnant and lactating women can be found at www.choosemyplate.gov [6]; MyPlate allows women to plan the amounts of each food from the five food groups that are needed during each trimester of pregnancy, tailored to their height, prepregnancy weight, activity levels, and due date.

Special Concerns During Pregnancy

Common Complaints

The hormonal changes that occur during pregnancy can cause a host of uncomfortable symptoms for women, including morning sickness, heartburn, constipation, and food cravings. Women should be discouraged from taking herbal or "folk" remedies for these ailments as the safety of many of these treatments has not been tested.

Despite its name, morning sickness can strike at any time of the day. Many women suffer from nausea and vomiting only in the early part of pregnancy, but, for others, the symptoms can last for the entire three trimesters. The following suggestions may alleviate the discomfort of morning sickness: having something dry to eat like toast or crackers before getting out of bed in the morning, consuming small frequent meals rather than three large meals, and consuming liquids separately from meals and snacks. Food odors that cause queasiness are often less offensive if foods are eaten cold. Fresh air may also help. Ginger, chamomile, vitamin B6, and/or acupuncture are recommended by the World Health Organization for the relief of nausea in early pregnancy [18].

Heartburn can occur as the growing fetus pushes up on the mother's internal organs, creating pressure on the lower esophageal sphincter. Helpful suggestions are to avoid spicy or greasy foods, consume liquids separately from meals, eat small frequent meals, and avoid lying down or exercising immediately after meals. Antacid tablets may also help.

The hormones of pregnancy can alter the muscle tone of the gastrointestinal tract and cause constipation; this may lead to hemorrhoids if there is much straining with bowel movements. In order to help prevent this, women should take care to consume adequate fiber during pregnancy, preferably from whole grain foods, fresh fruits and vegetables, and legumes. Bulk-forming laxatives may also provide some relief. Water intake must be adequate. Keeping active during pregnancy can be helpful.

While most cravings women experience during pregnancy are not harmful, neither do they have any basis in physiological need. However, some women develop cravings for nonfood items, a condition known as pica. Clay, dirt, laundry starch, and freezer frost are some of the substances most often craved. These items can cause toxicities, parasitic infection, or intestinal blockage. Women with diabetes can experience blood sugar abnormalities if large amounts of starch are eaten. If nonfood items replace nutritious foods in the diet, nutrient deficiencies can occur. Women with pica are also often found to be anemic. It is not known whether pica is the cause of the anemia or if the reverse is the case.

High-Risk Pregnancies

Gestational diabetes mellitus (GDM) is a condition of poor glucose tolerance diagnosed during pregnancy. Although blood glucose control usually returns to normal postpartum, women diagnosed with GDM are at higher risk for type 2 diabetes later in life. Other consequences of GDM include increased risk for preeclampsia and complications during labor and delivery. Infants born to mothers with GDM are at higher risk for some birth defects, macrosomia (larger than average birth weight), and related outcomes such as shoulder dystocia (obstruction during labor).

Women at high risk for GDM include those with a family history of diabetes, overweight, age over 35, a previous pregnancy affected by GDM, or from high-risk ethnic groups, such as Hispanic, Black, Native American, South or East Asian, and Pacific Islanders. People from these groups should be screened with a 50-g, 1-h, oral glucose challenge as early as possible in pregnancy. Other women are usually screened between weeks 24 and 28 of gestation.

Medical nutrition therapy for GDM includes meeting calorie needs as appropriate for recommended weight gain, carbohydrate control (40–45% of total calories coming from carbohydrates spread out evenly through the day), avoidance of concentrated sweets, high-fiber intake, avoidance of excess weight gain, and moderate exercise. Regular blood glucose monitoring by the patient is recommended. If diet and exercise fail to bring blood glucose levels under control, insulin may be necessary. A team approach is required, including the patient, the physician, a registered dietitian, and a diabetes educator.

Gestational hypertension is high blood pressure first diagnosed in pregnancy, usually around week 20 of gestation. This may progress to preeclampsia, a condition of hypertension and proteinuria. Women with preeclampsia are at high risk for preterm delivery and progression to eclampsia, a life-threatening condition characterized by convulsions, coma, and death. The exact cause of preeclampsia is unknown though it seems to be related to abnormal implantation followed by oxidative stresses that reduce blood flow to the placenta. In this light, preventive measures are limited, but women at their ideal body weight with diets that include healthy amounts of antioxidants and minerals are best prepared for pregnancy. The World Health Organization recommends daily calcium supplementation at doses of 1.5–2.0 g/day elemental calcium for pregnant women from populations with low dietary calcium intake to reduce the risk of preeclampsia [19]. Low-sodium diets are not beneficial for preventing or treating preeclampsia. Once preeclampsia is diagnosed, dietary measures are largely ineffective at controlling blood pressure, and treatment usually relies on pharmaceutical methods.

A multifetal pregnancy requires weight gains higher than for a singleton pregnancy. The IOM have provided *provisional* guidelines for gestational weight gain with multiple fetuses for women of normal weight and women with overweight or obesity. They stated that there was insufficient information to develop guidelines for underweight women. Guidelines for weight gain at term for multifetal pregnancy according to prepregnancy BMI are normal weight, 37–54 lb. (17–25 kg); overweight, 31–50 lb. (14–23 kg); and obese, 25–42 lb. (11–19 kg) [5].

Bariatric surgery as a treatment for obesity has increased in recent years, and many patients are women of reproductive age. The changes in gut physiology and potential for micronutrient inadequacy associated with bariatric surgery mean that there are specific considerations for women prior to conception, during pregnancy, and in the postpartum period. These considerations include timing of pregnancy, contraceptive choice, advice on food intake, nutrition supplementation, monitoring nutritional status, clinical follow-up of pregnancy (including diabetes screening and weight gain during pregnancy), and breastfeeding [20].

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Nutrition for Lactation

Breast milk is the gold standard for human nutrition [21]. The decision to breastfeed is often influenced by external factors, such as the support, or lack thereof, by family, friends, and health professionals; by work, school, or family responsibilities; and by the woman's knowledge of the benefits of breastfeeding.

Women should be provided with information regarding the benefits of breastfeeding. They should be given this information early in pregnancy and throughout the pregnancy. Benefits for the mother include increased levels of oxytocin, leading to increased uterine contractions, reduced postpartum bleeding, faster return of the uterus to prepregnancy size, and delayed return of menstruation. Women who breastfeed their infants also have improved bone density, reduced risk of breast and ovarian cancer, and reduced risk of rheumatoid arthritis.

Many women are concerned that they may not be able to breastfeed, but they should be assured that the vast majority of women are physically able to produce enough milk for their infants and that breast milk is produced on demand, i.e., the more often they feed their infants, the more breast milk they will

produce. Breastfeeding is medically contraindicated in only a few conditions: active tuberculosis, illegal drug use, HIV or AIDS (in developed nations), and galactosemia in the infant.

Nutritional needs during lactation can be provided by a carefully selected diet. Energy needs are increased by 500 kcal/day over prepregnancy needs, but some of these calories may be provided by maternal fat stores. Once breastfeeding is established, moderate calorie restriction and moderate exercise are acceptable ways to reduce postpartum weight without affecting the quality of breast milk quality and volume or infant growth [22]. Vitamin and mineral status in the lactating mother generally does not affect the quality of breast milk, unless deficiencies are prolonged and severe. There may be an increased need for some vitamins and minerals during lactation to support the mother's nutritional status. DRIs for selected nutrients are presented in Table 2.2. Additional information is provided in the table in Chap. 39. Women who are breastfeeding should, as during pregnancy, avoid eating fish known to contain high levels of mercury as described in the previous section on "Food Safety During Pregnancy."

Nutrition for the Postpartum Period

Practitioners can use postpartum visits as an opportunity to encourage women to develop strategies to return to or achieve a healthy BMI. These visits are also the ideal time to discuss preparations for future pregnancies, such as those described above for preconception.

Referrals for Services

There are some circumstances in which referrals for additional services should be made. Pregnant women with inappropriate weight gain, hyperemesis gravidarum (excessive nausea and vomiting), multiple gestations, chronically poor diets/dietary restriction/disordered eating, phenylketonuria, chronic diseases such as hypertension and diabetes, or a history of substance abuse may be referred to a RDN for medical nutrition therapy [15]. Lactating women who are experiencing difficulty with the breastfeeding process should be referred to a certified lactation consultant. In the USA, the Supplemental Food Program for Women, Infants, and Children (WIC) serves low-income pregnant, breastfeeding, and postpartum women, as well as children up to 5 years of age who are at high risk for medical or nutritional problems. Through WIC, women can receive health referral services, supplemental food vouchers, and nutrition assessment, education, and counseling.

Summary

For most women, good nutrition during pregnancy, including increased energy needs, can be achieved through a carefully selected, varied, nutrient-rich diet. Good nutritional practices should begin in the preconception period. Women are best prepared for pregnancy when they are at or near their ideal body weight, eat a nutrient-dense diet, take a folic acid supplement, and abstain from tobacco and alcohol. Weight gain during pregnancy should be based on prepregnancy BMI. Some women may benefit from iron or calcium supplements. Pregnant women should take extra precautions to avoid any foodborne illness. Common complaints of pregnancy may often be relieved through dietary measures. Herbal supplements have not been shown to be safe. High-risk pregnancy conditions, such as gestational diabetes, preeclampsia, and multifetal pregnancy, are best managed by a multidisciplinary health team. Maternal nutrition continues to be important in the postpartum period, particularly for mothers who choose to breastfeed their infants and to help with postpartum weight loss. Women with chronic disease, who are low income and at high risk for poor nutrition, or who have concerns about breastfeeding should be given referrals for specialized services. Women in high-risk pregnancies should be referred to a RDN for medical nutrition therapy.

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Infants: Transition from Breast to Bottle to Solids

3

Chenxi Cai, James K. Friel, and Wafaa A. Qasem

Keywords

Infants · Breast milk · Breastfeeding · Complementary feeding · Formula · Growth

Key Points

- Exclusive breastfeeding is recommended for the first 6 months of life.
- Formula feeding is only recommended to mothers who cannot or choose not to breastfeed.
- Breast milk has a degree of bioactivity, antioxidant ability, immunological defenses, minerals, and fatty acids not found in formula. These lacking elements may help explain the health benefits associated with breast milk. Complementary feeding should begin at 6 months of age with breast milk continuing until at least 2 years of age.
- Complementary feeding should help promote a positive association with hunger, food, appetite, and the person providing the feeding. Infants should also learn gross motor skills and form relationships.

What Is the Best Milk for an Infant?

Breastfeeding is recommended for the first 2 years of life [1, 2]. Exclusive breastfeeding is recommended for the first 6 months of life. Formula feeding is recommended only for those who choose not to or cannot breastfeed. The consumption of whole cow's milk is not recommended during the first year of life, while reduced-fat cow's milk is not recommended in the first 2 years [2, 3]. About four out of five mothers in the United States initiate breastfeeding, and over half will continue to 6 months space [4].

Breastfeeding is rarely contraindicated. Infants who have galactosemia or whose mother uses illegal drugs, has untreated active tuberculosis, or has been infected with HIV should not breastfeed. However, neither smoking nor environmental contaminants, moderate alcohol consumption, nor the

C. Cai (✉)
School of Public Health, Xiamen University, Xiamen, China
e-mail: chenxicai@xmu.edu.cn

J. K. Friel
Department of Food and Human Nutritional Sciences, University of Manitoba, Winnipeg, MB, Canada
e-mail: james.friel@umanitoba.ca

W. A. Qasem
Department of Human Nutritional Sciences, University of Manitoba, Winnipeg, MB, Canada
e-mail: wafaa.qasem@hsc.edu.kw

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use of most prescription and over-the-counter drugs should preclude breastfeeding. The WHO tentatively recommends breastfeeding when the mother is with suspected or confirmed COVID-19 [5].

With all the best intentions and technological expertise, "humanized" infant formulas do not compare to mother's own milk. It is therefore logical and appropriate for health professionals to encourage the consumption of human milk whenever possible. However, once the information is presented, there is no justification for attempting to coerce women into making a feeding choice [6]. Sometimes a formula-fed child and rarely a breastfed infant develop sensitivity to cow's milk, either cow's milk allergy (CMA) or lactose intolerance.

While human milk is "uniquely superior" for infant feeding and is species specific, the most acceptable alternative is commercial formulas. Manufacturers do their utmost to mimic human milk. A "formula" is just that a product that is proprietary, consisting of a composite mix of nutrients, emulsifiers, and stabilizers. Formulas in North America that are marketed for term infants are based on one of the following: (a) cow milk (casein or whey predominant), (b) soy protein, or (c) protein hydrolysate. The use of soy-based formulas, special formulas, or formulas for the feeding of the premature infant is beyond the scope of this review.

The success of formula companies financially is due to (a) aggressive marketing; (b) the lack of support for breastfeeding from family, friends, and the medical profession; (c) cultural and public perception; (d) convenience; and (e) some government programs giving infant formula away for free. With the increase in working mothers, formula feeding becomes a practical and attractive alternative. Guidelines for formula composition have evolved over the years to provide not only what must be in a formula but minimum and maximum levels as well. Standards may vary between countries.

Nutrient Content of Breast Milk and Infant Formula

The composition of a formula depends on many factors and differs between manufacturers. For example, cholesterol exists in human milk but is not added to formula because the public perceives it as "bad." Human milk has a caloric density of 670 kcal/L. Most term formulas are designed to have the same caloric density. Low-iron formulas are marketed even though health professionals do not recommend their use as a standard feed. They remain on the market because the public and some health professionals perceive them as beneficial in dealing with problems such as colic and constipation.

The nutrient composition of human milk changes over time. The composition also changes during feeding so that most of the fat in human milk is concentrated in the latter part of feeding, probably satiating the infant and providing a signal for the termination of feeding. It appears that breastfed infants have more control over the amount consumed at a feeding than do formula-fed infants [6]. Frequent feedings with small amounts at each feeding, as is seen in infants who are breastfed ad libitum, may lead to favorable changes in metabolism [7]. These differences may affect feeding habits later in life.

The protein content of human milk is high during early lactation (colostrum) and then gradually declines to a low level of 0.8–1% in mature milk. The high-protein concentration of colostrum is largely due to very high concentrations of secretory IgA and lactoferrin. These proteins provide protection against bacteria, giving benefits in early life beyond the role of building blocks for tissue synthesis. Indeed, human milk is truly the first and foremost "functional food."

Milk proteins are separated into various classes, mainly caseins (10–50%) and whey (50–90%) of total proteins [8]. Milk fat globule membrane proteins and proteins derived from cells present in milk comprise 1–3% of the total protein. For some years manufacturers prepared their formula with either whey or a casein base. For the term infant, there appears to be no advantage nutritionally of whey-predominant over casein-predominant formulas. Interestingly, digested fragments of human casein, but not bovine, may exert physiological effects such as enhancing calcium uptake by cells and playing

a role in infant sleeping patterns [8]. Little is known about the role of hormones that are present in human milk; they may play a role in the developing infant.

Human milk contains significant amounts of polyunsaturated fats. These include 10–12% linoleic acid (18:2, *n*-6), 1–2% linolenic acid (18:3, *n*-3), and a small but significant amount of docosahexaenoic acid (DHA, 22:6 *n*-3) and arachidonic acid (AA, 20:4 *n*-6) [9]. While the level of total polyunsaturated fats in human milk varies with the intake of the mother, it is generally 13–20%. Long-chain fatty acids (with chain length > 18C) present in human milk, and recently added in some formula, may confer some developmental advantage. Formula contains more of the shorter-chain fatty acids.

The primary carbohydrate source in formula and human milk is lactose with very small amounts of other sugars. No minimum or maximum level of carbohydrate is set for North America. Corn syrup solids and/or maltodextrin may also be used in certain formulas [6].

Minerals can be divided broadly into macro-, micro-, and ultra-trace elements. Mineral concentrations differ in human milk over the first 3 months of lactation [10]. The levels of Zn, Cu, Rb, and Mo decrease over time, suggesting homeostatic regulation and possible essentiality for human infants [10]. In general, the mineral content of human milk is not influenced by maternal diet, parity, maternal age, time of milk collection, different breasts, or socioeconomic status [11].

The ultra-trace elements (<1 μg/g dry diet) exist naturally in human milk but depend on protein sources in formulas where they occur as contaminants. Although many of these elements have no specified human requirement, we believe that recommendations for ultra-trace elements need to be established.

Human milk has all the essential vitamins required by the infant but is low in vitamins D and K. Vitamin K is given to all infants at birth, and vitamin D (also considered to be a hormone) is usually recommended as a supplement for breastfed infants and infants predominantly breastfed, receiving less than a liter per day of formula. Minimum and maximum levels of vitamins are regulated for formulas so that they are nutritionally complete but without having excessive amounts. Formula labels state the amount of all nutrients, including vitamins that must be present when the shelf life expires. Because of this, "overage" is necessary as some vitamins will break down over time. Thus, as much as 60% over label claim might be present for different nutrients, primarily vitamins [12].

The use of supplements for human milk-fed infants is controversial. Some see supplements as undermining the integrity of human milk and implying that milk is not adequate. Nonetheless, human milk is neither a perfect nor a complete food [13]. There are good data to support the administration of vitamin K soon after birth to prevent hemorrhagic disease of the newborn and vitamin D supplements during early infancy to prevent rickets [13] even in breastfed infants.

Current practice is for iron supplements to be deferred until 4–6 months of age. Some authorities [13] recommend iron supplements of 7 mg/day, beginning in the first few weeks of life. A significant increase in iron status has been documented in infants receiving a modest iron supplement (7.5 mg/day) [14]. Fluoride supplements, once recommended for all infants, are no longer recommended during the first year of life [13].

Formulas that conform to the specification of Canadian/American guidelines are complete and therefore do not require supplementation with any minerals or vitamins. A controversial nutrient is iron. The amount of iron fortification required is not yet certain; however, formulas that have a low content of iron (<4 mg/L) may lead to anemia. It was believed that consuming iron-fortified formulas would result in intolerance and gastrointestinal distress, but these theories have been discredited [15]. See Fomon [6] for a review of regulations for the nutrient content of infant formulas.

In general, the content of protein, lipid, carbohydrate, energy, minerals, and most water-soluble vitamins in human milk is not affected by poor maternal nutrition [16]. But fat-soluble vitamins and fatty acids are affected by the maternal diet [16]. It appears that there are mechanisms to ensure constant supply and quality of nutrients to the breastfed infant. The major difference between a breastfed and a formula-fed infant is that many of the components of human milk also facilitate the absorption of nutrients and have a function beyond nutrient requirements. Adding more of a nutrient to formula

is not necessarily as good as having a bioactive component in human milk, even if only present in small amounts (e.g., lactoferrin for both iron absorption and as a bactericide). There are many properties of human milk that attend to such details for the benefit of the infant.

Bioactivity of Human Milk and Formulas

Human milk is "alive," meaning it has functional components that have a role beyond simply the provision of essential nutrients. Bioactive compounds in human milk can be divided into several broad categories: (1) those involved in milk synthesis, nutritional composition, and bioavailability and (2) those compounds that aid in protection and subsequent development of the infant. Many bioactive compounds have been identified in human milk including cytokines, immune factors, growth factors, hormones, antimicrobial agents, nucleotides, antioxidants, and enzymes (*see* review [17]). Hormones, enzymes, cytokines for immunity, and cells present in milk have physiologically active roles in other tissues, so it is reasonable to assume that they play a role in infant growth and development. Indeed, many bioactive compounds can survive the environment of the neonatal stomach and are available; thus they can potentially exert important physiological functions [17, 18].

Early postnatal exposure to flavor passed into human milk from the mother's own diet can predispose the young infant to respond to new foods. The transition from the breastfeeding period to the initiation of a varied solid food diet can be made easier if the infant has already experienced these flavors. Cues from breast milk can influence food choices and enhance the acceptability of new foods with flavors already experienced in breast milk [19]. This does not happen with formula feeding.

Until recently, human breast milk was thought to be sterile, and the only time that bacterial organisms could be identified was when a woman develops "mastitis." But recent research has shown that breast milk contains various bacterial genera, including *Bifidobacterium* and *Lactobacillus*, with greater diversity in intra-phylotypes than previously thought, forming the milk microbiome [20, 21]. It is believed that the human milk microbiome plays a major beneficial role in shaping the development of the infant's intestinal microbiota and his/her immune system and may also play a role in other aspects of short- and long-term infant and maternal health [22]. Formula-fed infants have different microbiota profiles compared to breastfed infants; this may favor intestinal pro-inflammatory status, thereby leading to negative health outcomes [23].

A variety of other cells exist in human milk. Macrophages, polymorphonuclear leukocytes, epithelial cells, and lymphocytes have been identified in human milk and appear to have a dynamic role to play within the infant gut. These cells may offer systemic protection after transport across the "leaky gut," particularly in the first week of life [24]. Antiviral and antibacterial factors exist in human milk with secretory IgA produced in the mammary gland being one of the major milk proteins [8]. There may even be a pathway from the infant back to the mother, which tailors the production of antibodies against microbes to which the infant has been exposed.

Hamosh [17] classified enzymes in human milk into three categories: (1) those that function in the mammary gland, (2) enzymes that might function in the infant, and (3) enzymes whose functions are unclear. It is only recently that the physiological significance of enzymes in human milk has started to become appreciated. More than just protein, and not present at all in infant formulas, enzymes are another example of why human milk must be seen as alive. These enzymes appear to have a more highly organized tertiary structure than enzymes from other tissues, which may be to protect function by resisting denaturation in the gut [17]. We think that as well as serving an immediate function in the intestine, some enzymes may be transported across the gut or act within the body to offer protection to the infant. Interestingly, amylase, which is present in human milk, digests polysaccharides that are not present in human milk. Amylase is important after the initiation of starch-containing foods such as cereals [17]. It is as if the mammary gland is "thinking ahead" and assisting the infant gut in the

transition to weaning. Milk digestive lipase assists the newborn whose endogenous lipid digestive function is not well developed at birth.

Recent interest has investigated the antioxidant properties of human milk. Several groups have reported the ability of colostrum [25] and mature milk [26] to resist oxidative stress using a variety of end points. This feature of human milk appears to be heterogeneous rather than attributable to a specific compound. Infant formulas appear to be less resistive to oxidative stress than is human milk. This is noteworthy since formulas always have considerably more vitamin E and vitamin C, considered to be two of the more important antioxidants, than are found in human milk. Some have suggested that the attainment of adult levels of some antioxidants during infancy is dependent on human milk feeding [18].

Health Benefits of Human Milk

The health benefits of human milk are significant. Breastfeeding protects against a wide variety of illnesses, particularly the incidence and severity of diarrhea, otitis media, upper respiratory illnesses, botulism, and necrotizing enterocolitis [16, 27]. Prior to advancements in hygiene, infants who were not breastfed did not fare well, and mortality rates could be as high as 90% [6, 16]. Even with the use of current formulas, breastfed infants have a lower incidence of many illness and are generally sicker for shorter times than formula-fed infants [28]. Previous work has demonstrated that later in life breastfed infants have decreased risk of diabetes, cancer, and cardiovascular disease [28]. However, recent results from the National Longitudinal Survey of Youth (NLSY) shows that longer duration of breastfeeding may not necessarily lead to long-term healthier childhood and well-being [29].

The most practical measure of overall infant health and well-being is growth. One would expect that with all the advantages of human milk, a breastfed baby would gain more weight. It is a puzzling phenomenon that the growth of the exclusively breastfed infant is lower in weight-for-age than a formula-fed infant. Likely there is more energy intake by a formula-fed infant. However, reduced growth in breastfed infants has no known negative effect on functional outcomes. We found infants who had consumed home formulas made of evaporated milk grew more than either formula-fed or breastfed babies [30], yet they did not perform as well as breastfed infants on tests of visual function [31].

There is controversy in the area of cognitive development as it is difficult to carry out the ideal study. Breastfed infants appear to have enhanced cognitive and neurological outcomes in comparison to formula-fed infants [32]. Small differences have been seen even in later childhood [32]. Increased duration of breastfeeding is associated with higher verbal IQ scores. In addition, increasing the period of exclusive breastfeeding appears to enhance infant motor development [33]. We found enhanced visual acuity in full-term breastfed infants compared to formula-fed infants; this was related to blood fatty acid levels [31]. The explanation for these consistent observations is highly controversial. Possibly, there are components of human milk that enhance cognitive development. Other factors that may be responsible are the act of breastfeeding itself, maternal education, and social class.

A paper by Allan Lucas [32] that reported improved neurological development in breastfed infants sparked a major debate on which factors really explain increased cognitive development. It is reasonable to assume that the long-chain polyunsaturated fatty acids, enzymes, hormones human milk, trophic factors, peptides, and nucleotides present in breast milk may enhance brain development and learning ability. Further, it would be sensible to feed human milk whenever possible if any or all of the above differences turn out to be true. Whether a breastfed infant has better development because of maternal factors or biological factors does not lessen the value of enhanced development to the infant.

Transition to Solid Foods

During the second 6 months of infancy, breast milk no longer meets all the nutritional needs of the infant. Solid foods should therefore be introduced. However, continuation of breastfeeding is recommended for the first 2 years of life and can be continued until the mother and infant decide to cease. The introduction of solid foods is known as "complementary feeding," A proper transition between a liquid diet and a diet with solids is crucial for the development of infants. The WHO gives four goals of complementary feeding: it should be timely, adequate, safe, and properly administered [34].

The timely introduction of complementary foods should begin around 6 months of age. Most infants start consuming complementary foods at 3–4 months. The early introduction of complementary foods was once believed to promote a healthy appetite, food acceptance, and a full night of sleep; however, those theories have been discredited. Delaying the introduction of solid foods till 6 months and thereby extending formula or breastfeeding has been shown to decrease gastrointestinal infections and morbidity rates in infants [16, 28]. Delaying complementary feeding allows for the infant to gain more benefits from breastfeeding.

Complementary foods need to meet the infants' growing nutritional needs. These foods need to be nutritionally adequate to provide enough energy, macronutrients, and micronutrients to support normal development [34]. Traditionally, the first solid foods a baby consumes are cereals and other grain-based products. Fruits and vegetables are normally the next food groups introduced, with meats and other protein-rich foods being introduced later. Breast milk is a poor source of iron and zinc; the ideal complementary food would be rich in both of these micronutrients. Some have suggested that iron-rich foods like meat should be one of the first solids consumed [35]. Currently, meats are not consumed regularly until 7–10 months of age, with other food groups starting at 4–6 months [36].

The physical act of feeding is important to a developing infant. As they age, infants become more aware of feeding methods and eventually learn how to self-feed by mimicry. The development of gross and fine motor skills is encouraged through self-feeding. Formation of emotional connections with other people is facilitated through feeding. Many of the infant's attitudes about food, hunger, and appetite can be affected by the type of relationship the infant forms with his or her feeder. The frequency of feedings should start with 2–3 meals a day from 6–8 months and then increase to 3–4 meals per day to the end of toddlerhood (9–23 months). Feeding should promote a positive correlation with food, appetite, hunger, and emotional relationships. Food safety is also a concern for infant nutrition. Food must be prepared in a hygienic environment including clean water, utensils, and storage facilities.

The proper transition to solid foods is key to the growth and development of infants. The type of foods and feeding methods presented to the infant have an impact on food preferences and future eating habits [36]. There have been correlations made between unbalanced diets in infancy and being overweight or obese later in life [37]. The protein content of the infant's diet may be related to the risk of obesity. Diets high in protein in infancy have been shown to be associated with obesity later in childhood. A balanced amount of all the macronutrients and micronutrients is critical to the health and growth of the infant. Stunting is often the result of inadequate micronutrient intakes and can result in growth and developmental retardation.

Summary

There is no doubt that human milk is the best food for a human infant. The reasons are endless and convincing. However, it is a challenge for the formula industry to make the best alternative to human milk. There are, were, and always will be some women who are unable or choose not to follow recommendations to breastfeed for whatever reason. We have a responsibility to those mothers and their infants to produce a formula that meets their needs. Future changes in infant formulas are likely to be

designed to have a positive effect on physical, mental, and immunological outcomes. Our hope is that in the future formula will include bioactive ingredients that perform some of the same functions found in that exemplary fluid, human milk.

When breast milk is no longer adequate, the correct approach needs to be taken for complementary feeding. Incorporating the themes of timely feeding, nutritionally sound and safe meals, and properly administering meals into complementary feeding will prompt appropriate development and growth [35]. The importance of proper complementary feeding practices is not normally stressed; however, several incentives have been proposed to address the current practices. The lengthening of exclusive breastfeeding to 6 months and delaying complementary feeding until then is recommended. The benefits for this are similar to the benefits of breastfeeding. Molding the infant's diet to include appropriate amounts of micronutrients, especially iron and zinc, is a primary concern for parents. A suitable transition to a diet of solid foods sets the pace for the rest of the infant's life.

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Young Children: Preparing for the Future

4

Jennifer Shiel, Lindsay M. Boland, and Kathrina Prelack

Keywords

Children · Growth charts · Pediatric malnutrition · Dietary recommendations · Childhood obesity Physical activity · Food insecurity · Food allergies · Iron-deficiency anemia · Dental caries

Key Points

- A well-balanced diet can provide the energy and nutrients that children need to grow, learn, and play.
- The Centers for Disease Control and Prevention growth charts are typically used to monitor growth.
- The Dietary Guidelines for Americans and MyPlate are appropriate tools to support healthy food choices for children.
- Childhood overweight and obesity is a multifactorial issue which requires a comprehensive approach, including diet, physical activity, psychological support, behavior modification, and caretaker involvement.
- Food insecurity, iron-deficiency anemia, dental caries, and food allergies are all issues which may affect dietary quality and may necessitate referrals to registered dietitians or nutrition assistance programs.
- Nutritional and vitamin supplements are not necessary for well-nourished children.

Introduction

Childhood is a time of rapid growth and development, and proper nutrition is essential for supporting this. Adequate nutrition not only supports development but can help promote academic success and reduce the risk of chronic diseases such as obesity [1]. It is important for children to establish a

J. Shiel
Clinical Nutrition Department, Shriners Hospitals for Children, Boston, MA, USA
e-mail: jennshiel@shrinenet.org

L. M. Boland
Department of Nutrition, Brigham and Women's Hospital, Boston, MA, USA
e-mail: lboland@bwh.harvard.edu

K. Prelack (✉)
Clinical Nutrition Department, Shriners Hospitals for Children, Boston, MA, USA

Simmons University, Boston, MA, USA
e-mail: kathrina.prelack@simmons.edu

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foundation of healthy dietary habits early on in order to carry these skills into adulthood. Children should have a well-balanced diet providing a variety of nutrient-dense foods in order to ensure adequate nutrient intake. Eating habits can be impacted by a variety of factors, but parents and caregivers play an especially important role in modeling healthy eating behaviors and influencing a child's relationship with food later in life [1].

Monitoring Growth

The Centers for Disease Control and Prevention (CDC) recommends that the World Health Organization (WHO) growth standards be used to monitor the growth of children under 2 years of age and the CDC growth charts for children age 2 years and older [2]. Children under 2 years should be weighed without clothes or diapers and measured in a recumbent position. Children over the age of 2 should be weighed and measured in light clothing without shoes and standing for a measure of stature. The growth charts can be used to plot trends in weight-for-age, height-for-age, head circumference-for-age, weight-for-height, and body mass index (BMI)-for-age. Trends for these measures should be monitored and can be used to determine whether there is potential nutritional risk [3].

BMI is measured in children over the age of 2 years and can be used as a screening tool to determine underweight, overweight, or obesity, paying particular attention to changes in percentiles and z-scores over time [4]. A BMI below the fifth percentile for age indicates underweight, while between the 85th and the 95th percentiles indicates overweight, and a BMI greater than the 95th percentile indicates obesity [3]. It is important to note that other factors can impact growth trends, such as gestational age, chronic illness, and biological parents' stature, and therefore these should also be taken into account when trending growth over time [3].

Assessing Growth and Nutrition Risk

Assessment of growth involves close monitoring of growth chart percentiles and z-score trends. Growth chart percentiles indicate where a child fits compared to the reference standard [5]. Z-scores denote units of standard deviation from the median and can detect movement toward or away from the median. Z-scores are more sensitive and precise than percentile changes [6]. Both weight-for-length and BMI-for-age assess the appropriateness of an individual's weight compared to length or height, even in patients with chronic malnutrition or growth stunting. Further evaluation is often warranted if the weight for length z-score is less than −1 or at approximately the 10–15th percentile [7]. Growth velocity is another measure used to assess growth and identify patients at nutrition risk.

Pediatric Malnutrition

Pediatric malnutrition is defined as an imbalance between nutrient requirement or intake and expenditure or loss, resulting in cumulative deficits of energy, protein, or micronutrients that negatively affect growth, development, and other relevant outcomes. The etiology of malnutrition can be illness related or non-illness related. Illness-related malnutrition occurs when a disease or injury directly results in nutrient imbalance mechanisms including decreased intake, altered nutrient utilization, increased nutrient losses, or hypermetabolism not matched by intake [8]. Non-illness-related malnutrition can be a result of environmental, socioeconomic, or behavioral factors directly contributing to decreased nutrient intake or delivery. The diagnosis of malnutrition includes pediatric malnutrition which can be classified as either acute (<3 months) or chronic (>3 months). Malnutrition diagnostic

Table 4.1 Primary indicators of pediatric malnutrition when single data point is available (use weight-for-length or weight-for-height z-scores from the growth chart. Use only BMI for children >2 years old [9])

Indicator	Mild malnutrition	Moderate malnutrition	Severe malnutrition
Weight-for-height *z*-score	−1 to −1.9 *z*-score	−2 to −2.9 *z*-score	−3 or greater *z*-score
BMI-for-age *z*-score			
Length/height-for-age *z*-score	No data	No data	−3 *z*-score
Mid-upper arm circumference	Greater than or equal to −1 to −1.9 *z*-score	Greater than or equal to −2 to −2.9 *z*-score	Greater than or equal to −3 *z*-score

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Table 4.2 Primary indicators of pediatric malnutrition—*two* or more data points available [9]

Indicator	Mild malnutrition	Moderate malnutrition	Severe malnutrition
Weight gain velocity (<2 years of age)	Less than 75% of the norm for expected weight gain	Less than 50% of the norm for expected weight gain	Less than 25% of the norm for expected weight gain
Weight loss (2–20 years of age)	5% usual body weight	7.5% usual body weight	10% usual body weight
Deceleration in weight-for-length/height *z*-score	Decline of 1 *z*-score	Decline of 2 *z*-score	Decline of 3 *z*-score
Inadequate nutrient intake	51–75% estimated energy/ protein need	26–50% estimated energy/ protein need	≤25% estimated energy/ protein need

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criteria often includes the following: weight-for-length z-scores (<2 years old), BMI-for-age z-score (>2 years old), height- or length-for-age z-score, mid-upper arm circumference (MUAC) z-score (3 months to 18 years), MUAC measurement (6 months to 5 years), weight gain velocity (1 month to 2 years), weight loss (2–18 years), deceleration in weight-for-length or BMI-for-age z-score, and inadequate nutrient intake (Tables 4.1 and 4.2) [9].

Nutrition Guidance

Energy and Nutrient Needs

Estimated energy requirements are based on age, weight, height, sex, and level of physical activity. Table 4.3 shows the estimated energy requirements for different gender and age groups. The table also states the recommended dietary allowance amounts and adequate intakes for selected nutrients. Requirements for energy and most nutrients rise steadily with age.

A diet rich in fiber provided by fresh fruits and vegetables, whole grains, and legumes is essential for preventing constipation [11]. Several studies have indicated that a diet rich in fiber is also associated with better nutrient intake, reduced risk of obesity, and better cognitive function in children [12–14]. These improved health outcomes are associated with the fact that whole grains and legumes are excellent sources of fiber, protein, B vitamins, and minerals including potassium and magnesium [15]. Simple swaps to whole grain breads and pastas, as well as including fruits and vegetables at snack time, can increase daily fiber intake. When increasing fiber content, ensure adequate fluid intake to prevent worsening of constipation [16].

Table 4.3 Recommended dietary allowance (RDA) and adequate intake (AI) for selected nutrients in childhood based on the estimated energy requirements (EER) for age, weight, height, and sex at a sedentary level of activity [10]

Gender and age (year)	EER energy (kcal/day)	RDA protein (g/day)	AI fiber (g/day)	RDA iron (mg/day)	AI calcium (mg/day)	RDA vit D (IU/day)
Male (1–3)	1000	13	14	7	700	600
Male (4–8)	1400	19	19.6	10	1000	600
Male (9–13)	1800	34	25.2	8	1300	600
Female (1–3)	1000	13	14	7	700	600
Female (4–8)	1200	19	16.8	10	1000	600
Female (9–13)	1600	34	22.4	8	1300	600

Adapted from Dietary Guidelines 2015–2020 [10]

Fluids in the diet should be provided primarily by water and milk. Milk not only contributes to daily fluid needs but also provides protein and several micronutrients including calcium and vitamin D. Various food sources with high water content, such as fruits and vegetables, can contribute to fluid intake [17]. Fluid requirements can be calculated based on the weight of the child, calculating 100 mL of fluid/kg of body weight under 10 kg (22 lb.), and adding 50 mL/kg up to 20 kg (44 lb.), and another 20 mL/kg above 20 kg [17, 18]. The requirement for fluid is increased with physical activity, fever, vomiting, diarrhea, and other medical conditions as well as hot, dry, or humid weather [17, 18].

Sugar-sweetened beverages, including soda, sports, and energy drinks, are an increasing concern in children's diets. Evidence suggests that consumption of these beverages is associated with overweight and obesity in children, as well as increased risk of dental caries [19–21]. The WHO therefore recommends limiting free sugars to less than 10% of total energy intake. Free sugars include sugars added to food and drinks by the consumer or manufacturer, as well as sugars naturally found in fruit juices, syrups, and honey [20].

Children consuming a diet in compliance with the Dietary Guidelines for Americans (see below) are likely to consume adequate amounts of vitamins and minerals. However, children's diets may often be below the RDA for iron, calcium, or vitamin D. Dietary strategies for increasing iron intake and absorption include limiting milk or soy beverage intakes, consuming meat and meat alternatives along with a source of vitamin C to increase absorption, and including iron-fortified breakfast cereals in the diet. Calcium can inhibit iron absorption, so calcium-rich products should therefore be consumed at a different time than foods containing iron. If calcium is a concern, intake can be increased by offering a variety of low-fat dairy products, dark-green leafy vegetables, and calcium-fortified foods such as cereal or soy milk. Children who do not consume adequate milk or fortified alternatives daily should consider a supplement in order to ensure adequate intake to meet the RDA of 600 IU/day [22].

Dietary Guidance

The Dietary Guidelines for Americans, 2020–2025 provide recommendations across the life cycle from birth to adulthood [23]. Current average intakes for vegetables, whole grains, and dairy among young children are lower than recommended intake ranges, while exceeding limits for added sugar, saturated fat and sodium. Recommendations for children parallel those for the general US population. They include:

- Consume a variety of vegetables and fruits (particularly whole fruits).
- Choose whole grain over refined grains or starches.
- Include a variety of protein choices such as seafood, lean meats, nuts, beans, eggs, and low fat dairy.
- Limit sodium, added sugars, and saturated and trans fats.

Although 100% fruit juice can be part of a healthy diet, it is low in fiber and should not exceed 4 ounces per day in children. Fats are an important part of the diet supplying vitamin E and essential fatty acids. Fat intake should come primarily from monounsaturated fatty acids (MUFAs) and polyunsaturated fatty acids (PUFAs), such as those found in nuts, seeds, and fish.

The MyPlate resource from the USDA provides education regarding food groups, appropriate serving sizes, and recipes, all geared to support the recommendations made by the Dietary Guidelines [24]. MyPlate plans can be personalized for children and adolescents by entering their age, sex, and physical activity level. Following the personalized recommendations can help children meet their energy and nutrient needs and encourage physical activity.

Healthy Eating Behaviors

As children enter their toddler years, the rate of growth slows, and there is a corresponding decrease in appetite. This can be a great source of worry to parents who may become overwhelmed with the task of achieving nutritional recommendations with a toddler who has suddenly become less interested in food. This decrease in appetite coincides with developmental stages in which asserting independence and establishing self-control are central to the child.

Ellyn Satter's [25] work on eating competence recommends a division of parental and child responsibility. It is the parent's responsibility to offer a variety of healthy foods at meals and snacks, and the child's responsibility to decide how much they will eat, and even whether they will eat at all. Research by Fildes et al. [26] has shown that exposure to a variety of foods in infancy can increase acceptance in toddler years, and it is established that children with repeated exposure to different foods have increased acceptance of those foods [27].

The following suggestions may help to encourage children to eat a variety of healthy foods:

- Offer a variety of different foods starting in infancy. A new food may need to be offered up to 15 times before it is accepted.
- Serve new foods in small portions, along with familiar foods, and at the beginning of the meal when the child is hungry and more likely to try something new.
- Try eating regular mealtimes together as a family as much as possible, and model good food choices for children.
- Mealtimes should be a time for socialization and nourishment, and not a time for television or working.
- Discourage "grazing" throughout the day. Instead, offer regular meals and snacks during the day, giving the child a chance to build up an appetite between eating occasions.
- For safety, children should be seated and supervised any time that they eat.
- Encourage children to participate in food selection at the grocery store, food preparation, and serving of the meal.
- Serve age-appropriate portion sizes, and use MyPlate as a meal portion tool.
- Encourage self-feeding and food exploration which will allow the child to become familiar with new tastes and textures.
- Never force a child to eat, and avoid using food as a reward.

Many studies have looked at parent/caregiver feeding style and their influence on eating behaviors in young children. An authoritative feeding style where parents are supportive, nondirective, and in tune with a child's preferences while still creating boundaries and expectations around food intake is associated with the healthiest outcomes [28]. Using this approach, children learn to eat from internal cues of hunger instead of external indicators such as time of day or emotional/social influences. Parental modelling of healthy eating practices and a supportive home environment that includes

family mealtimes and physical activity are also important in establishing such healthy eating patterns [29]. Conversely, a highly directive or demanding parenting style around food, known as the authoritarian feeding style, can negatively impact eating patterns and weight. The use of controlling feeding practices that include pressure or restriction disrupts the development of healthy eating behaviors including self-regulation and instead lead to an unhealthy relationship with food. Over the long term, this can reinforce negative behaviors such as eating in the absence of hunger and emotional eating [30].

Nutrition Concerns During Childhood

Childhood Obesity

The prevalence of overweight and obesity in children has been rising steadily over the past three decades. According to CDC data for 2015–2016, the prevalence of obesity, defined as a BMI-for-age greater than the 95th percentile, was 18.5%, with the highest rates seen in 12–19-year-olds [31]. Besides the social and emotional problems associated with overweight status, these children are also at higher risk for chronic diseases, including hypertension, the beginnings of atherosclerosis, and type 2 diabetes [32].

The causes of overweight are multifactorial, and approaches for prevention and treatment should address not only diet and physical activity but also necessary psychological support, behavior modification, and caregiver involvement. The goal of treatment is to slow the rate of weight gain and allow for growth in height to catch up to weight. In children with severe overweight, moderate weight loss may be advised but should be overseen by a physician and registered dietitian. When calories are restricted, it becomes difficult to achieve sufficient intake of necessary vitamins and minerals; therefore, nutrient-dense foods must be emphasized. A focus on setting small attainable goals over time can help promote lifestyle changes as opposed to setting restrictions that may initially offer results, but will not prove to be sustainable for the long term.

Parents should be encouraged to follow the suggestions outlined above for improving intake of a variety of healthy foods. In addition, three factors have a pronounced impact on weight status in children: physical activity, consumption of sugar-sweetened beverages, and television viewing.

The importance of exercise for children was emphasized above. Children should be encouraged to go outside, participate in sports, and engage in active play throughout the day. Children age 6 years and older are recommended to have at least 60 minutes of physical activity daily, through a variety of activities [33]. Sedentary activities, such as screen time, video games, sitting in a stroller, and being in a car, can contribute to overweight and obesity in children. Sedentary activities use very little energy, and time spent viewing television often replaces physical activity in the daily schedules of children, and therefore should be limited. Sugar-sweetened beverages have been shown to be a significant factor in the development of obesity in children [23]. These beverages, including soft drinks and artificially sweetened fruit beverages, offer little or no nutritional value and should be offered in child-sized portions on special occasions, rather than for daily intake.

Food Insecurity

A 2018 report from the USDA noted that approximately 7% of American children were food insecure, meaning households were unable to provide adequate nutritious food for children due to the lack of resources [34]. The characteristics of households more likely to be food insecure include incomes near or below the poverty level; headed by a single parent; and Black- or Hispanic-headed

households. Chronic food insecurity can result in poor nutrition and poor academic performance. Children from low-income, food-insecure households are at increased risk of iron-deficiency anemia (see below). Children from food-insecure households should be referred for food assistance programs such as the National School Lunch and Breakfast Programs, Food Stamps, and Special Supplemental Nutrition Program for Women, Infants, and Children (WIC).

Food Allergies and Sensitivities

True food allergies involve an antibody response to large molecules in the blood; therefore, the only way to make a diagnosis is to test for antibodies. Food allergies are estimated to affect about 8% of American children, with the most common food allergens being milk, eggs, fish, crustacean shellfish, wheat, soy, peanuts, and tree nuts [35]. Children may outgrow allergies to milk, eggs, and soy. Previously, the consensus among the medical community had been to avoid early introduction of potential common food allergens, in particular peanuts. However, recent reviews have shown there is no need to delay the introduction of potentially allergenic foods beyond 6 months of age, but that they should not be introduced before 4 months of age [36]. Recent evidence also suggests that early introduction of peanut products such as bamba or peanut powder (avoiding whole peanuts due to choking hazard) can actually prevent peanut allergy [36].

When a true food allergy is present, the only remedy is strict avoidance of the offending food. Children with food allergies must be taught skills to recognize and refuse foods to which they are allergic and to recognize symptoms of a possible allergic attack, such as tingling of the mouth and throat. Children who have serious food allergies should carry a supply of epinephrine in case of accidental ingestion of the allergen. If whole food groups, such as dairy, must be eliminated, a dietitian should work with the family to ensure that all nutrient needs are met. See Chap. 20 for more about food allergies. In contrast, children with food sensitivities or intolerances may experience symptoms such as nausea, vomiting, headache, or hives, but without an antibody response. Foods that are commonly implicated in intolerances include lactose-containing dairy products or gluten.

Iron Deficiency Anemia

Iron deficiency anemia is a global problem, affecting approximately half of children under the age of 5 around the world [37]. The overall rate is lower in the United States, estimated at approximately 6% of children age 5 years and under; however, low-income children are at greater risk [37]. Iron is vital for children's neurological development, and iron deficiency anemia may lead to developmental issues with learning, memory, or behavior [37]. Strategies to improve iron intake were discussed in the Nutrition Guidance section. When dietary methods to improve iron intake do not resolve the problem, iron supplements may be necessary. When iron deficiency is suspected, it is important to evaluate serum markers before suggesting iron supplementation.

Dental Caries

Oral health is an important part of a child's overall health, and dental caries have become one of the more common childhood chronic diseases. About one in five children aged 5–11 years old will have at least one decayed and untreated tooth, and children in lower-income families are twice as likely to have dental caries [38]. Children should routinely have dentist visits and in between should be encouraged to actively brush and floss daily, and especially after meals. Dietary recommendations are to

avoid sodas or sugar-sweetened beverages and snacks, and instead replace these with water throughout the day, as well as fruits and vegetables at snack times. Calcium and vitamin D intake is also important for building strong bones and teeth, so meeting intake goals through inclusion of a variety of sources (dairy foods, dark-green leafy vegetables) is essential.

Vitamin and Mineral Supplementation

When children consume a well-balanced and nutrient-dense diet, vitamin and mineral supplements are not necessary. Some children may benefit from iron or vitamin D supplementation, as noted above. When supplements are given, parents should be cautioned to use a brand specifically formulated for children and to make sure that the doses given do not exceed the tolerable upper intake for the child's age/weight. Iron supplements should be stored out of children's reach, as excess iron intake from supplements is a major cause of poisoning in children. Herbal supplements are not tested for safety in children and are therefore not recommended.

Conclusion

Pediatric nutrition has a major impact on growth and development. Childhood is an important time to establish healthy eating and activity behaviors, in order to serve as a foundation for healthful practices over the life span. It is therefore important to ensure that children are offered a variety of nutrient-rich foods early on. Energy-dense foods, such as refined carbohydrates and sugar-sweetened beverages, should be limited as they can lead to adverse health outcomes. Parents/caregivers should be encouraged to practice Ellyn Satter's division of responsibility, where "parents are responsible for deciding *what*, and children are responsible for deciding *how much*" [25]. In addition to healthy eating habits, children should also be encouraged to play and engage in physical activity every day. Parents/caregivers should act as role models and model healthy living behaviors for their children to provide the framework for lifelong healthful habits.

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Nutrition in Adolescence

5

Jamie S. Stang and Junia Nogueira de Brito

Keywords

Adolescent · Adolescent nutrition · Disordered eating · Adolescent obesity

Key Points

- Rapid changes in body weight, shape, and composition due to pubertal growth place adolescents at high risk for body dissatisfaction, disordered eating, and health-compromising eating behaviors.
- Many adolescents skip meals but frequently snack.
- Adolescence is often a time of increased athletic activities, disordered eating behaviors, experimentation with smoking and alcohol and other factors that all impact nutritional needs.
- A stepped approach to obesity treatment is recommended for adolescents, with strategies in each step based on the degree of obesity and the presence of comorbid conditions.
- Screening for body mass index and hypertension should be performed at least annually.
- Screening for hyperlipidemia and insulin resistance is recommended only for adolescents who are obese or those with a family history of cardiovascular disease and/or type 2 diabetes.

Nutrition, Growth, and Development

Adolescence is a time of dramatic physical, social, and cognitive development, which directly affects nutritional status. Since the chronological age of sexual maturation varies dramatically, Tanner's stages are generally used to describe periods of adolescent growth and development based on the assessment of secondary sexual characteristics. Approximately 15–25% of adult height is gained during early to middle adolescence (typically within Tanner stages 2 and 3); the average gain among females is 9.5 in (24.1 cm) with up to 12 in (30.5 cm) gained by males [1]. Up to half of adult body weight is gained during the growth spurt. In females, gains in height precede weight gain by about 3–6 months, dramatically slowing around the onset of menses. Girls will gain an average of 18 lb (8.1 kg) per year during the active growth spurt, with up to 14 lb (6.3 kg) gained after menses [1]. Body fat levels rise among females throughout adolescence as a result. Consequently, body composition changes tremendously within females which places them at risk for body dissatisfaction, dieting,

J. S. Stang (✉) · J. N. de Brito
Division of Epidemiology and Community Health, University of Minnesota School of Public Health, Minneapolis, MN, USA
e-mail: stang002@umn.edu; nogue013@umn.edu

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and disordered eating [2]. In males, peak weight and height accretion occur simultaneously [1]. Males will gain about 20 lb (9 kg) per year during the peak of growth; however, body fatness decreases due to the larger percentage of lean body mass which is gained reflecting the increase in testosterone.

Approximately half of adult bone mass is gained during adolescence, with more than 90% of adult bone mass formed by age 18 [1, 3]. Adolescence is a critical time for bone development, and bone accretion is sensitive to adequate intakes of many nutrients including calcium, vitamins D and K, phosphorus, boron, strontium, magnesium, iron, and protein [3]. Nutrient and energy needs are higher during adolescence than at any other period in life as a result of the velocity of physical development. The growth spurt ceases by age 16 in females but may continue in small increments in males until age 20 [1].

Social and cognitive development also occurs rapidly during adolescence. The teenage years are a time during which individuals develop a sense of personal identity and a moral and ethical value system [4]. Self-esteem is critical during adolescence and can be dramatically affected by changes in body shape and size and the timing of development in comparison to other adolescents. Peer pressure peaks between the ages of 13 and 16; thus, teens are very self-conscious about their appearance and strive to adopt behaviors consistent with their peer group [4]. In terms of nutrition, this can place adolescents at risk of nutrition deficiencies and disordered eating. Some of the common behaviors are described below.

Nutrition Behaviors and Their Effects on Nutritional Status

US adolescents do not consume adequate amounts of many nutrients including folate; vitamins A, B6, C, D, and E; and iron, zinc, magnesium, phosphorus, potassium, and calcium [5]. Dietary fiber intake is generally low, while teens exceed recommendations for total and saturated/solid fats, sodium, and added sugar. Only about 11% of teens meet recommendations for fruit intakes, and less than 2% meet recommendations for vegetable intake (even with the inclusion of starchy vegetables such as fried potatoes) [5, 6]. Alarmingly, more than 6% of teens consume no fruit, and up to 8% consume no vegetables on an average day [5–7]. About half of adolescents consume less than the recommended amounts of total protein foods, and only 20% of teen males and less than 5% of teen females consume the recommended amounts of dairy each day.

Meal skipping is common among adolescents and increases with age. Between 14% and 27% of teens skip breakfast on an average day, with one-third reporting daily breakfast consumption [6–9]. Almost one in every four teens skips lunch and about 8% skip dinner on any given day [6–9]. Skipping meals can reduce the intakes of many nutrients. As a result of skipped meals, adolescents frequently snack.

Snacking is reported by 83% of teens with almost half reporting three or more snacks per day [5, 6–12]. Snacks provide about 25% of the daily energy intake, but nearly 50% of daily added sugar intake [5, 6, 9–12]. Soft drinks are the most common snack reported by adolescents and are the single largest source of energy and added sugar in their diets [5, 6, 10–12]; soda accounts for 9% of daily calories and 45% of daily sugar intake alone [5, 6, 10, 12]. It is imperative that teens be encouraged to consume snacks wisely and that parents be advised to provide easy access to healthy snack foods, such as flavored or sparkling water, baked chips with salsa, crackers, low-fat cheese, whole grain ready-to-eat cereal and low-fat milk, or hummus with vegetables or pita chips.

The prevalence of disordered eating behaviors among adolescents, and in particular among adolescent girls, tends to be alarmingly high. In fact, the Youth Risk Behavior Surveillance Survey (YRBS) suggests that 66% of Hispanic, 59% of White non-Hispanic, and 55% of Black non-Hispanic girls report dieting [7]. Among males, 46% of Hispanic, 29% of Black, and 31% of White males report dieting. This is particularly concerning given unhealthy food patterns that are often associated with dieting such as fasting and severely restricting energy intake which may result in fatigue, impaired growth and sexual maturation, irritability, poor concentration, impulse to binge, and increased risk for disordered eating.

Dieting is a known risk factor for developing eating disorders and disordered eating patterns. Eating disorders are defined by the frequency, intensity, and individual patterns noted below [9, 13, 14]. They are discussed in more detail in Chap. 23.

- Anorexia nervosa: An eating disorder characterized by extreme weight loss, poor body image, and irrational fear of weight gain and obesity.
- Bulimia nervosa: A disorder characterized by repeated bouts of uncontrolled rapid ingestion of large quantities of food (binge eating), followed by self-induced vomiting, fasting, vigorous exercise to prevent weight gain, or use of laxatives or diuretics.
- Binge-eating disorder: A disorder characterized by periodic binge eating, which normally is not followed by vomiting or the use of laxatives. People must experience eating binges twice a week on average for over 6 months to qualify for this diagnosis.

Disordered eating behaviors is a term that encompasses many health-compromising behaviors seen with actual eating disorders, such as binge eating, purging, fasting, and excessive exercise to burn calories, but are present at a level that does not meet with full classification for eating disorders [13, 14]. It is estimated that such unhealthy and extreme weight-control behaviors are used by approximately 10–20% of the adolescent population; however, estimates for some behaviors can exceed 40% [13, 14]. Although not all disordered eating behaviors meet the formal criteria needed to be defined as an eating disorder, they can still negatively impact adolescents' health and development. Therefore, adolescents who have been found to have a nutrition-related health risk, such as an eating disorder, should be referred for in-depth medical assessment and nutrition counseling.

Nutrition Concerns of Athletes

Sports nutrition enhances the athletic performance of adolescent athletes and enables them to optimize their training and recovery. Therefore, dietary intakes of athletes should follow the general healthy eating recommendations while also recognizing that high levels of training and competitive physical activity, combined with growth and development, increase adolescents' needs for carbohydrate, protein, and select vitamins and minerals (e.g., vitamin D, calcium, phosphorous, iron). Athletes should be encouraged to eat a pre-event meal containing proper amounts of carbohydrates to increase body glycogen stores but should not consume foods high in fat, protein, and/or dietary fiber for at least 4 hrs prior to exercise as those foods may bring about indigestion and physical discomfort [15]. Post-event meals (up to 4 hrs) should contain 1–1.2 g/kg/h of foods high in carbohydrate and adequate amounts of non-caffeinated fluids (e.g., water, milk) [15]. Teen athletes should start exercise hydrated and maintain optimal hydration status during and after sports participation. The type, timing, and amount of foods and fluids in the pre- and post-event meals should be individualized not only according to the teen's needs but also to their preferences and tolerance.

In certain instances, such as during prolonged, vigorous sports participation, the use of ergogenic aids to improve energy availability (such as sports drinks, carbohydrate, creatine, caffeine) and promote recovery (carbohydrate, protein, and essential amino acids) may be recommended by coaches or trainers [15]. However, they are not always safe or effective. The consumption of sports drinks in place of water may lead to excessive energy intake consumption, which increases youth risk for overweight and obesity [16]. Common ergogenic aids used by teens include creatine, amino acids or protein powders, caffeine, carnitine, anabolic steroids, anabolic steroid precursors such as dehydroepiandrosterone (DHEA) and androstenedione, beta-hydroxy-beta-methylbutyrate, growth hormone, and Xenadrine [17]. Steroids and ergogenic aids including high (physiologically active) doses of caffeine from supplements are forbidden by national and the National Collegiate Athletic Association (NCAA) regulations, yet few high school athletic programs test athletes for their use.

Nutrition Management of Chronic Health Issues

Overweight and Obesity

Appropriateness of weight status for teens is assessed by calculating body mass index (BMI), a measure of a person's weight (kg) divided by their height^2 (m^2). The Centers for Disease Control and Prevention (CDC) BMI calculator, available online at https://www.cdc.gov/healthyweight/bmi/calculator.html [18], is an accurate and quick way to calculate and find corresponding BMI-for-age percentiles for youth aged 2 through 19 years to determine the appropriateness of weight status. Adolescents with a BMI > 85th but <95th percentile are considered overweight, while those with a BMI ≥95th percentile are considered obese [19]. Growth curves based on the CDC BMI values are available and should be incorporated into the medical records of all teens.

In 2015–2016, the prevalence of obesity was 21% among youth aged 12–19 years [20]. Obesity prevalence was higher among Black (18%) and Hispanic (18%) students than among White students (13%). A range of medical and psychosocial complications accompanies overweight and obesity among adolescents, including hypertension, dyslipidemia, insulin resistance, hyperglycemia, type 2 diabetes mellitus, sleep apnea and other hypoventilation disorders, orthopedic problems, liver disease, body image disturbances, and lowered self-esteem [19, 21, 22]. Longitudinal studies of obesity and chronic disease risk among youth suggest an increased risk of morbidity and premature mortality from coronary heart disease, stroke, hypertension, type 2 diabetes, and asthma among adults who were overweight or obese during adolescence [21].

All adolescents should be screened for appropriateness of weight-for-height yearly, or more frequently if there are concerns about excessive weight gain (or loss) for height. Teens with multiple risk factors for obesity require an in-depth medical assessment to diagnose potential comorbid complications [19, 22]. Adolescents who are assessed as overweight or obese should have their medical and family history (e.g., maternal history of diabetes type 2 or gestational diabetes, dyslipidemia, family history of diabetes in first- or second-degree relative, signs of insulin resistance [hypertension, dyslipidemia, polycystic ovary syndrome]) assessed and screened for cardiometabolic risk factors (e.g., glucose, cholesterol, triglycerides, blood pressure, alanine aminotransferase [ALT]), associated with adolescent overweight or obesity [22–25]. Adolescents with overweight or obesity should also have panel pancreatic antibodies tested to rule out the possibility of type 1 diabetes.

Table 5.1 lists common cardiometabolic biomarkers and their respective cut-points for screening pediatric overweight- and obesity-related cardiometabolic risk factors. Table 5.2 provides an overview of assessment and referral recommendations based on an adolescent's personal risk factors.

Table 5.1 Recommended indices for common chronic health issues in adolescents

	Acceptable	Borderline	Unacceptable
Fasting plasma glucose	<100 mg/dL	≥100–<126 mg/dL	≥126 mg/dL
Hemoglobin A1c	5.7%	<6.5%	≥6.5%
Fasting cholesterol			
Total cholesterol (mg/dL)	<170 (<4.4 mmol/L)	170–199 (4.4–5.15 mmol/L)	≥200 (≥5.18 mmol/L)
Non-HDL cholesterol (mg/dL)	<120 (<3.11 mmol/L)	120–144 (3.11–3.73 mmol/L)	≥145 (≥3.76 mmol/L)
LDL cholesterol (mg/dL)	<110 (<2.85 mmol/L)	110–129 (2.85–3.34 mmol/L)	≥130 (≥3.37 mmol/L)
HDL cholesterol (mg/dL)	>45 (<1.17 mmol/L)	40–45 (1.04–1.17 mmol/L)	<40 (≥1.04 mmol/L)
Triglycerides (mg/dL)	<90 (<2.33 mmol/L)	90–129 (2.33–3.34 mmol/L)	≥130 (≥3.37 mmol/L)
ALT			
Boys	>25 U/L		
Girls	>22 U/L		

Source: Based on Refs [22–25]
Notes: Fasting is defined as no caloric intake for at least 8 hrs

Table 5.2 Assessment and screening recommendations for health promotion among adolescents

Health concern	Screening and assessment recommendation
Anthropometric measurements	Measure and plot height, weight, and BMI Review weight status with teen and family Teens who are overweight: provide step 1 counseling or refer to a registered dietitian/nutritionist for weight management counseling; schedule follow-up appointments Adolescents who are obese: refer to a comprehensive weight management program for step 2 counseling
Family history of premature cardiovascular disease, diabetes, or obesity	Assess for risk factors for chronic health conditions (hypertension, hyperlipidemia, diabetes) based on family history and weight status as necessary
Blood pressure	Review blood pressure with teen and family In the presence of elevated blood pressure, counsel adolescents and caregivers to follow DASH dietary pattern based on energy needs to achieve ideal body weight Assess changes in blood pressure at follow-up and institute management with medication as needed, if dietary changes have not been successful Refer teens who are overweight and obese to an appropriate weight management program
Blood lipids	Review blood lipid indices with teen and family Order blood lipid panel for overweight or obese adolescents Adolescents who are overweight: provide counseling regarding DASH diet based on energy needs to achieve ideal body weight or refer to a registered dietitian/nutritionist for medical nutrition therapy Adolescents who are obese: refer to a comprehensive weight management program Up to 2 g/day of plant sterols or stanols can be recommended for use by adolescents Manage dyslipidemia with medication if dietary changes and weight loss are not effective
Dietary intake and eating behaviors	Assess usual food intake using 24-h recall or 3- to 7-day food diary Provide appropriate nutrition counseling or refer to a registered dietitian/nutritionist for medical nutrition therapy as needed
Physical activity and sedentary activity	Review usual daily physical and sedentary behavior patterns Discuss recommendation for at least 60 min/day of moderate-to-vigorous physical activity Emphasize the importance of limiting sedentary activity, for example, limiting screen time to no more than 2 hrs/day
Diabetes	Assess for family history of diabetes, presence of acanthosis nigricans, and symptoms consistent with diabetes among overweight or obese adolescents Review fasting blood glucose levels with teens and caregivers or refer to a primary care provider for treatment and measurement of a fasting blood glucose level if laboratory data are not available Provide medical nutrition therapy and nutrition counseling as appropriate Refer teens who are overweight and obese to a comprehensive weight management program

Adapted from the US Department of Health and Human Services, National Institutes of Health, National Heart, Lung, and Blood Institute [24]

Treatment for overweight and obesity among adolescents is based on the degree of excessive body fat and the presence of comorbid health conditions [26]. Overweight teens with no personal risk factors or significant family history should follow Step 1 treatment guidelines which includes advice to:

- Consume five or more servings of fruits and vegetables each day.
- Remove sugar-sweetened beverages from the diet including soft drinks, sports drinks, energy drinks, fruit drinks, lemonade, and fruit punch.

- Limit fruit juice to 6 oz. (180 mL) per day or less of 100% fruit juice.
- Participate in at least 60 min of moderate to vigorous physical activity daily. Muscle- and bone-strengthening physical activity should also be performed at least 3 days a week.
- Limit discretionary screen time; many parents opt for 2 hrs or less per day.
- Limit intake of fast foods, convenience foods, and foods with added fats and/or sugars.

If Step 1 has not resulted in weight maintenance or modest weight loss within 2–3 months, teens should move on to Step 2 treatment. All adolescents who are overweight and with personal risk factors should begin treatment at Step 2 as should all teens who are obese. Recommendations for Step 2 include all of those in Step 1 plus:

- Keep discretionary screen time to 1 hour or less.
- Introduce a structured meal plan of 1400–1800 kcal/day that follows DASH dietary guidelines (see Table 5.3).
- Monitor daily food intake and physical activity to assure that adolescents are meeting their goals.

Step 2 should be implemented for 6–8 weeks to determine if weight is maintained or modest weight loss has occurred. If necessary, teens should move to Step 3 (as should all teens who are obese who have significant risk factors), which includes all recommendations from Step 2 plus:

- Weekly visits for at last 8–12 weeks that include structured behavior modification techniques; more frequent contact may be desired or required by some teens.
- Supervised physical activity may be provided to assure that teens are safely able to exercise vigorously.
- Mental health screening with a referral for depression or other identified issues.
- Further structure to meal plans or reduction to 1400 kcal/day may be required; teens should be monitored weekly when on low-calorie diets.

Step 4 treatment is implemented when Step 3 is not effective, or for teens who are significantly obese and have comorbid conditions that require intensive intervention. This level of care is provided only in a tertiary care center that specializes in pediatric obesity and may include medication management, meal replacement, very-low-calorie or protein-sparing-modified fast diets, or bariatric surgery.

Hypertension

Screening for hypertension is recommended at each medical visit [27]. Classification of resting blood pressure based on the average of three readings are presented in Table 5.4.

Adolescents with a family history of hypertension or hyperlipidemia, who are overweight or obese, who use tobacco, and who report a poor dietary intake and inactive lifestyle should be considered at risk for hypertension [19, 22, 24, 25]. Nutrition counseling according to the DASH diet which encourages teens to decrease sodium intake, to limit fat intake to 35% or less of calories, to reduce the intake of added sugars, and to consume adequate amounts of fruit, vegetables, whole grains, and low-fat dairy products should be provided when hypertension is diagnosed (Table 5.3). Weight loss according to national guidelines (outlined previously in this chapter) should be recommended for teens who are overweight or obese.

Table 5.3 DASH eating plan to reduce hypertension and other chronic diseases: servings per day by food group and total energy intake

Food group	Serving size	1400 kcal	1600 kcal	1800 kcal	2000 kcal
Grains (with whole grains the majority of choices)	One slice bread 1 oz. (28 g) dry cereal 1/2 C (0.12 L) cooked rice, pasta, or cereal	6	6	6	6–8
Vegetables	1 C (0.24 L) raw leafy greens 1/2 C (0.12 L) raw or cooked vegetable 1/2 C (0.12 L) vegetable juice	3–4	3–4	4–5	4–5
Fruits	1 medium fruit, 1/4 C (0.06 L) dried fruit 1/2 C (0.12 L) fresh, frozen, or canned fruit 1/2 C (0.12 L) fruit juice	4	4	4–5	4–5
Milk and milk products (fat-free or low-fat choices) or substitutes	1 C (0.24 L) milk or yogurt 1 C (0.24 L) soy, almond, rice, or other milk substitute 1.5 oz. (42 g) cheese	2–3	2–3	2–3	2–3
Lean meats, poultry, or fish	1 oz. (28 g) cooked meats, poultry, or fish 1 egg	3–4	3–4	≤6	<6
Nuts, seed, and legumes	1/3 C (0.08 L) or 1.5 oz. nuts 2 Tb (30 mL) peanut or other nut butter 2 Tb (30 mL) or 0.5 oz. (14 g) seed 1/2 C (0.12 L) cooked legumes	3/week	3–4/week	4/week	4–5/week
Fats and oils	1 tsp. (5 mL) margarine 1 tsp. (5 mL) vegetable oil 1 Tb (15 mL) mayonnaise 2 Tb (30 mL) salad dressing	1	2	2–3	2–3
Sweets and added sugars	1 Tb (15 mL) sugar 1 Tb (15 mL) jelly or jam 1/2 C (0.12 L) sorbet or gelatin 1 C (0.24 L) lemonade	≤3/week	<3/week	<5/week	<5/week

Source: Based on the US Department of Health and Human Services, National Institutes of Health, National Heart, Lung, and Blood Institute [24]

Table 5.4 Classification of blood pressure children aged 1–13 years [27]

Blood pressure	Children aged 1–13 years	Adolescents aged 13 years or older
Normal	<90th percentile	Systolic: <120 mmHg Diastolic: <80 mmHg
Elevated	>90th and <95th percentile	Systolic: 120 to 129 mmHg Diastolic: <80 mmHg
Stage 1 Hypertension	>95th and <95th percentile +12 mmHg or 130/80 to 139/89 mmHg	Systolic: 120 to 139 mmHg Diastolic: 80 to 89 mmHg
Stage 2 Hypertension	≥95th percentile +12 mmHg or ≥140/90 mmHg	Systolic: ≥140 mmHg Diastolic: 90 mmHg

Notes: Percentiles are for age, gender, and height

Hyperlipidemia

About 25% of US teens have hyperlipidemia [24, 25, 27]. Table 5.1 outlines suggested cut-points for blood lipids and other biomarkers for cardiovascular disease (CVD) specific to teens. Total and LDL cholesterol levels drop by up to 20% during the growth spurt; thus, screening for hyperlipidemia at age 10 and after age 17 will provide the most accurate measures [24, 25]. Youth who have a family history of premature CVD or who are overweight or obese should be screened for blood lipids and CVD biomarkers; however, routine screening for all adolescents is not necessary [24, 25].

The National Institutes of Health, National Heart, Lung, and Blood Institute (NHLBI) has developed the CHILD 1 (Cardiovascular Health Integrated Lifestyle Diet-1) and nutrition guidelines which integrate dietary approaches to prevention hypertension, hyperlipidemia, and obesity [24]. These guidelines include the DASH dietary guidelines (Table 5.3) as well as recommendations for dietary fiber (14 g/day/1000 kcal), limited intake of juice (4–6 oz or 120–180 mL/day), limited sodium intake, limiting fast food meals and salty/savory snacks (such as chips and crackers), and eating breakfast daily.

Diabetes and the Metabolic Syndrome

It is estimated that 215,000 people aged 20 years or younger have diabetes with the majority of the cases being type 1 (a rate of 1.7 per 1000 youth) [28]. The majority of adolescents treated for type 2 diabetes have obesity and a family history of the disease. The disorder among teens appears to be highest among 15–19-year-old American-Indian youth (5.4/1000 among all tribes and 50.9/1000 among Pima Indian teens) [28]. Prevention of type 2 diabetes among youth includes early intervention for overweight or obesity, 60 min of daily activity, and the DASH diet or the Diabetes Prevention Program approach with careful attention paid to removing sugar-sweetened beverages and foods from the diet (Table 5.3).

Metabolic syndrome, the clustering of risk factors for CVD, affects between 2% and 9% of US adolescents; rates are much higher among youth who are obese, estimated at 12–44% [24, 27]. Teens who are overweight and obese and those with a strong family history of CVD and/or diabetes should undergo screening for the metabolic syndrome. Females who are diagnosed with polycystic ovary syndrome may also be at higher risk for the metabolic syndrome. Dietary recommendations to prevent CVD should be encouraged for teens that show evidence of developing the metabolic syndrome.

Nutrition Education and Counseling of Teens

Adolescents make many of their own food choices outside of the home; thus, nutrition counseling should focus on the busy lives of teens and should incorporate strategies for eating at school and other venues away from home. Adolescents should be encouraged to engage in decision-making processes during nutrition counseling. Setting too many goals may seem overwhelming to the adolescent and may reduce the likelihood of following through with changes in behavior. Accordingly, no more than two goals should be set during a counseling session. Communication methods such as text messaging, podcasts, YouTube, and social media (e.g., Instagram) are popular with adolescents and can be a highly engaging way to convey reliable nutrition information. Mobile apps also hold the potential to promote healthy nutrition behaviors and can be suitable to support the quality of nutrition care and counseling delivered by the clinician [29].

Summary

Adolescence is a period of rapid physical and mental growth and development, which requires important nutritional consideration. Health professionals should appropriately educate and counsel teens in healthy eating behaviors, achieving and maintaining a healthy weight, and screen for chronic health issues. Addressing the physical and psychological changes that take place during the adolescence life stage can positively impact current health and wellness, as well as shape health in later stages of the life cycle.

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Nutrition Considerations of Girls and Women

6

Margaret A. Maher

Keywords

Female athlete triad · Polycystic ovary syndrome · Premenstrual syndrome · UTI

Key Points

- Reproductive anatomy and function affect nutrition, appetite, and weight regulation, with effects on female health distinct from those of males.
- Most chronic diseases in women, like men, have diet associations that affect health risk, management, and outcomes. Lifestyle modification, including nutritional intervention, should be considered a first-line intervention when applicable.
- Cultural and social factors that emphasize gender-specific roles, body shape, and weight in females increase the risk of disordered eating and likelihood that women will seek assistance with medical and/or nonmedical management of weight.
- Neural and hormonal regulation of appetite varies by gender and among females at different stages of the life span; these differences may affect success of nutritional and medical management of body composition and appetite.
- The (female) athlete triad, a condition involving inadequate energy intake, menstrual dysfunction, and lowered bone mineral density, is most often recognized in female athletes due to activity-associated pain and stress fractures but also occurs in more sedentary girls and women.
- Polycystic ovary syndrome (PCOS) is associated with the metabolic syndrome including overweight or obesity, insulin resistance and associated glucose intolerance, carbohydrate craving, disordered eating, and other metabolic anomalies. Weight and drug management (with antidiabetics and spironolactone) and attention to carbohydrates, chromium, and cinnamon in the diet may improve insulin sensitivity and reduce negative outcomes.
- Urinary and genital tract conditions may be associated with dietary strategies.
- Women may seek nutritional and medical management strategies for age-related weight and body changes and for relief of premenstrual and peri- and postmenopausal symptoms.

M. A. Maher (✉)
Department of Biology and Nutrition Minor, University of Wisconsin – La Crosse, La Crosse, WI, USA
e-mail: mmaher@uwlax.edu

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Introduction

There are long-recognized associations among female gender, fertility, and food, reflected in imagery of iconic goddesses and mothers. Nutrients may impact, and be impacted by, menstrual cycling, fertility, pregnancy, labor and delivery, lactation, and peri- and postmenopausal adaptations [1]. In addition, reproductive function in women has long-lasting effects on other body systems, such as the skeletal system. Therefore, clinicians providing care for girls and women need a solid understanding of unique nutritional considerations specific to females.

It should also be emphasized that the leading causes of death in women – heart disease, stroke, and cancer (especially breast cancer) – are all associated with diet and other lifestyle factors [2]. Recommendations related to prevention of chronic disease put forth in the Dietary Guidelines for Americans 2015–2020 [3] are applicable to girls and women. Key elements include limiting daily calories from sugars and saturated fats each to less than 10% of total calories; limiting sodium to less than 2300 mg/day; and limiting alcohol intake to one drink per day for women, a notable difference from previous recommendations being the absence of defined limits for intake of total fat and cholesterol [3]. Consumption of a high-quality nutrient-dense diet (calcium, vitamin D, n-3 fatty acids, antioxidants), fewer and less processed foods, and emphasis on plant-based foods are generally recommended to lower chronic disease risk and adverse outcomes [3]. Risk is also lowered with maintenance of a healthy weight (body mass index <25 with waist circumference <35 inches) [2].

Specific Nutrient Considerations for Females

Dietary Fat

No significant associations of total dietary fat with cardiovascular disease risk are included in the current recommendations. However, types and sources of dietary fat are still of great interest and are a topic discussed by Sapp, Petersen, and Kris-Etherton in Chap. 29. While reduction of total fat leads to reduced intake of saturated and trans fats, which have been related to higher risk, it may also lead to reduced intake of unsaturated fats, some of which are related to lower risk. Women's cohort and intervention studies do not support a significant association between total fat intake and risks of breast and colorectal cancers [4]. Consumption of vegetable fats has been associated inversely with diabetes development in women [4]. However, a recent systematic review of studies of high-fat dairy consumption reported either no association or an inverse association with obesity and associated cardiometabolic risk [5]. A recent cohort study revealed that higher fat dairy consumption was associated with less weight gain in middle-aged and older women [6].

Iron

Women of reproductive age are at greater risk of anemia due to iron loss during menstruation and reduced dietary iron intake. Increased anemia risk is associated with heavy or frequent menses, frequent blood donation, and athletic-induced hemolysis and anemia [7]. Signs and symptoms of non-anemic iron deficiency may include fatigue, restless legs, sleep disturbance, and fingernail breakage. Routine iron supplementation for those without iron deficiency is not recommended. When iron deficiency is present, supplementation is recommended as well as education on the difference between heme and non-heme iron sources with regard to bioavailability. Non-heme iron is better absorbed in the presence of meat protein and should be consumed in the same meal with foods rich in vitamin C so as to enhance absorption [7]. Iron deficiency in women who are not menstruating may merit exploration of nutrition intake or occult bleeding from gastrointestinal sources [8].

Folate and Vitamin B_{12}

Adequate periconceptional and pregnancy intake of folate is well known to decrease the risk of neural tube defects and may also help prevent other complications of pregnancy including preeclampsia and miscarriage [9]. Repeated miscarriages and infertility have been linked to insufficient amounts of vitamin B_{12} and folate. Pregnancy and lactation increase the need for both of these micronutrients. Women with history of limiting animal protein sources, such as vegans and vegetarians, during pregnancy or lactation are at higher risk of vitamin B_{12} deficiency and may need supplementation. In older women, vitamin B_{12} deficiency has also been associated with increased hip bone loss [10].

Calcium

Adequate calcium is recommended for women of all ages, especially during adolescence and in young women; this is because peak bone mass is developed during the growing years, up to age 30 [2], as is more thoroughly discussed in Chap. 11. Because of common preoccupation of girls and women with weight, they may consume low levels of foods containing calcium, for instance, replacing milk with diet drinks. Promotion of three servings per day of low-fat dairy products that provide both calcium and vitamin D is recommended. If a vegetarian lifestyle or lactose intolerance are considerations, other calcium-fortified beverages or foods, such as orange juice, or a calcium and vitamin D supplement may be warranted. Though small increases in bone mineral density (BMD) have been observed in studies reviewed, a recent meta-analysis does not report increased dietary calcium or calcium supplementation, beyond general recommendations, as likely to be beneficial in persons over age 50 years [11].

Premenstrual Symptoms, Dysmenorrhea, and Nutrition Associations

Premenstrual Symptoms and Nutrition Associations

Premenstrual symptoms, both physical (breast tenderness, bloating, headache, etc.) and mental (depression, mood swings, irritability, sleep disturbance, etc.), can range from mild to debilitating. Dietary modifications for preventing or reducing premenstrual symptoms have included reductions in salt, sugar, caffeine, whole grains, and meal sizes and multiple botanicals [12, 13]. Diets enriched with whole grains where shown to reduce premenstrual syndrome scores. Individual nutrients, including vitamins B_6 and E, calcium, vitamin D, and magnesium, as well as some herbs, have been linked to improved management of premenstrual symptoms (premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD)) [12, 13]. A review of this area concluded that calcium supplementation (1200 mg/day in divided doses), vitamin B_6 in doses up to 50–100 mg/day, and 20–40 mg/day of chasteberry (*Vitex agnus-castus*) show limited evidence for reduction of one or more premenstrual symptoms [12]. Generally well-controlled studies have not demonstrated much improvement over placebo and may not merit the potentially harmful side effects with routine use. Additional lifestyle interventions with limited evidence base include regular exercise, relaxation, and stress reduction interventions for ameliorating mild to moderate symptoms. Certain SSRIs are considered first-line pharmacotherapy for more severe PMS or PMDD [12, 13]. Additional botanicals including *Angelica sinensis* (dong quai), *Viburnum opulus* and *Viburnum prunifolium* (cramp bark and black haw), *Zingiber officinale* (ginger), *Valeriana officinalis* (valerian), and *Oenothera biennis* (evening primrose) have been studied, although effective PMS treatment has been difficult to document. Myometrial relaxation, anti-inflammatory, and/or various receptor activities have been suggested as mechanisms of actions for active agents in these botanicals [12].

Dysmenorrhea and Nutrition Associations

Dysmenorrhea, the most common gynecologic complaint in females, has varied levels of severity and comorbid conditions. A small number of studies have explored thiamin, magnesium, vitamin E, or n-3 fatty acids and some of the aforementioned botanicals for their effectiveness at alleviating painful menses with limited or nonconclusive results [12].

Females, Body Dissatisfaction, and Nutrition

Girls and women of all ages, many ethnicities, and environments report struggling with body dissatisfaction that may affect nutrition [14]. This dissatisfaction may lead females or their loved ones to express concern and seek healthy or unhealthy ways to change their bodies [15]. While girls and women of all ages report dissatisfaction with their bodies, as women age the self-reported importance of their body shape and size declines [14]. Girls and boys undergo great body changes during adolescence, and sometimes into early adulthood, that can impact body image [15]. Females have monthly body changes associated with menstrual cycling, enormous changes in physical size and shape associated with pregnancy and postpartum, as well as changes in body composition and fat deposition associated with midlife hormonal changes. Referral of girls and women (as well as boys and men) for counseling to explore and resolve body image as well as aging issues may improve nutrition outcomes and mental and physical health. The passage of mental health parity legislation should improve treatment options for individuals and families struggling with eating and body image disturbances.

Weight Management in Females

Body Weight and Reproduction

Weight issues should be addressed with women who are underweight or overweight; this is necessary for both health and reproductive reasons. Help should also be offered to women who have significant anxiety about weight and shape changes associated with varied life stages. Very high or low body mass index (BMI >35 or <20, respectively) are associated with reduced probability of conceiving; this is related to leptin and gonadal axis dysregulation [16]. Pregnancy and peripartum complications as well as the health of prospective children [17] are affected by prepregnancy weight and maternal weight gain. Women should be assessed for disordered eating before they are advised to gain or lose weight; this assessment should continue while they are gaining or losing weight. A history of dieting and dietary restraint has been associated with increased weight gain during pregnancy in all but underweight women [17]. The health benefits of ideal weight range for both mother and prospective children should be emphasized. Risks and management of overweight and obesity are discussed further in Chap. 9. Generally, if weight loss intervention is needed in nonpregnant and non-lactating women, a diet supplying 1200–1500 kcal/day or 500 kcal/day deficit is recommended with recognition that choosing a nutritious diet that is most likely to be adhered to is more important than macronutrient composition (low fat, low carb, etc.) [2, 18].

Recent gut microbiome studies have revealed that maternal intestinal flora, which have significant associations with body weight, metabolic syndrome, and diet, affect not only maternal health but may also affect fetal gut microbiome and postnatal health outcomes [19]. Inclusion of probiotics in the diet has been shown to increase glucose tolerance and reduce risk of gestational diabetes in pregnancy, perhaps reflecting change in gut microflora [20].

Overweight, Obesity, and Weight Loss Considerations

Both obesity and eating disorders (as a group) are more common in females than males in developed countries. Although there is a well-known difference in body fat distribution among most women versus most males, the interaction of factors dictating gender-specific fat storage and mobilization are not clear. Multiple appetite-regulating hormones are currently under investigation for their roles in energy balance and inappropriate imbalance [21]. Weight management and appetite regulation in girls and women are complicated by gender-specific roles as family meal preparers, menstrual cycle fluctuations, major changes in sex hormone levels at the onset and end of the reproductive years, and body weight and shape changes associated with pregnancy and lactation [21]. When weight reduction is indicated, strong evidence-based recommendations include prescription of individualized nutritionally adequate diets designed with regard to patient preferences and other health considerations. Caloric intakes from 1200 to 1500 kcal/day or energy deficit of approximately 500 to 750 kcal/day for women are recommended. Macronutrient densities ideal to promote compliance with caloric deficit and consumption of most calories earlier in the day have been shown to improve success [18].

Success rates for weight-loss maintenance in overweight women and recovery from eating disorders are not encouraging. Eating disorders are explored in more detail by Allison and Bruzas in Chap. 23. It is important for clinicians to recognize that a one-size-fits-all approach to the treatment of disordered eating issues and weight management is likely less effective than individualized nutrition assessment and management approaches. Evidence is mixed with regard to whether reasonable calorie restriction is effective in the long term or if it predisposes to eating disorders; however, any dieting should be done with caution, supervision, and with adequate dietary carbohydrate and protein to preserve lean body mass. There is also evidence that a size-acceptance approach (health at all sizes) that emphasizes attention to internal hunger, satiety, and appetite cues may improve health and self-esteem more than dieting [22].

The Female Athlete Triad

The female athlete triad (TRIAD) is a spectrum disorder that involves three interrelated conditions, which may profoundly affect the skeletal and reproductive health of girls and women: inadequate energy intake, menstrual dysfunction, and lowered BMD [23]. Inadequate energy intake leading to promotion of the other two conditions may occur with or without eating disorder and in girls and women in all weight categories. The prevalence of the TRIAD varies depending on the age group, number, and definition of components [23]. Athletes with the TRIAD are at significantly higher risk of sports-related injuries and declining performance. Screening for the TRIAD should occur at physical examinations [24]. Detected presence of any one of the TRIAD components with screening or patient presentation of amenorrhea, stress fractures, or low body weight indicates assessment for the other two components. It is recommended that the diagnosis of the TRIAD should be followed by comprehensive evaluation and intervention, including a primary care provider, a behavioral health professional, and registered dietitian [23]. Key considerations for the assessment of the TRIAD and for intervention planning are shown in Table 6.1.

The goals of treatment are normalization of eating patterns and weight, nutrition education and oversight to ensure energy balance (caloric intake ≥ caloric expenditure), restoration of regular menses, and elevation of BMD. BMIs for resumption of regular menses may be higher in athletes than that required in more sedentary females. Rest (exercise restriction) may also be required for the restoration of normal physiological and reproductive function. Behavioral health support may be needed to help athletes deal with associated feelings of guilt or loss because of not exercising. Protein, calcium, and vitamin D consumption should also be monitored for adequacy. Oral contraceptive therapy to replace

Table 6.1 Assessment for diagnosis, monitoring, and evaluation of the female athlete triad

Assessment category	Key tools
Screening and behavioral	Preparticipation physical exam [24], EDI, EAT-26, SCOFF, etc. Interview to assess body image, food, and/or exercise focus
History	Weight, diet, physical activity, social, medical (evidence of bone injuries, pain)
Anthropometrics[a]	Height, weight, BMI calculation, application to ideal body weight (IBW) range and % IBW, % UBW if recent weight loss
Dietary	Use 24-hr or usual day recall, dietary log, direct observation, and/or interview of parents as applicable
Laboratory	Glucose, protein, iron status, CBC, gonadal axis hormones
Body composition[a]	Bone density (whole body and regional), % fat mass

[a]Body image concerns considered if sharing this information with the patient

Table 6.2 Clinical features and related medical or lifestyle and dietary interventions for PCOS

Clinical feature	Medical or surgical intervention	Lifestyle/dietary intervention
Hyperandrogenism	Spironolactone	Phytochemicals
Dysmenorrhea	Contraceptives Ovulatory induction with clomiphene citrate or letrozole	Phytochemicals
Android pattern Overweight/ obesity	Orlistat Phentermine	Support for achievement and maintenance of lower body weight through dietary and exercise interventions Screening and support for BED/NES eating disorders
Insulin resistance	Metformin Thiazolidinediones GLP-1 mimetics[a] DPP-4 inhibitors[a]	Focus on carbohydrate amount and type, inclusion of chromium and cinnamon
Ovarian cysts		Phytochemicals
Hirsutism, alopecia	Topical 5-alpha reductase inhibitors	Zinc supplementation

[a]Under investigation

estrogen with amenorrhea is controversial and has not been effective in preserving BMD as intended. Hormone challenge may be helpful for jump-starting menses following weight restoration. Noncompliance with the treatment plan and/or continued amenorrhea indicates the need for more intensive behavioral and medical therapy to prevent poor present and future health outcomes [23, 24].

Polycystic Ovarian Syndrome

Polycystic ovarian syndrome (PCOS), also known as Stein-Leventhal syndrome, is associated with an array of clinical features and management options shown in Table 6.2. The prevalence of the condition is estimated to be 5–15% of women of reproductive age, and there is often family history of PCOS or its signs [25, 26]. Besides the well-known difficulties with fertility that women with PCOS can experience, the metabolic disturbances significantly increase the risk of developing type 2 diabetes and cardiovascular disease [1, 25, 26].

Indications of hyperandrogenism in women include *hirsutism* (male pattern hair growth in females), acne, dysmenorrhea, and alopecia (head hair loss). The presence of insulin resistance and hyperinsulinemia is suggested by episodic hypoglycemia and related carbohydrate craving, acanthosis nigricans (dark patches on the skin), and unexplained weight gain. Other symptoms that may also be present include significant mood disorder, body image disturbance, and disordered eating, secondary to attempts to control weight gain. Results of sex hormone tests, standard diagnostics for diabetes

(fasting glucose and insulin, oral glucose tolerance test, HbA1c), and transvaginal pelvic ultrasound may provide differential diagnosis [25, 26].

Dietary management of PCOS should emphasize foods low in saturated fat and high in fiber. In addition, specific nutrients, plant extracts, and supplements, including *Cinnamomum* sp., inositol, and fish oil, have been explored to reduce clinical features of PCOS, with a recent meta-analysis identifying no high-quality evidence for their effectiveness [26]. Counseling may also be indicated for mood disorder and helps with body image and acceptance and disordered eating if present [24, 25]. Regular exercise, including both strength-building (resistance) and endurance components, will assist with weight loss, improve insulin sensitivity, and increase self-esteem. Medical management of sex hormone dysregulation may involve drugs to regulate menses, stimulation of ovulation, and inhibit masculine hair patterns and acne. Medical management of metabolic dysregulation may involve drugs to improve insulin secretion and sensitivity, reduce hepatic glucose output, improve dyslipidemia, and promote weight loss. Early detection and management of PCOS, or the proposed male equivalent (androgenic alopecia), can improve physical and mental health outcomes and reduce the risks of chronic diseases and infertility later in life [24, 25].

Peri- and Postmenopausal Nutrition

The peri- and postmenopausal periods may pose challenges for women's health and well-being that may be influenced by diet [12]. This topic is discussed in greater detail in Chap. 8, which deals specifically with this stage of life including considerations of diet, hormone replacement therapy, and supplement use, and Chap. 11, which deals specifically with related changes in bone health during this life cycle transition. A healthy diet, weight-bearing exercise, avoiding smoking, and limiting alcohol intake can prevent bone loss as well as promote healthy body weight and image in the postmenopausal period [2]. Cooperative diet, alcohol and supplement assessment, and referral to reliable sources for exploration of the evidence base for supplement use will help patients make informed decisions.

Urinary and Genital Tract Conditions

Bacterial and Fungal Vaginosis

Bacterial and fungal vaginosis are common conditions, especially in immunocompetent and immunocompromised women. Various specific probiotic strains administered vaginally or orally in clinical have been shown to improve bacterial vaginosis and in some cases antibiotic co-treatment efficacy. Consumption of yogurt with live cultures may be an advisable dietary intervention in women who are at risk or have recurrent or drug-resistant conditions [27, 28].

Urinary Tract Infections (UTI)

Women are 30 times more likely to suffer from urinary tract infections throughout their lives compared with men [12]. They are also more likely to develop infection-related stones which are also associated with higher urinary pH. Besides microbiota mentioned above, cranberries and cranberry juice have been shown to help with the treatment of UTI. The proanthocyanidins in these fruits and their juices are associated with reduction in adhesion to urinary tract mucosa of the most common infective *E. coli* strains. The effective dose has been elusive due to cranberry strain variations in proanthocyanidin contents [12]. Adequate water intake should also be encouraged for the prevention of UTI and all types of kidney stones.

Interstitial Cystitis/Bladder Pain Syndrome

Women are more likely to experience interstitial cystitis/bladder pain syndrome than men [29]. This condition is associated with debilitating urinary tract pain and urinary frequency and urgency of urination. Recent studies have shown benefit of diet manipulations that seek to exclude irritating foods, often including coffee, tomatoes and tomato products, soybean products, specific spices, citrus, and those with excessive potassium [29, 30]. As with any elimination-type diet, reporting of symptoms and tolerance with the help of a dietitian can reduce the likelihood of malnourishment due to unnecessary elimination of nutritious foods.

Summary

Helping girls and women navigate the vast, often contradictory, dietary information related to female-specific issues is a challenging task that may be asked of primary care providers. Anthropometrics, diet and eating pattern analyses, and questions about body image and satisfaction should be routine aspects of annual physical examinations. This is especially important during puberty, pregnancy, and postpartum and perimenopausal periods. These may help detect and monitor conditions that warrant special nutritional, medical, and/or exercise interventions that will improve girls' and women's health and well-being.

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Suggested Further Readings

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National Eating Disorders Association. http://www.NationalEatingDisorders.org.
National Institutes of Health: National Center for Complementary and Integrative Health. Menopausal symptoms. https://nccih.nih.gov/health/menopause.
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Nutrition and Aging: Meeting the Unique Needs of Older Adults

7

Kathryn N. Porter Starr, Michael S. Borack, Jamie C. Rincker, and Connie W. Bales

Keywords

Older adults · Nutrient requirements · Food intake · Anorexia of aging · Sarcopenia · COVID-19 Malnutrition · Community dwelling · Care transitions

Key Points

- Older adults constitute the fastest growing segment of the population and have the most intensive use of healthcare services, including for nutrition-related chronic health conditions.
- The need for interprofessional collaboration in providing this care and to reinforce the importance of nutrition across the continuum of care is paramount.
- Calorie needs gradually decline with age, while other nutrient requirements remain the same or even increase, necessitating a diet of higher nutrient density to achieve nutritional adequacy, which may include nutritional supplements.
- Physiological, psychological, and environmental factors combine to intensify the risk of nutritional deficiencies in older adults.
- The COVID-19 pandemic has dramatically affected the older adult population; they experience the highest rates of infection and a greater likelihood of disease complications. Moreover, the entire population has been impacted by the social isolation of stay-at-home efforts, with reduced access to a varied diet and delayed medical appointments contributing to poor nutrition and health outcomes.
- Malnutrition in this population is associated with an array of detrimental health outcomes, underscoring the need for comprehensive nutritional assessment and intensive nutrition interventions.
- Hospitalized older patients, those undergoing surgery, and residents of long-term care, especially those experiencing cognitive decline, are at very high risk of poor nutritional status.

K. N. Porter Starr (✉) · C. W. Bales
Center for the Study of Aging, Duke University School of Medicine, Durham, NC, USA

Department of Medicine, Duke University School of Medicine, Durham, NC, USA

Geriatric Research, Education, and Clinical Center, Durham VA Medical Center, Durham, NC, USA
e-mail: kathryn.starr@duke.edu; bales001@mc.duke.ed

M. S. Borack · J. C. Rincker
Center for the Study of Aging, Duke University School of Medicine, Durham, NC, USA
e-mail: michael.borack@duke.edu; jamie.rincker@duke.edu

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Introduction

Adults 65 years of age and older represent the fastest-growing segment of the population in the United States. In 2017, 15.6% of the US population was 65 and older, and by 2040 that will increase to 21.6% [1]. An additional concern is the 85 and over population, which is projected to increase from 6.5 million in 2017 to 14.4 million in 2040 [1]. With the increased number of older adults will come increased chronic health conditions that have, and will continue to have, a substantial impact on the healthcare system. Furthermore, many of the chronic health conditions that afflict middle-aged and older adults face are significantly impacted by nutritional status. This chapter will help provide insight into the unique nutritional risks – and needs – that face our older adult population.

Optimal Nutrition in Later Life

Optimal nutrition is hindered in many ways due to aging. As we age, energy requirements diminish, food intake lessens, and some nutrient needs increase. Meanwhile, overall diet quality often suffers due to an increased reliance on convenience foods that are high in fat, high in low-quality carbohydrates, and low in micronutrients [2].

General Nutrition Recommendations for Older Adults

Consuming a diet high in nutrient-dense foods and limiting excessive energy-dense, nutrient-poor foods later in life is extremely important due to reduced calorie needs as metabolism slows, while requirements for other nutrients increase or remain the same. The National Academies of Sciences, Engineering, and Medicine (NASEM) has summarized the recommendations for nutrient intakes for healthy individuals based on age and gender. However, these recommendations do not take into account acute and chronic health conditions. Needs should be assessed and individualized depending on the development and severity of acute and chronic conditions, but standardized target ranges for macro- and micronutrients provide a rough estimate of needs.

Energy-Yielding Nutrients and Alcohol

Total and resting energy expenditures decrease with age, due to reductions in metabolic rate, loss of muscle mass, and reduced physical activity [3]. According to the acceptable macronutrient distribution range (AMDR), the percentages of each macronutrient remain similar in older adults regardless of reduced caloric needs (Table 7.1). While these ranges may be an acceptable guideline, published guidelines do not account for the individual physiological differences of the aging body. For instance, the recommended dietary allowance (RDA) for protein in older adults is the same as younger adults, 0.8 g/kg of body weight per day, but many researchers are convinced that the protein requirement may actually be higher for older adults, in part due to anabolic resistance, which leads to an increased rate

Table 7.1 Acceptable macronutrient distribution range

Sex, age (y)	Protein (% kcal)	Carbohydrate (% kcal)	% Fat (% kcal)
Female 51+	10–35	45–65	20–35
Male 51+	10–35	45–65	20–35

Source of information: Ref [8]

of muscle loss in later life [4]. It is estimated that up to 46% of older adults fall short of even the current RDA for protein, with even more failing to meet higher amounts of protein likely needed to overcome anabolic resistance [5].

Carbohydrates are estimated to be the bulk of caloric needs, yet with the burden of prediabetes and diabetes management for many older adults, the quality and timing of carbohydrates should be considered priorities. Limiting refined starches and sugars while increasing whole grains to half of daily grain intake is recommended by the Dietary Guidelines 2015–2020 [6].

The recommended intake range for fat is reduced slightly for older adults compared to younger adults. Healthy fats (mono- and polyunsaturated fatty acids) should be prioritized, and saturated and trans fatty acids should be limited for this population. High-fat diets are associated with greater mortality, yet certain fats are essential, especially to cognitive health. Consuming monosaturated and polyunsaturated fats with omega-3 fatty acids appears to have an especially protective effect on brain health.

Alcohol intake should be kept to a moderate or low level of consumption; older adults are at higher risk of the negative impacts of alcohol. Unintended drug interactions with alcohol, increased risk of falls, poor mental health effects, and excess nutrient poor calories can all have a more severe impact on older adults [7].

Micronutrients: Vitamins, Minerals, and Trace Elements

Micronutrients (vitamins, minerals, and trace elements) perform a variety of essential functions in the body. They serve as enzyme cofactors, antioxidants, hormones, in structural roles, and for one-carbon metabolism and DNA synthesis. Given the common emphasis on protein/calorie malnutrition in older adults, the simultaneous risk of micronutrient deficiency associated with diminished food intake is often underappreciated. When micronutrients are inadequately consumed (sources include foods, fortified or enriched products, and dietary supplements), marginal deficiencies will lead to impaired cellular and physiological function even before a "classic" deficiency syndrome develops.

Micronutrients that are of particular concern for this population include folate, B_{12}, and B_6 for cognitive and overall metabolic functions; vitamin E for immune function; and vitamin D, calcium, vitamin K, magnesium, and potassium for bone and cardiovascular health [9]. Whenever possible these nutrients should be obtained from foods rather than supplements, although the usefulness of supplements varies by nutrient and the extent of deficiency (see subsequent section on nutritional supplements). The topic of vitamin supplements is also discussed in greater length by Temple in Chap. 42.

Water and Fiber

Water requirements for older adults are estimated by the NASEM to be 2.7 L/day for women and 3.7 L/day for men to avoid dehydration [8]. Water and other comparable fluid intake can be impacted by a multitude of factors such as reduced perception of thirst and medications, as well as by metabolic and physiological changes including, but not limited to, the renal and endocrine systems [7].

Fiber is another key nutrient for older adults to prioritize in order to promote gut motility, maintain gastrointestinal health, contribute to the vitality of the gut microbiome, aid in blood glucose control, and play a role in cardiovascular health relating to lipoprotein levels [7]. The adequate intake of fiber is 21 g/day for older women and 30 g/day for older men; however, many older adults fail to meet these recommendations [8]. Drivers of poor fiber consumption are reduced appetite, chewing difficulties, and an inability to procure and prepare fibrous foods regularly. The topic of dietary fiber is also discussed in Chap. 33.

Nutritional Supplements

In the event of acute deficiencies, supplements may play a key role in therapy. This is true for calories, protein, and a variety of micronutrients. However, in the community setting, choosing what to take and what to avoid is a confusing space for many older adults. There is no shortage of all types of nutrient supplements in the commercial market. As described above, certain nutrients become a higher priority for various reasons later in life such as B_{12}, B_6, folate, vitamin D, and calcium. Supplementing with dietary supplements is not the optimal way to achieve diet quality but can assist with achieving baseline needs in the event of chronic low food intake [10]. Furthermore, if caloric and/or macronutrient intake is poor, oral nutrition supplements may be a useful alternative.

Causes of Nutritional Risk in Late Life

As we age, total and resting energy requirements decline as a result of reduced physical activity, decreased muscle mass, and increased adiposity, putting older adults at an increased risk for nutrient deficiencies. This is because, while calorie consumption needs to be slightly reduced, vitamin and mineral requirements remain the same or may even increase. This is challenging for anyone, but especially for older adults who, in addition to physiological changes, are encountering psychological, environmental, and social factors that have deleterious effects on dietary intake. The myriad causes of increased nutritional risk from three domains – physiological, psychological, and environmental/social – are summarized in Fig. 7.1.

Physiological Factors

Compared to younger age groups, older adults have inherent physiologic and metabolic risk factors that make their nutritional risk exceedingly complex. Anorexia of aging, or loss of appetite that may result in decreased food intake, is a complex condition that emerges as a result of changes in taste and smell, appetite signaling hormones, gastric motility, and environment [11]. Poor oral health, a problem seen in up to 68% of older adults, is associated with reduced fruit and vegetable intake and increased consumption of softer foods that are easier to chew but lacking in fiber and micronutrients [12]. Furthermore, swallowing becomes difficult due to xerostomia (dry mouth) which can limit food choices even further. These particular food choices, coupled with gastronomical changes – such as atrophic gastritis – that occur as we age, may result in malabsorption of essential nutrients. To come full circle, another detrimental effect on appetite is gastric emptying, which also slows as we age. These elements can occur in any number of different combinations and lead to reduced food intakes.

Another major physical factor that changes as we age is body composition. Namely, fat mass increases, and lean muscle mass and strength decreases (sarcopenia), a topic discussed at greater length in Chap. 25. Lean muscle mass declines from about 50% of total body weight in young adults to about 25% at 75–80 years [13]. The progressive deterioration of muscle quantity and quality leads to slower movement, a decline in strength and power, and an increased risk for falls. Furthermore, obesity in older adults is growing rapidly, such that 42.8% of adults 60 and older have a body mass index (BMI) ≥ 30 kg/m^2 [14]. Obesity concomitant with undernutrition is due to chronic overeating coupled with underconsumption of nutrient-rich foods and lack of physical activity. As a result, many older adults suffer with obesity-related health problems, such as type 2 diabetes, hypertension, and heart disease, further amplifying their health risk.

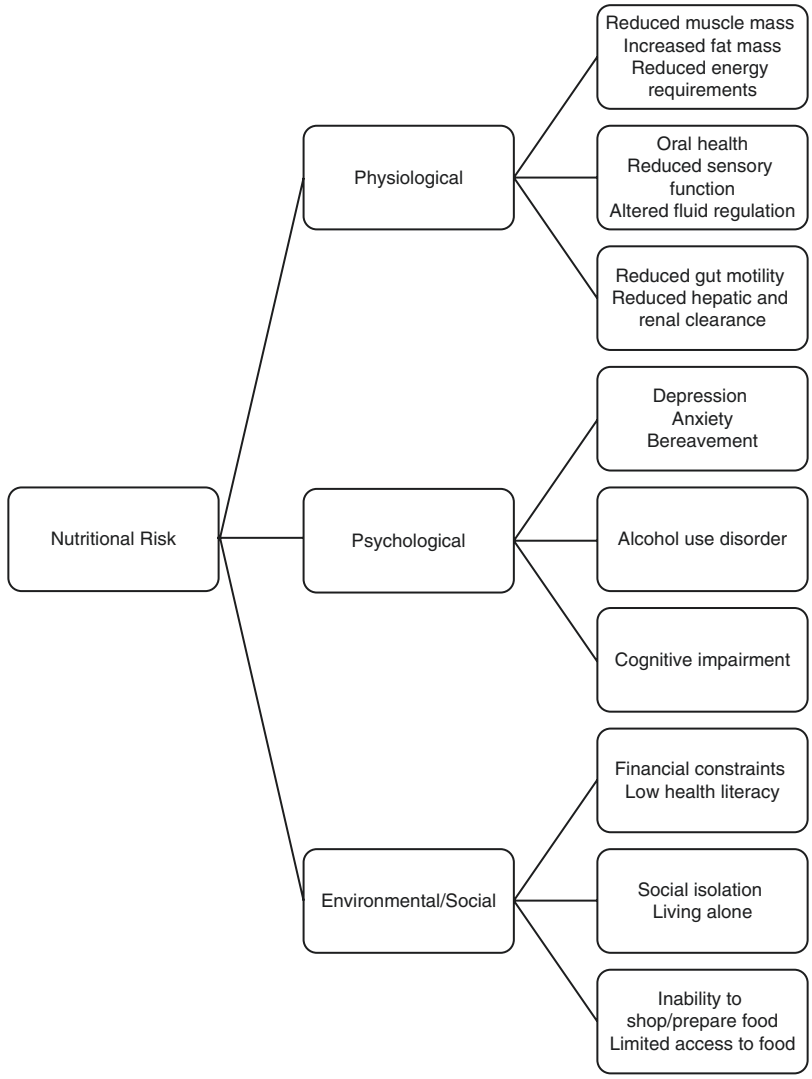

Fig. 7.1 Age-related nutritional risk factors

Psychological Factors

Depression, alcohol addiction, and cognitive impairment are just a few of the psychological factors that may lead to decreased food intake and ultimately poor nutrition. A small percentage of older adults have major depression; however, up to 15% have clinically significant depressive symptoms, and the prevalence increases with age [15]. Compared to younger adults, older adults with depression are more likely to report loss of appetite and weight loss. Anorexia of aging is often seen in this older population and is coupled with macro- and micronutrient deficiencies [11]. Finally, older adults with depression are at greater risk for functional impairment, coexisting medical illness, and mortality.

Alcohol use disorders have steadily increased in adults 60 and older, specifically among females. Adults with a heavy level of alcohol intake are more likely to be malnourished, as well as deficient

in a wide range of micro- and macronutrients. Alcohol use disorders often go underreported and undertreated resulting in what is being called an "invisible epidemic" that is rapidly growing in this population [16].

Environmental/Social Factors

Many older adults attempt to maintain their independence by staying in their home or "aging in place" as long as possible. In doing so, many of them face copious environmental and social challenges that impact their nutritional status. These include food cost, availability, distance to obtain food, walkability, safety, and available transportation. When even one of these factors is disrupted, it can negatively impact nutritional status. Furthermore, low socioeconomic status is a nutritional risk factor due to money being spent on bills, medication, or unexpected expenses rather than nutrient-dense food. In 2018, 5.3 million older adults were food insecure, which has been linked to poorer health, increased chronic health conditions, functional disability, and psychological distress [17].

Another social factor that older adults encounter is social isolation and loneliness. These factors are extremely detrimental to older adults and are associated with cognitive impairment, emergency department admissions, longer lengths of stay, and mortality [18]. Individuals who experience social isolation and loneliness are more likely to eat alone and not meet their energy, or macronutrient and micronutrient needs, putting them at greater risk for malnutrition.

COVID-19: A New Threat to the Well-Being of Older Adults

The impact of COVID-19 on older adults is one of the most important topics of concern emerging during this pandemic. Vulnerable populations tend to suffer disproportionately in times of global health concerns, and the COVID-19 pandemic is no exception. Older adults have shown extreme vulnerability to COVID-19, both in terms of susceptibility and seriousness of complications after infection. The current data being collected by the CDC suggests that individuals over 65 who contract COVID-19 are at the greatest risk for hospitalizations, intensive care unit admissions, and deaths. Between February 12th and March 16th of 2020, individuals over 65 constituted 31% of cases, 45% of hospitalizations, 53% of ICU admissions, and 80% of deaths associated with COVID-19 [19]. Considering that this age group accounted for roughly 15% of the population (as of 2016), the percentage of deaths they account for is particularly staggering [19].

Older adults are at risk for malnourishment, and this risk has been exacerbated during the pandemic as appetites may be decreased while experiencing typical symptoms of COVID-19: fever, bodily aches, vomiting, diarrhea, and loss of taste. One cohort of 141 patients over 65 years of age admitted to the Renmin Hospital of Wuhan University in China between January 28, 2020, and March 5, 2020, that were diagnosed with a COVID infection was assessed for nutritional risk [20]. Depending on the assessment tool employed for measuring nutritional status, 14.9%–58.8% were found to be nutritionally normal, while 41.1%–85.1% were found to be at risk for malnutrition [21]. Some potential consequences of being hospitalized with an "at-risk" nutritional classification include longer length of stay, decreased appetite, increased disease risk, and greater weight change than patients who are not at nutritional risk.

Furthermore, millions of older Americans who did *not* contract the virus had their lives dramatically altered by the sudden need to isolate. This disruption, followed by a long period of social isolation, led to problems not accounted for statistically. Prior to the onset of the COVID-19 stay-at-home orders, approximately one-third of older adults already experienced social isolation or loneliness [22]. This has been found to negatively impact many health outcomes in older individuals including cognition, stress, quality of sleep, disability, depression, and increased mortality. During this period of

social isolation, many adults no longer have access to the support networks or healthcare providers as they once did, which is resulting in even more isolation and delays in seeking essential medical treatments and follow-up [21]. With typical avenues for social engagement – such as religious services, social clubs, exercise classes and gyms, in-person health or business appointments, and volunteer commitments – being temporarily suspended, the effect of social isolation is compounded even further.

While the data concerning the impact of COVID-19 on older adults is still limited, and the currently published studies on this topic utilize small sample sizes, it is becoming clear that many factors are negatively affecting the older adult population during this pandemic. Not only are older adults bearing the brunt of the effects of the actual virus, risk factors derived from the isolation caused by stay-at-home orders and delays in medical and dental care are exacerbating the malnutrition risk which older adults are already susceptible. All of these factors lead to increased negative health outcomes, both for those who contract COVID-19 and those who do not.

Nutritional Concerns by Care Setting

As previously outlined, older adults encounter numerous factors that can lead to nutritional shortfalls. The majority of older adults have at least one chronic health condition, with 47% having two to three and 15% having four or more [22]. As a result of the high prevalence of chronic health conditions, coupled with age-related nutritional risk, it is not surprising that health utilization is highest in this population and that an estimated 51 billion dollars is spent on disease-associated malnutrition [22]. There is an urgent need to identify nutritional risk, intervene with patient-centered approaches, and develop clear nutrition care plans across the continuum of care for this vulnerable population.

Hospitalized Older Adults

The hospital setting inevitably contributes to nutritional decline, especially for older adults. It is estimated that 38.7% and 47.3% of older adults are malnourished or at nutritional risk, respectively [23]. Regardless of BMI, hospitalized older adults experience undernutrition as a result of frequent meal interruptions, lack of culturally appropriate foods, unnecessary nothing by mouth (NPO) orders combined with increased energy requirements for healing, poor appetite, and reduced ability to chew and/or swallow. Early identification of malnutrition is essential to ensuring that this population receives the appropriate interventions so that their hospitalization does not further their nutritional decline. In order for this to happen, a comprehensive, interdisciplinary approach must be taken. The following six principles represent a sustainable model that puts nutrition at the forefront of patient care: "(1) create an institutional culture where all stakeholders value nutrition, (2) redefine the clinicians' roles to include nutritional care, (3) recognize and diagnose all malnourished patients and those at risk, (4) rapidly implement comprehensive nutritional interventions and continued monitoring, (5) communicate nutritional care plans, and (6) develop a comprehensive discharge nutritional care and education plan" [24].

Nutritional Concerns and Surgery

Older adults account for one-third of all outpatient surgical procedures in the United States [25]. Surgical procedures, even when minor, cause accelerated catabolism of protein, fat, glycogen, reduced insulin sensitivity, and increased release of "stress factors," including catecholamines, cortisol, glucagon, and inflammatory cytokines [26]. The challenge of surgical recovery includes a heightened

requirement for key nutrients. The postoperative hypermetabolic state leads to a dramatic increase in calorie requirements. Protein needs are also increased, often by 100% or more, for a variety of aspects of the recovery, including immune responses and wound healing. These accelerated nutritional needs occur at a time when food intake is frequently curtailed as outlined in Table 7.2. In the face of this negative balance of nutrient supply and demand, protein needs cannot be fully met, and rapid degradation of muscle often occurs, putting older adults at even greater risk [26]. In total, surgery – coupled with malnutrition – increases postoperative vulnerability, reducing the patient's ability to overcome these stressors and leading to poor long-term outcomes, including weight loss and reduction in strength and ambulatory ability and ultimately the ability to live independently. For this reason, the American College of Surgeons Geriatric Surgery Verification Program has made screening for malnutrition 1 of the 32 surgery standards for older adults, to insure identification and optimization of nutrition throughout the perioperative period [27].

Transitions from Hospital to Home or Skilled Nursing Facility

Whenever a transition in care setting occurs, continuity of care can be at risk, and this is especially true for the continuity of the nutritional care plan. There are a number of opportunities for a disconnect to bring nutritional harm, including neglect of diet quality/safety, problems of food accessibility, or lack of recognition of therapeutic diet needs, albeit metabolic (e.g., special diets for diabetes, renal disease, heart failure) or mechanical (e.g., dysphagia restrictions, other needed texture modifications). Involvement of multidisciplinary care providers will reduce this risk, as well as assignment of a "case manager" of the transition process and the involvement of family/caregivers whenever possible.

Nutritional Issues in Long-Term Care

Older adults residing in long-term care (LTC) facilities, including assisted living facilities and skilled nursing homes, have a very high level of nutritional risk. Malnutrition is especially common in this population and, whether manifested as undernutrition or obesity, may seriously exacerbate health problems and reduce the quality of life for older nursing home residents. Advanced dementia and other cognitive problems also dramatically magnify nutritional risk.

Table 7.2 Nutritional risks following surgery

Decreased food intake	Poor appetite Dysphagia Difficulty chewing Depression Restrictive diets NPO orders/testing
Increased energy requirements	Catabolic conditions caused by: Surgery Inflammation Infection Support tissue/wound healing
Malabsorption	Pathologic conditions in gut, intestine, pancreas, or liver
Excess loss	Vomiting Diarrhea Fistulae

Malnutrition in LTC

Complaints about menu choices and meal quality are common in the institutional setting and often contribute to poor nutritional intake. Problems often stem from overburdened staff and rushed mealtimes, as well as unpleasant meal environments and unappetizing restricted diets, such as reduced sodium, sugar-free, and low-fat diets. In particular, LTC residents who eat alone in their rooms miss the social interactions and pleasant aspects of meals. The prevalence of malnutrition in this setting can be as high as 80% when accompanied by functional impairment or cognitive deficit and contributes directly to frailty, disability, and increased mortality [28].

Obesity is another form of malnutrition that has become a significant concern in the nursing home setting, contributing to comorbidity and serious physical challenges, e.g., limited mobility, inability to transfer, and bathing difficulties. The rates of moderate to severe obesity (BMI > 35 kg/m^2) in nursing homes in the United States have grown by nearly 90%, increasing from 14.7% in 2000 to 28.0% in 2015 [29].

Special Concerns for the Older Adult with Dementia

For both institutional and home-dwelling persons with dementia, mealtime difficulties can lead to chronic undernutrition, bringing profound effects on health and quality of life. These difficult behaviors can include major changes in taste and food preferences, difficulties in chewing and swallowing, and wandering/pacing that increase calorie needs and interrupt meals, along with a variety of other behavioral changes that interfere with eating. Mealtime interventions during the earlier stages of disease include removing mealtime distractions (noise, unpleasant odors), using strong color contrast in meal service, special utensils, and assuring comfortable room temperatures. The use of feeding cues, such as naming the foods on the plate and reminders to bring the food to the mouth, can be helpful. Individualized intervention for the gradual worsening of mealtime difficulties is essential. With progression to advanced dementia, barriers to self-feeding can be profound, to the point of causing serious nutritional deficits. However, the emphasis should remain on maintaining oral intake in preference to institution of tube feeding. It is widely endorsed that careful hand feeding is preferable to percutaneous gastrostomy feeding to support oral intake of food and fluids in the case of advanced dementia [30].

Summary

The number of older adults in the United States will continue to rise for the foreseeable future, exceeding one fifth of the population (21.6%) by the year 2040. This population consumes the largest percentage of healthcare-related costs, much of which is linked to chronic health conditions that have nutritional determinants. More research is needed to establish a full evidence base for the management of nutritional health in this population. Interventions for conditions ranging from anorexia of aging and sarcopenia to the medical complications of multiple comorbidities are needed [1]. Community emphasis on the availability of affordable, nutritious food and solutions to reduce to impact of loneliness and social isolation on at-risk older adults is becoming more important than ever. When providing care for older adults, whether in the community, hospital, or long-term care facilitates, their basic nutritional requirements as well as the underlying physiological, psychological, and environmental causes for malnutrition need to be appreciated.

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Dietary Considerations for Postmenopausal Women

8

Kara L. Marlatt, Linda A. Gilmore, Emily W. Flanagan, and Leanne M. Redman

Keywords

Menopause transition · Metabolism · Mental health · Bone density · Diet · Exercise

Disclosure Statement KLM, LAG, EWF, LMR have nothing to declare

Key Points

- Menopause is associated with declines in cardiometabolic, physical, and psychosocial health that extend well into the postmenopausal years.
- Weight gain is a common concern among perimenopausal and postmenopausal women, and its treatment requires a multidisciplinary team of physicians, register dietitians, and behavioral and social support professionals to adequately address weight gain concerns.
- Balanced, calorie-controlled diets, including a variety of fruits, vegetables, lean meats, whole grains, dairy, and unsaturated fats, can aid in healthy aging and menopause symptom management.
- Social stigmatism of menopause is a common barrier to receiving adequate treatment for their menopause-related concerns (e.g., vasomotor symptoms, psychosocial, mental health, etc.), which can lead to reduced quality of life if left untreated.
- Medical professionals should frequently screen for common menopause-related concerns, including vasomotor symptoms, sleep disturbances, mental health, and osteoporosis – even if not brought up by the patient – and refer the patient to the appropriate healthcare professional and resources if indicated.

Introduction

Women experience an array of health disturbances that arise as a consequence of menopause, including disrupted cardiometabolic health, physical and psychosocial symptoms, reductions in bone health, and changes in gastrointestinal health. Collectively, these disturbances can have detrimental effects on

K. L. Marlatt · E. W. Flanagan · L. M. Redman (✉)
Pennington Biomedical Research Center, Baton Rouge, LA, USA
e-mail: leanne.redman@pbrc.edu

L. A. Gilmore
UT Southwestern Medical Center, Department of Clinical Nutrition, Dallas, TX, USA

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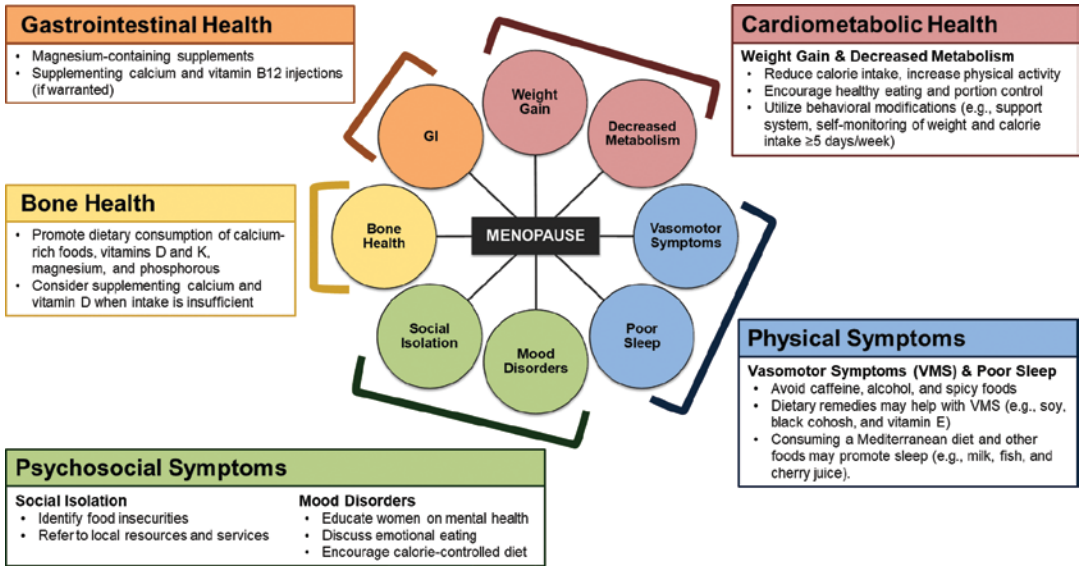

Fig. 8.1 Dietary strategies to minimize the consequent health outcomes of menopause. Women experience an array of health disturbances that arise as a consequence of menopause, including disrupted cardiometabolic health, physical and psychosocial symptoms, reductions in bone health, and changes in gastrointestinal health. Here, we provide a visual summary of various dietary strategies to help minimize these detrimental outcomes. Treatment strategies are the most successful when a multidisciplinary team of medical professionals is assembled to adequately address these health disturbances

a woman's overall quality of life. Importantly, changes in dietary patterns and food preferences often occur in parallel with menopause, which can amplify these health disturbances. Total energy intake, as well as consumption of protein, polyunsaturated fat, dietary fiber, and micronutrient-dense foods, have been reported to decline with menopausal progression and into the postmenopausal years [1]. In contrast, saturated fatty acid and cholesterol intake is reportedly higher in the postmenopausal years compared with menopause onset and tends to increase over time [1, 2]. It is critical that medical professionals understand the consequences of menopause and employ sufficient screening and treatment strategies to mitigate them. This chapter will provide a brief overview of menopause and its staging, as well as detail the health challenges that midlife women experience and nutritional strategies that medical professionals should consider when treating postmenopausal women (Fig. 8.1).

The Menopause Transition

Menopause is a naturally occurring biological process of reproduction when menstrual cycles permanently cease and estrogen levels decline as a result of progressive ovarian failure. *Natural menopause* typically begins in a woman's mid-to-late 40s and is diagnosed retroactively after 12 months of amenorrhea and an elevated follicle-stimulating hormone (FSH) level of 30 mIU/mL or higher. The median age of natural menopause is 51.4 years, yet its onset can vary widely from 40 to 58 years [3]. Approximately 5% of women experience *early menopause* if they have their final menstrual cycle between ages 40 and 45 years. A minority of women (1%) also go through *primary ovarian insufficiency* (*POI*) if they experience menopause before 40 years of age. Finally, a woman can undergo

premature menopause after having a bilateral oophorectomy surgery or iatrogenic ablation of ovarian function (e.g., chemotherapy, pelvic radiation). Given the inherent variability in menopause transition timelines, routine surveillance of cycles (i.e., flow, duration) and menopausal symptoms should be considered starting at 40 years of age or when symptoms begin to arise.

In the 4 to 5 years leading up to menopause – known as the menopause transition (or perimenopause) – women can be divided into early- or late-stage perimenopause [4]. "Early perimenopause" is marked by menstrual cycle length of 7 days or more and possible coincident vasomotor symptoms (i.e., hot flashes, night sweats). Intervals of amenorrhea for at least 60 days with increased prevalence of vasomotor symptoms characterize "late perimenopause." The Stages of Reproductive Aging Workshop (STRAW) +10 guidelines provide a comprehensive staging system to determine where a woman is at in her transition [4] and is provided here in an abbreviated form (Table 8.1).

Table 8.1 The Stages of Reproductive Aging Workshop +10 staging system for reproductive aging in women

	Menarche					FMP (0)				
Stage	-5	-4	-3b	-3a	-2	-1	+1a	+1b	+1c	+2
Terminology	REPRODUCTIVE				MENOPAUSAL TRANSITION		POSTMENOPAUSE			
	Early	Peak	Late		Early	Late	Early			Late
					Perimenopause					
Duration	*variable*				*variable*	1-3 years	2 years (1+1)		3-6 years	*Remaining lifespan*
PRINCIPAL CRITERIA										
Menstrual Cycle	Variable to regular	Regular	Regular	Subtle changes in Flow/ Length	*Variable Length:* Persistent ≥7-day difference in length of consecutive cycles	Interval of amenorrhea of ≥60 days				
SUPPORTIVE CRITERIA										
Endocrine FSH AMH Inhibin B			Low Low	Variable * Low Low	↑ Variable * Low Low	↑ >25 IU/L ** Low Low	↑ Variable* Low Low		Stabilizes Very Low Very Low	
Antral Follicle Count			Low	Low	Low	Low	Very Low		Very Low	
DESCRIPTIVE CHARACTERISTICS										
Symptoms						Vasomotor symptoms *Likely*	Vasomotor symptoms *Most Likely*			*Increasing* symptoms of urogenital atrophy

Abbreviations: *FMP* final menstrual period; *FSH* follicle-stimulating hormone; *AMH* anti-Müllerian hormone

†This table was adapted from the previously published STRAW+10 staging guidelines [4]

*Blood draws during early follicular phase (cycle days 2–5)

**Approximate expected level based on assays using current international pituitary standard

↑ = elevated

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Changes in Cardiometabolic, Physical, and Psychosocial Health

The website of the North American Menopause Society (NAMS) is an excellent menopause treatment resource for medical professionals and provides a great overview of recommendations for clinical care of midlife women [3]. These recommendations range from managing common body changes and disease risk to complementary and alternative medicine and prescription-based treatment approaches. Common consequences of menopause include changes in cardiometabolic, physical, and psychosocial health. Together, these changes can significantly and negatively affect a woman's health and life span. While changes in diet quality and eating patterns likely contribute to some of these changes, the relationship is often bidirectional and cyclical in nature. These relationships deserve consideration when evaluating nutrition recommendations and treatment strategies. Table 8.2 summarizes the nutritional recommendations for postmenopausal women relative to energy intake requirements, as well as macronutrient and micronutrient intake recommendations with suggested food sources.

Table 8.2 Nutrition recommendations for postmenopausal women

Nutrient	Dietary reference intake	Food sources
Energy	Estimated energy requirement (EER) = 354 – (6.91 × age [y]) + PA × (9.36 × weight [kg] + 726 × height [m] …where PA is the physical activity coefficient: – PA = 1.00 if *sedentary* (i.e., 1.0 ≤ PAL <1.4) – PA = 1.12 if *low activity* (i.e., 1.4 ≤ PAL <1.6) – PA = 1.27 if *active* (i.e., 1.6 ≤ PAL <1.9) – PA = 1.45 if *very active* (i.e., 1.9 ≤ PAL <2.5) If weight loss is indicated, consider individualized energy deficit prescription	
Carbohydrates	**Total carbohydrate:** AMDR: 45–65% of kcal (RDA: 130 g/day) **Added sugar AMDR:** <25% of kcal; dietary guidelines state that added sugar should account for <10% of kcal	Whole grains, fruit, legumes, and starchy vegetables
Fat	**Total fat:** AMDR 20–35% of kcal – **ALA:** ADMR 0.6–1.2% of kcal (AI: 1.1 g/day) – **DHA and EPA:** No DRI; approximately 10% of ALA ADMR – **Saturated fat:** No DRI; dietary guidelines state that saturated fat should account for <10% of kcal/day – **Trans fat:** No DRI; dietary guidelines state that consumption of trans fats should be limited as much as possible	**ALA:** Plant oils, flax and chia seeds, soybeans, and walnuts **DHA and EPA:** Cold-water fish, such as salmon, tuna, herring, sardines, and mackerel
Protein	RDA: 0.8 g/kg body weight per day AMDR: 10–35% of kcal	Eggs, nuts, soy, fish, chicken, pork, beef, cheese, milk, and yogurt
Fiber	AI: 14 g/1000 kcal/day (20 to 25 g/day)	Nuts, seeds, beans, whole grains, fruits, and vegetables
Vitamin E	RDA: 15 mg/day	Nuts, seeds, vegetable oils, vegetable greens, avocado, pumpkin, and butternut squash
Vitamin B12	RDA: 2.4 mcg/day	Beef, clams, fish, cow's milk and dairy, and fortified cereals
Iron	RDA: 8 mg/day	Fortified cereals, oysters, beef, spinach, tofu, beans, sardines, chickpeas, and cashews

Table 8.2 (continued)

Nutrient	Dietary reference intake	Food sources
Folate	RDA: 400 mcg/day DFE	Dark green leafy vegetables, fortified cereals and enriched grains, asparagus, and Brussels sprouts
Calcium	RDA: 1200 mg/day	Cow's milk dairy products, fortified soy, sardines, salmon, fortified cereals, kale, and turnip greens
Vitamin D	RDA: 600 IU/day (or 800 if 70+ years old)	Fatty fish, mushrooms, cow's milk and cheese, fortified soy and nut milks, and eggs
Magnesium	RDA: 320 mg/day	Nuts, green leafy vegetables, legumes, milk and yogurt, soy, fortified cereals, and oatmeal
Vitamin K	AI: 90 mcg/day	Green leafy vegetables, broccoli, soy, okra, vegetable juices, pine nuts, blueberries, and grapes
Phosphorus	RDA: 700 mg/day	Dairy, beef, poultry, fish, pork, eggs, nuts, legumes, and grains

Abbreviations: *AI* adequate intake (this is established when evidence is insufficient to develop an RDA; intake at this level is assumed to ensure nutritional adequacy in healthy individuals); *ALA* α-linolenic acid (e.g., *omega*-3 fatty acids); *AMDR* acceptable macronutrient distribution range (this was developed to express macronutrient distribution in the context of a complete diet); *DFE* dietary folate equivalent; *DHA* docosahexaenoic acid; *DRI* dietary reference intake; *EPA* eicosapentaenoic acid; *RDA* recommended dietary allowance (this is the average daily level of energy intake sufficient to meet the nutrient requirements of nearly all (97–98%) healthy individuals)

Cardiometabolic Health

Weight gain is one of the most common concerns among midlife women and the medical professionals that care for them. According to the 2017–2018 National Health and Nutrition Examination Survey, the prevalence of obesity among women ages 60 years and older in the United States was 43.3% [5]. Despite reports that women gain an average of 5 to 7 lb. (2 to 3 kg) during perimenopause [3, 6], it is not uncommon for midlife women to report weight gain in excess of 20 pounds, much of which is in the form of increased abdominal adiposity (i.e., subcutaneous and visceral) [1, 6]. The gain in abdominal adiposity is likely due to a complex interaction between existing body adiposity, reproductive hormones (particularly the decline in estradiol, or E2), race, and genetics [7–10], which collectively may accelerate the progression of midlife women to overweight, obesity, or even severe obesity. Moreover, abdominal adiposity predisposes postmenopausal women to increased cardiometabolic risks, including dyslipidemia, hyperinsulinemia, and insulin resistance [11].

Declines in energy expenditure, fat oxidation, and physical activity further contribute to menopause-induced weight and abdominal adiposity gains. Clinical models of menopause using gonadotropin-releasing hormone (GnRH) analog therapy and a landmark observational study across the menopause progression report decreases in the number of calories expended both at rest and over 24 hours in postmenopausal women [1, 12]. Furthermore, postmenopausal women had a 32% reduction in fat oxidation, which suggests that physiological and hormonal changes coincident with menopause reduce a woman's ability to burn fat [1]. Physical activity also declines, as evidenced by ovariectomy models in rodents [13], clinical models with GnRH analog therapy [14], and studies of natural menopause [1]. When E2 is given as an add-back treatment, physical activity is restored or maintained, which further supports the importance of E2 in regulating metabolism [14]. It is not clear from the clinical studies whether the origin of this decline in physical activity is behavioral or physiological.

Treatment Strategies To compensate for the declines in calories expended, physical activity, and the body's ability to burn fat, postmenopausal women should be encouraged to reduce their caloric (energy) intake with a focus on portion size and consuming a variety of nutrient-dense foods. MyPlate aids in portion control and adopting a healthy eating pattern by dividing a smaller dinner plate into quadrants. Specifically, the quadrants are filled with a serving of the following: (1) fruit; (2) non-starchy vegetable; (3) lean protein (e.g., fish, chicken breast, lean beef, pork); and (4) whole grains. In addition, women should consume approximately three servings of dairy (e.g., plant or animal milk, cheese, yogurt) per day. The estimated energy requirement (EER) for women 19 years and older is EER = 354 – (6.91 × age [y]) + PA × (9.36 × weight [kg] + 726 × height [m]), where PA is the estimated physical activity level ranging from 1 to 2.5 (sedentary to very active). Unfortunately, this equation and most other equations that estimate energy expenditure (e.g., Mifflin-St. Jeor, Harris-Benedict, FAO/WHO equations) do not consider differences in energy needs based on race or stage of menopause (peri- vs. postmenopause).

If weight loss is indicated (i.e., BMI ≥ 30 kg/m^2 or BMI ≥ 27 kg/m^2 with a comorbidity), a caloric deficit of 400 to 600 kcal/day alongside an intensive behavioral lifestyle intervention (≥14 in-person counseling sessions in 6 months) is recommended [3, 15]. Of course, the 400 to 600 kcal/day deficit is not a one-size-fits-all recommendation. Instead, caloric deficit targets will need to be individualized to each woman's weight loss goals and current health status. Adding in exercise or physical activity to any caloric-deficit plan is important so that muscle mass and bone mineral density (BMD) can be preserved as much as possible while losing fat mass [16]. In cases of severe obesity (i.e., BMI ≥ 40 kg/m^2) under medical supervision, a very-low-calorie-high-protein diet or surgical intervention can be used. Various pharmacotherapies are even recommended as adjuncts to caloric deficit and increased exercise, yet some women may not be ideal candidates for such therapies or prefer not to take medications altogether [3, 15]. Behavior modification strategies associated with successful weight management include: (1) self-monitoring of weight, physical activity, and food intake at least 5 days/week; (2) utilizing a support and accountability system; (3) high levels of physical activity; (4) consistent eating patterns; (5) mindful eating; and (6) stimulus control (e.g., keep healthier foods around, reduce snacking between meals).

Physical and Psychosocial Health

While concerns about cardiometabolic health often arise during clinic visits and are, therefore, more easily diagnosed and treated, the physical and psychosocial consequences of menopause are often overlooked. Here, we detail some of the physical and psychosocial health concerns of midlife women.

Vasomotor Symptoms

Vasomotor symptoms (VMS), which include hot flashes and night sweats, occur in approximately 70 to 80% of menopausal women and are most prevalent in late perimenopause and early postmenopause. Yet despite their prevalence, only 25% of midlife women seek help from medical professionals to manage VMS. Risks for VMS include premature or surgical menopause, Black race or Hispanic ethnicity, a high body mass index (BMI) or high level of adiposity, sedentary lifestyle, smoking, stress, anxiety, and depression [17]. VMS are also associated with decreased sleep quality, mood swings, reduced quality of life, and bone loss and are linked to an increased risk of cardiovascular disease and cognitive decline [17].

Treatment Strategies Hormone therapy remains the most efficacious treatment for VMS. However, not all menopausal women are good candidates for hormone therapy, and many women prefer to avoid hormone therapy. Non-pharmacotherapy treatments for VMS include lifestyle changes, such as

keeping body temperature low, maintaining a healthy weight, exercising regularly, practicing relaxing techniques, and refraining from smoking [3]. Dietary considerations include avoiding caffeine, alcohol, and spicy foods to help reduce the frequency and intensity of VMS and improve sleep quality. While nonprescription dietary remedies such as soy, isoflavone supplements, black cohosh, vitamin E, and omega-3 fatty acids may provide some VMS relief; the scientific data does not currently support their use as first-line treatments.

Sleep Disturbances

Sleep disruption is one of the primary reasons why midlife women seek medical care, with up to 60% of women reporting reduced sleep quality and increased sleep disturbances (i.e., trouble falling asleep, early morning waking, interrupted sleep) with menopause [18]. Women experiencing VMS also tend to report higher levels of sleep disturbances [17] and are at the greatest risk for clinical insomnia. While VMS and psychological symptoms are strongly associated with sleep disturbances, trouble sleeping can arise independently of VMS. Poor sleep is also linked to increased dietary intake, increased intake of high-fat and high-sugar foods, reduced physical activity, weight gain, and reduced quality of life [19].

Treatment Strategies Sleep habits and the presence of sleep disturbances should be routinely assessed by medical professionals during clinic visits since metabolic abnormalities (e.g., obesity, insulin resistance, and hyperglycemia) are associated with inadequate sleep. Indeed, intervening with hormone therapy may improve sleep quality and, therefore, increase the likelihood that women become less symptomatic and can continue with their daily lives with fewer disturbances. While women report improved sleep quality when they receive hormonal and nonhormonal treatment for VMS, cognitive behavior therapy for insomnia is also a potentially safe and efficacious treatment strategy [20]. Specific dietary recommendations to curb sleep disturbances somewhat mirror those recommendations to curb VMS, including avoidance of alcohol and caffeine. Following a Mediterranean diet, as described in greater detail by Bray and Champagne in Chap. 15, may also attenuate age-related declines in sleep duration and quality [21]. Certain foods, such as milk products, fatty fish, tart cherry juice, and kiwifruit, may have sleep-promoting effects as well, but more research is needed [22].

Mood Swings

Life events that induce psychological stress are also more common among menopausal women. These life events include children leaving the home, as well as caring for aging or sick parents or relatives. While many women may not have overt clinical depression, many adverse psychological symptoms arise (e.g., decreased mood, self-worth, sense of well-being) and present with increased anxiety with menopause progression [3]. These symptoms should be treated, as these types of mood disorders can lead to poor dietary habits, including increased intake of fats, sugars, and salty foods. Furthermore, menopause and related mental health challenges are often socially stigmatized, which results in fewer women discussing their physical and mental health concerns with their doctors. Menopause begins for many women while still in the workforce, yet the majority of women are not comfortable with admitting to mental health issues that arise from menopause with employers or colleagues. Fighting this mental health stigma means more midlife women will be comfortable with asking for help regarding their symptoms.

Treatment Strategies Medical professionals should routinely screen during midlife for psychological symptoms and treat these problems when indicated. Education is critical to help women cope with the challenges of menopause. Pairing education with psychotherapy or non-pharmacologic remedies can even further reduce menopause-related stress, such as counseling and stress-reducing techniques (e.g., meditation, yoga). While antidepressants are commonly used as a more aggressive method of

treating mood disorders, an unwanted side effect of taking some antidepressants is weight gain (see Chap. 9 on obesity). Stress and emotional eating also contribute to and are a result of depressive symptoms during menopause. Eating a calorie-controlled diet rich in fruits, vegetables, and omega-3 polyunsaturated fatty acids is recommended to improve mood. Adequate intake of omega-3 polyunsaturated fatty acids, vitamin B12, iron, calcium, and folate may contribute to improved cognition and mood as well.

Social Isolation and Loneliness

Social transitions may occur independently and concurrently with menopause and may be initiated when children leave home, with changes in partnerships (e.g., divorce, separation, sexual intimacy), retirement, and with aging and death of loved ones. Such changes may disrupt previous routines and social interactions and may result in food insecurity, decreased motivation to prepare and consume meals, loss of appetite, and decreased physical activity.

Treatment Strategies To combat social isolation and feelings of loneliness, government-subsidized medical and social services have been established to support optimal nutrition in older adults. In the United States, the Older Americans Act Nutrition Programs provides financial support for in-home and community-based programs that provide meals, as well as nutrition screening, assessment, education, and counseling for those who find themselves more alone. Clinicians can screen for food insecurity using screening tools such as the Hunger Vital Sign [23], become familiar with local resources, and refer patients to social work and services as needed.

Bone Health

Menopause is the major risk factor for bone loss and osteoporosis and is thought to be responsible for an average annual bone loss of 2 to 3% during the first few years and 0.5 to 1% thereafter (see Chap. 11 on bone health). While osteoporosis is thought to affect one out of three postmenopausal women, many postmenopausal women do not receive standard osteoporosis screening. Osteoporosis is diagnosed by measuring BMD with dual-energy X-ray absorptiometry (DXA) of the spine, hip, and/or forearm (i.e., a T score of −2.5 or lower indicates osteoporosis) or by the presence of a low-trauma or fragility fracture. Since osteoporosis increases risk of subsequent pathologic fractures, which leads to future morbidity, mortality, and poor quality of life, adequate screening and treatment for osteoporosis is incredibly important among postmenopausal women – especially if weight loss treatments are undertaken.

Treatment Strategies Current screening recommendations for osteoporosis include screening BMD for all women ages >65 years, as well as younger women with risk factors [24]. Specific micronutrients that are important for bone health should be considered during menopause to attenuate age-related BMD loss. The consumption of oral calcium supplements is associated with attenuation of BMD loss, but the reduction in fracture incidence with calcium supplementation is inconclusive. In addition, bone demineralization and remineralization are orchestrated events dependent of the balance of several micronutrients including (but not limited to) calcium, vitamin D, vitamin K, magnesium, and phosphorus. While calcium and vitamin D supplementation is supported by the National Osteoporosis Foundation and the American Society for Preventive Cardiology to address dietary gaps in intake, women are also encouraged to consume a variety of calcium-rich foods (e.g., milk, cheese, yogurt, green vegetables such as kale and broccoli, and calcium-fortified foods such as soy products, cereals, and fruit juices) throughout the day. These calcium-rich foods are often also high in vitamin D, magnesium, phosphorus, and other nutrients critical to bone health and carry less health risk than single-nutrient supplementation. The recommended dietary allowance for calcium from foods and

supplements for postmenopausal women is 1200 mg/day (consuming no more than 500 mg at one time). Supplementation of any nutrient should be specific to the individual and based on clinical signs and symptoms particularly circulating concentrations of the nutrient when possible. Supplementation in the presence of adequate intake and blood metabolite concentrations, however, can lead to adverse health effects. In addition, given whole foods may have more bioavailable nutrients and synergistic effects of multiple compounds not found in dietary supplements, a "food-first" approach is encouraged.

While the benefits of weight loss on cardiometabolic health often outweigh the risks among middle-aged adults with overweight and obesity, its benefits may be countered by the accelerated loss of bone strength and BMD [7, 25] even if muscle mass is preserved [25]. Thus, medical professionals should track BMD regularly if a postmenopausal woman decides to undertake a weight loss program. Medical professionals should also prescribe resistance training exercises (versus endurance only) alongside any diet program to limit reductions in BMD and bone strength [7, 16].

Gastrointestinal Health

Changes in estrogen and progesterone levels throughout menopause may be responsible for slower gut motility and constipation in women in midlife. In addition to lower gut motility, atrophic gastritis is common with aging and leads to loss of gastric glandular cell function. Loss in function can result in decreased stomach acid production, which can decrease the digestion and absorption of nutrients including calcium. Indeed, atrophic gastritis is associated with osteoporosis in postmenopausal women.

Treatment Strategies The American Cancer Society recommends women have colonoscopy screening every 10 years beginning at age 50 years. Furthermore, gradually increasing fiber and fluid intake or consuming prune or plum juice may help alleviate constipation. If dietary modifications are not enough, magnesium-containing supplements and medications such as milk of magnesia may be considered. In cases where stomach acid production is reduced, calcium supplementation in the form of calcium citrate may be recommended as it is less dependent on stomach acid for absorption than calcium carbonate. In addition, atrophic gastritis causes a decrease in the production of intrinsic factor, which aids in the absorption of vitamin B12. Vitamin B12 injections may be prescribed to prevent or treat vitamin B12 deficiency.

Clinical Care Suggestions Throughout Menopause and Beyond

A woman can spend 40% or more of her life in a postmenopausal state; therefore, it is crucial to identify and manage gaps in nutrition, changes in body weight, menopause symptoms, and other comorbid conditions. Management of postmenopausal women is complicated by high interpatient variability and, thus, consideration needs to be given for each individual person. The lack of prescription-based weight loss advice and difficultly understanding how all these cardiometabolic risk factors and symptoms interact cause much frustration among midlife women and leave many medical professionals defenseless. Furthermore, many women do not consult an OB-GYN or their primary care physician about menopause-related concerns, and, therefore, these concerns often go unaddressed. Indeed, one of the biggest problems with treating menopause-related health outcomes is navigating its social stigmatization and the discomfort that women have talking about their physical and psychosocial challenges. As a result, medical professionals should frequently screen for common menopause-related problems – even if not brought up by the patient – and refer the patient to the appropriate healthcare professional and resources if indicated.

As noted above, the treatment guidelines for adults with overweight and obesity recommend an intensive lifestyle intervention that includes ≥14 in-person counseling sessions over the course of 6 months as the first-line treatment. It is unrealistic that the OB-GYN has the nutritional and behavioral expertise and time to deliver such an intervention on her/his own. Instead, nutrition and weight management concerns are best handled through the ongoing, coordinated care of multidisciplinary teams that include physicians, registered dietitians, and behavioral and social support professionals. Nutrition care plans and treatment are often reimbursable by the Centers for Medicare and Medicaid Services and other health plans.

COVID-19 Addendum

Since this chapter on *Dietary Considerations for Postmenopausal Women* was completed, the novel coronavirus (designated as SARS-CoV-2 or COVID-19) emerged and quickly resulted in a worldwide pandemic. Beginning in March 2020 in the United States, many state and local governments issued strict shelter-in-place orders to slow the coronavirus transmission [26]. Businesses and places of work were forced to temporarily close, and, thus, the usual structure of daily life for Americans and people around the world was altered. As a result, daily physical activity declined and self-reported snacking and overeating increased [27]. A recent study revealed a 0.27 kg (or 0.60 pounds) increase in weight every 10 days from February through June 2020, translating to approximately 2 pounds of weight gain every month [28]. An online survey of 7700 adults averaging 51 years of age (80% women) confirmed these findings, but additionally reported that levels of anxiety substantially increased especially among individuals with obesity [29]. These survey findings are important because the age and sex of these adults are similar to that of perimenopausal and postmenopausal women.

As detailed in our chapter, perimenopausal and postmenopausal women already experience a decline in physical and psychosocial health which we hypothesize was (and still is being) exacerbated by the COVID-19 pandemic. Before the pandemic, weight gain was already a concern for perimenopausal and postmenopausal women. Major life events such as death of a loved one, disability after an injury, pregnancy, and now the COVID-19 pandemic are known to cause weight gain. While life events themselves are relatively short-term, the resulting weight gained (on average about 40 pounds) may be retained for years after and potentially contribute to progressive increases in body mass index over the lifetime [30]. Techniques to reduce weight gain (i.e., increase physical activity and reduced food intake) and a shift to focus on losing that gained weight should be employed. Moreover, the anxiety and stress that midlife women frequently experience during menopause also increased during the COVID-19 pandemic [29] which likely increased the prevalence of mood swings, vasomotor symptoms, and sleep disturbances among women. Thus, in addition to weight loss, techniques to curb the added anxiety and stress fueled by the pandemic should also be utilized so that the overall quality of life is not further jeopardized.

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Suggested Further Readings

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Part III

Nutrition for the Prevention and Management of Chronic Conditions

Obesity: Understanding and Achieving a Healthy Weight

9

George A. Bray and Catherine M. Champagne

Keywords

Obesity · Body mass index · Diet · Treatment · Bariatric surgery

Key Points

- Obesity is a chronic, relapsing, stigmatized disease process that is increasing in prevalence, affecting both adults and children.
- A small positive energy imbalance from too much food or too little activity causes the obesity that is influenced by many environmental factors.
- The food we eat is more than "calories." Focusing on calories alone may not be as productive as focusing on patterns of eating and the role of sugar and fat in the diet.
- Obesity increases the risk of many diseases and shortens life span.
- Weight loss provides benefits in reducing health risks and improving the quality of life.
- Management of obesity must redress the energy imbalance with diet, lifestyle modification, exercise, medications, and, potentially, bariatric surgery.
- Five drugs are approved by the FDA for long-term treatment of obesity, and they can effectively improve health-related risks.
- Bariatric surgery has become a major treatment strategy and can reduce long-term health risks from obesity.

Introduction

Obesity is a chronic, relapsing, stigmatized disease that is increasing in prevalence worldwide and affecting both children and adults [1]. This chapter reviews the key facts around obesity with a primary focus on prevention and treatment. Since the subject is a large one, and we cannot cover all of its details, we have provided additional sources of information.

G. A. Bray (✉) · C. M. Champagne
Pennington Biomedical Research Center, Baton Rouge, LA, USA
e-mail: George.bray@pbrc.edu

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Definition

Obesity means having too much body fat, but measuring body fat accurately requires facilities that are not generally available. For this reason, measures of height and weight are usually substituted. Of these, the body mass index (BMI) is the most widely used. The BMI is defined as weight divided by the square of height [weight/height^2]. Table 9.1 provides the definitions of BMI used in the United States and some, but not all other countries, the exceptions being largely Asian countries.

Prevalence of Obesity

Using BMI as the criterion, a worldwide epidemic of obesity began in the 1980s and continues today [3]. Table 9.2 provides the most recent information from the Centers for Disease Control using the National Health and Nutrition Examination Survey data.

From the survey in 1999–2000 through the survey in 2017–2018, the prevalence of obesity increased from 30.5% to 42.2% and the prevalence of severe obesity, that is, individuals with a BMI $\geq$ 40 kg/m^2, increased from 4.7% to 9.2% indicating that heavier people are getting fat even faster than people with less fat. There are also clear effects of ethnicity and of gender (Table 9.2).

Centrally Located Body Fat

Excess fat located as intra-abdominal fat in deposits such as the liver or visceral adipose tissue is particularly hazardous to health. Measuring centrally located fat can be done accurately with magnetic resonance imaging (MRI) or computed tomographic (CT) scans, but these are costly to use for this purpose. The waist circumference is a practical alternative for use by healthcare professionals to

Table 9.1 Classification of weight status in the Unites States using the body mass index

BMI range	Weight status
Below 18.5	Underweight
18.5–24.9	Normal or healthy weight
25.0–29.9	Overweight
30.0 and above	Obese
30.0 to 34.9	Class I obesity
35.0 to 39.9	Class II obesity
≥40.0	Class III obesity

Data from CDC. Overweight and Obesity. Defining Adult Overweight and Obesity. https://www.cdc.gov/obesity/adult/defining.html [2]

Table 9.2 Prevalence of obesity using body mass index in data calculated by measuring a random sample of Americans over Age 20

Prevalence of obesity (BMI ≥30 kg/m^2)			
	Total	Male	Female
Non-Hispanic White	42.2%	44.7%	39.8%
Non-Hispanic Black	49.6%	41.1%	56.9%
Hispanic	44.8%	45.7%	43.7%
Non-Hispanic Asian	17.4%	17.5%	17.2%

Data from: Hales CM, Carroll MD, Fryar CD, Ogden CL. Prevalence of obesity and severe obesity among adults: United States, 2017–2018. NCHS Data Brief, no. 360. Hyattsville, MD: National Center for Health Statistics [4]

estimate central adiposity. If the BMI is between 20 and 35 kg/m^2, a waist circumference of >40 in. in American men and > 35 in. in American women provides a high-risk category. Most other areas of the world use lower cut points of 90–94 cm [35.5–37 in.] for men and 80 cm [31.5 in.] for women.

Basic Facts About Obesity

Etiology

At its simplest, obesity results from an imbalance between energy intake and energy expenditure [5, 6]. However, it is the connection between these two components that provides clues about how we should understand, prevent, and manage obesity [7]. Modification of future obesity begins with the pregnant woman and her fetus. This is a time where the healthcare professional can easily intervene – advise a pregnant woman not to smoke, to avoid consumption of sugary beverages, keep her weight gain within prescribed levels, and treat gestational diabetes if it occurs since all of these increase risk to the infant for obesity later in life [7].

Postnatal factors also affect the risk of obesity, but intervention is more challenging. Genes clearly underlie the risk of obesity [8], and "genes can be said to load the gun, while the environment pulls the trigger" [9].

Food patterns including the "Western" high-fat/high-sugar diet and sugary beverages enhance the risk of weight gain [5, 7]. Social settings including watching television and the amount of sleep an individual gets are other factors which an individual can modulate [7]. Portion sizes have increased, providing more energy to people with each portion, and people tend to eat more when larger portions are provided. Medications, toxins, viruses, and the microbiome are additional factors that play a role in the risk of obesity. Obesogens, a group of chemical agents used in many manufacturing processes including plastics, can produce obesity in animals and are of concern for humans. Viruses are known to produce obesity in animals, and their potential role in obesity in humans needs further study.

Some medications are known to cause weight gain, and these are listed in Table 9.3 along with potential alternatives. The health professional can use this knowledge to intervene by replacing the medications which cause weight gain with the ones that do not when this is medically reasonable. Physical activity has gradually declined, meaning we need less food energy for our daily life [7].

Pathology and Pathogenesis of Diseases Associated with Obesity

The pathology of obesity results from enlarged and/or too numerous fat cells. The fat they contain and the adipokines they release have effects on distant tissues that can cause disease. Increasing body fat increases demands from many other organ systems and can be the basis for causing many of the diseases associated with obesity including diabetes mellitus, hypertension, nonalcoholic fatty liver disease, sleep apnea, osteoarthritis, coronavirus (SARS-2-CoV-2) or COVID-19, and cardiovascular disease as described in the paper by Bray et al. [1].

Costs Associated with Obesity

Obesity is an expensive disease process, costing between 3% and 8% of healthcare budgets [10].

Table 9.3 Medications that produce weight gain and possible alternatives

Category	Drugs that may cause weight gain	Possible alternatives
Antipsychotics	Thioridazine; olanzapine; quetiapine; risperidone; haloperidol; perphenazine; clozapine	Molindone Ziprasidone
Antidepressants Tricyclic antidepressants Monoamine oxidase inhibitors Selective serotonin Reuptake inhibitors	Amitriptyline; nortriptyline Imipramine; trimipramine Mirtazapine Paroxetine Doxepin	Protriptyline Bupropion Nefazodone Fluoxetine (short-term) Sertraline (<1 year)
Anticonvulsants	Valproate, Carbamazepine Gabapentin	Topiramate Lamotrigine Zonisamide
Antidiabetic drugs	Insulin Sulfonylureas Glinides Thiazolidinediones	Acarbose Miglitol Metformin Pramlintide Exenatide; liraglutide SGLT-2 inhibitors
Antiserotonin	Pizotifen	
Antihistamines	Cyproheptidine	Inhalers Decongestants
β-Adrenergic blockers α-Adrenergic blockers	Propranolol Terazosin	ACE inhibitors Calcium channel blockers
Steroids for chronic inflammatory disease	Glucocorticoids	Nonsteroidal anti-inflammatory agents and disease-modifying anti-rheumatic drugs
Contraceptives	Progestational steroids	Barrier methods
Endometriosis	Depot leuprolide acetate	Surgical intervention

Treatment

The first step in treating any patient with obesity is to evaluate them and their needs and wishes [11]. Guidelines for the management of the patient with obesity have been published by three organizations [11–13]. The Guidelines for Obesity from the AHA/ACC/TOS provide an algorithm to help in making this assessment [11]. It is a useful framework on which to hang basic clinical information that is collected during the examination. Effective weight loss requires a reduction in energy (calorie) intake relative to energy expenditure that lasts over time [11]. The energy in our diet comes from protein, fat, and carbohydrate. It is the manipulation of the amounts of these macronutrients, and the foods that provide them that is the basis for all dietary approaches to weight loss.

There is high variability of weight loss with all weight loss programs. Some patients will lose a lot of weight, others a modest amount, and some will actually gain weight. In one clinical trial with over 3000 people (Look AHEAD) which used the best available lifestyle intervention, 10% of the individuals lost less than 1 kg after 1 year and 25% loss less than 3 kg, while the average loss was about 7.5 kg, meaning that some patients lost a lot of weight – 25% lost more than 12 kg and 10% lost more than 17 kg [14]. Thus, no matter what program you and your patient/client select, there will be some great successes and other dismal failures. The patient needs to be prepared for this because we have no way of predicting success or failure with any confidence before treatment begins.

The fourth concern for patients and healthcare providers is that with all weight loss programs, initial weight loss slows and then stops at a "plateau" which is often less than the patient's desired weight loss which is followed in turn by frustration and weight regain. This is one of the most perplexing problems for patients and healthcare providers alike. For many patients, a "dream weight loss" would be the amount of a loss of nearly 30% of their body weight, which is outside the efficacy of any program other than surgery [15]. A loss of less than 17%, which is also greater than can be delivered by most lifestyle programs, was considered by many patients to be a disappointment. It is thus important for the patient and healthcare provider to recognize that an initial weight loss of 10% is a success and is one that will produce measurable health benefits.

A final issue is the "false hope syndrome." Each year sees the publication of new diet books which promise amazing results. Each year people who have regained weight the year before vow to try again using the next popular diet or weight loss plan, believing they can overcome last year's failure. They labor under the delusion of the "false hope syndrome," i.e., that having failed last time, they are sure to succeed this time [16].

Components of a Comprehensive Program

The cornerstone of treatment for obesity is a comprehensive program involving diet, exercise, and behavioral therapy aimed at helping patients lose and maintain weight loss [11]. The elements of such a program are outlined in Table 9.4.

Table 9.4 Key components of comprehensive behavioral weight loss interventions to achieve a 7–10% weight loss [11]

Component	Weight loss	Weight loss maintenance
Frequency and duration of treatment contact	Weekly contact, in person or by telephone, for 20–26 weeks (internet/e-mail contact yields smaller weight loss) Group or individual contact	Every-other-week contact for 52 weeks (or longer) Monthly contact likely adequate Group or individual contact
Dietary prescription	Low-calorie diet (1200–1500 kcal for those <250 lb.; 1500–1800 kcal for those ≥250 lb) Typical macronutrient composition: ≤30% fat (≤7% saturated fat), 15–25% protein, remainder from carbohydrate (diet composition based on individual needs or preferences)	Consumption of a hypocaloric diet to maintain reduced body weight Typical macronutrient composition similar to that for weight loss
Physical activity prescription	180 minutes/week of moderately vigorous aerobic activity (e.g., brisk walking), strength training also desirable	200–300 minutes/week of moderately vigorous aerobic activity (e.g., brisk walking), strength training also desirable
Behavior therapy prescription	Daily monitoring of food intake and physical activity by the use of paper or electronic diaries Weekly monitoring of weight Structured curriculum of behavior change (e.g., diabetes prevention program) Regular feedback from an interventionist	Occasional to daily monitoring of food intake and physical activity by the use of similar diaries Twice weekly to daily monitoring of weight Curriculum of behavior change, including relapse prevention and individualized problem solving Periodic feedback from an interventionist

Adapted from Jensen MD, Ryan DH, Donato KA et al. Guidelines (2013) for managing overweight and obesity in adults. Obesity 2014;22(S2):S1–S410

Diet

Diet has two meanings. On the one hand, it describes the sum total of foods that we consume to maintain health. On the other hand, diet focuses on specific combinations of foods for specific health purposes. It is this latter meaning that we explore below.

Each year the US News and World Report publishes a list of "healthy" diets for Americans based on the review by a panel of experts [17]. We have included their sub-list that ranks weight loss diets (Table 9.5).

Since the calories (energy) in food comes from proteins, fats, carbohydrates, and alcohol in those foods, it is the reduction of one or more of these components of the diet that is essential if calorie

Table 9.5 Popular weight loss diets based on their ranking of the US News and World Report in 2020. Information from US News and World Report 2020. https://www.usnews.com/info/blogs/press-room/articles/2020-01-02/us-news-reveals-best-diets-rankings-for-2020 [17]

Diet name	Rank	Score	Type of diet
Weight Watchers diet	1	3.6	Healthy fast weight loss
Vegan diet	2[a]	3.5	Extremely restrictive diet
Volumetrics diet	2[a]	3.5	Safe, nutritious diet focusing on low energy dense foods
Flexitarian diet	4[a]	3.4	Mostly vegetarian, meat occasionally
Jenny Craig diet	4[a]	3.4	Weight loss diet
Ornish diet	6	3.3	Heart-healthy, low-fat diet
Engine 2 diet	7[a]	3.2	Restrictive diet
Mayo Clinic diet	7[a]	3.2	Healthy lifelong eating habit
Raw food diet	7[a]	3.2	Impossible to follow
DASH diet	10[a]	3.1	Moderate fat, balanced
HMR program	10[a]	3.1	Fast weight loss, pricey
Nutrisystem diet	10[a]	3.1	May have nutrient deficiencies
Slim fast diet	10[a]	3.1	Less healthy, better for weight loss on short term
Vegetarian diet	10[a]	3.1	Plant-based diet
Atkins diet	15[a]	3.0	High-fat, not a good all-purpose diet
Biggest loser diet	15[a]	3.0	Fast weight loss
Keto diet	15[a]	3.0	High-fat, low-carb, using fat for energy
Mediterranean diet	15[a]	3.0	Higher fat, healthy
Nutritarian diet	15[a]	3.0	Plant-based nutrient density focus
Optavia diet	15	3.0	Low for healthy eating, quick weight loss
South Beach diet	15[a]	3.0	Restrictive rapid weight loss
Asian diet	22[a]	2.9	Traditional Asian diet
Nordic diet	22[a]	2.9	Healthy plant-based diet
Macrobiotic diet	24[a]	2.8	Strict macrobiotic plan
TLC diet	24[a]	2.8	Promotes cardiac health
Zone diet	24[a]	2.8	Tedious with macronutrient targets
MIND diet	27	2.7	Aims to prevent mental decline
The fast diet	28[a]	2.6	Lack of nutritional guidance
Paleo diet	28[a]	2.6	Caveman diet
Dukan diet	30[a]	2.5	Too restrictive, no evidence
Glycemic index diet	30[a]	2.5	Good carb, bad carb diet
Dr. Weil's anti-inflammatory diet	32[a]	2.4	Cardiovascular-focused diet
Fertility diet	32[a]	2.4	Pregnancy-aimed diet
Whole30 diet	34	2.3	No science; severely restrictive
Alkaline diet	25	2.1	Avoids acidic foods

[a]Tie; diets were rated by the experts on a scale of 1 to 5 with 5 being best

intake is to be reduced below daily energy expenditure for successful weight loss. Protein usually makes up 12–20% of dietary calories, fat anywhere between 25% and 45%, and carbohydrate the rest. Since carbohydrate and fat are the major sources of calories, they are the central focus for most diets.

Balanced Low-Calorie Diets

Diets in this category reduce the intake of both fat and carbohydrate which may increase the percentage of protein. The underlying hypothesis is that reducing calories is essential for weight loss [11]. Examples would be the DASH diet; a lower calorie diet based on MyPyramid food guide; Weight Watchers diet, a derivative of the Prudent Diet; and the Volumetrics diet. However, most meal plans can be balanced yet provide lower calorie intake if the individual self-monitors their calorie intake.

Low-Carbohydrate/Keto Diets

The low- and very-low-carbohydrate or keto diets reduce the quantity of carbohydrate below 30% and often go as low as 10% or less. They have been popular for more than 100 years, and books touting them occur on a regular basis. The hypothesis behind this diet is the carbohydrate-insulin hypothesis which argues that dietary carbohydrate stimulates insulin which drives fat formation and thus obesity [18], a concept which isn't universally accepted [19]. Two large trials have compared the diet composition and found that very low, moderately low, or normal carbohydrate made no difference in weight loss [20, 21]. In a meta-analysis comparing low-fat and low-carbohydrate diets where the two diets had the same amount of protein, Hall and Guo [22] concluded that there was no clinically significant difference.

Low-Fat Diets

The low-fat diet is premised on the idea that reducing fat will decrease energy intake and thus produce weight loss. These diets like the low-carbohydrate diets have been popular for more than 100 years. Examples of these diets include the Ornish diet, the Pritikin diet, the T-factor diet, and others.

Table 9.6 is a compilation of several of diet types which provide the main elements for many diets. Assessing the value of diets is best done with a meta-analysis of head-to-head comparisons. A recent such meta-analysis examined 121 trials with 21,942 patients comparing 14 named diets and 3 control diets. Compared with the usual diet, diets low in carbohydrate or low in fat had similar effects on weight loss at 6 months (4.63 kg vs 4.37 kg) and reduction in systolic blood pressure and diastolic blood pressure [23]. Moderate-macronutrient diets resulted in slightly less weight loss and blood pressure reductions. Low-carbohydrate diets had less effect than low-fat diets and moderate-macronutrient diets on reduction in LDL cholesterol but an increase in HDL cholesterol, whereas low-fat diets and moderate-macronutrient diets did not. Among popular named diets, those with the largest effect on weight reduction and blood pressure in comparison with a usual diet after 6 months were the Atkins diet, the DASH diet, and the Zone diet. No diets significantly improved levels of HDL cholesterol or C-reactive protein at 6 months. Weight loss diminished at 12 months with all dietary patterns and

Table 9.6 Comparison of diet programs and eating plans to the typical American diet

Type of diet	Example	General dietary characteristics	Comments	AHA/ACC/TOS evaluation
Typical American diet		Carb: 50% Protein: 15% Fat: 35% Average of 2200 kcal/d	Low in fruits and vegetables, dairy, and whole grains High in saturated fat and unrefined carbohydrates	

(continued)

Table 9.6 (continued)

Type of diet	Example	General dietary characteristics	Comments	AHA/ACC/TOS evaluation
Balanced nutrient, moderate-calorie approach	DASH diet or diet based on the MyPyramid food guide; commercial plans such as diet center, Jenny Craig, NutriSystem, Physician's weight loss, Shapedown pediatric program, Weight Watchers, Setpoint diet, Sonoma diet, and Volumetrics	Carb: 55–60% Protein: 15–20% Fat: 20–30% Usually 1200–1800 kcal/d	Based on a set pattern of selections from food lists using regular grocery store foods or prepackaged foods supplemented by fresh food items Low in saturated fat and ample in fruits, vegetables, and fiber Recommended reasonable weight loss goal of 0.5–2.0 lb./week Prepackaged plans may limit food choices Most recommend exercise plan Many encourage dietary record keeping Some offer weight-maintenance plans/support	
Low- and very-low-fat, high-carbohydrate approach	Ornish diet (eat more, weigh less), Pritikin diet, T-factor diet, choose to lose, fit or fat	Carb: 65% Protein: 10–20% Fat: ≤10–19% Limited intake of animal protein, nuts, seeds, and other fats	Long-term compliance with some plans may be difficult because of the low level of fat Can be low in calcium. Some plans restrict healthful foods (seafood, low-fat dairy, poultry) Some encourage exercise and techniques for *stress management*	The same weight loss at 6 months comparing <30% fat to >40% fat Strength of evidence – Moderate
Low energy density	Volumetrics	Carb: 55% Protein: 10–25% Fat: 20–35% Focus on fruits, vegetables, and soups	Four food categories: Very low energy density – Non-starchy fruits and veggies, nonfat milk, broth-based soups Low energy density – Starchy fruits/veggies, grains, breakfast cereal, low-fat meats, and mixed dishes Medium energy density – Meat, cheese, pizza, fries, dressings, bread, etc. High energy density – Desserts, nuts, and butter, oils Focus on categories 1 and 2, some from 3, minimum from 4	More weight loss at 6 months with low-energy-dense diet: RCT

Table 9.6 (continued)

Type of diet	Example	General dietary characteristics	Comments	AHA/ACC/TOS evaluation
Portion-controlled	The use of meal replacements, both liquid and solid meals			Weight loss at 1 year in the look AHEAD trial related to the frequency of consuming portion-controlled meals
Mediterranean style diets		Carb: 35–40% Protein: 12–20% Fat: 40–50% Approximately 25–30% of energy from monounsaturated fat	Eat primarily plant-based foods (fruits, vegetables, whole grains, legumes, and nuts) Healthy oils (olive) instead of saturated fats Limit red meat to a few times a month Eat fish and poultry at least twice a week Red wine in moderation, if you choose to drink alcohol Be active and enjoy meals with family and friends	Meta-analysis showed more weight loss with Mediterranean diet than low-fat diets (weighted-mean difference = 2.2 kg)
Low-carbohydrate, high-protein, high-fat approach	Atkins new diet revolution, protein power, Stillman diet (*the Doctor's quick weight loss diet*), *the carbohydrate Addict's diet*, Scarsdale diet	Carb: ≤20% Protein: 25–40% Fat: ≥55–65% Strictly limits carb to less than 100–125 g/d	Promotes quick weight loss (much is water loss rather than fat) Ketosis causes loss of appetite. Can be too high in saturated fat Low in carbohydrates, vitamins, minerals, and fiber Not practical for long term because of rigid diet or restricted food choices	The same weight loss at 6 months comparing <30 g/d vs 55% carb, 15% protein, or 40% carb and 30% protein: Strength of evidence – Low
Higher-protein, moderate-carbohydrate, moderate-fat approach	The zone diet, sugar busters, south beach diet	Carb: 40–50% Protein: 25–40% Fat: 30–40%	Diet rigid and difficult to maintain Enough carbohydrates to avoid ketosis Low in carb; can be low in vitamins and minerals	The same weight loss at 6 months comparing 25–30% vs 15% protein Strength of evidence – High
Glycemic load (GL)	The glycemic-load diet – Rob Thompson	Carb: 40–>55% Protein: 15–30% Fat: 30%	Focus on low-GL foods	The same weight loss at 6 months comparing high vs low GL Strength of evidence – Low
Low- or no sugar-sweetened beverages (SSBs)	Not really a diet but just a call to reduce SSB intake as a preventive strategy	No recommendations other than to reduce/remove SSBs from the overall diet plan	Meta-analyses show that the consumption of SSBs is related to the risk of obesity, diabetes, and heart disease	In sustained intervention studies, low-energy beverages showed lower energy intake and less weight gain than sugar-containing beverages

(continued)

Table 9.6 (continued)

Type of diet	Example	General dietary characteristics	Comments	AHA/ACC/TOS evaluation
Novelty diets	Immune power diet, rotation diet, cabbage soup diet, Beverly Hills diet, Dr. Phil	Most promote certain foods, or combinations of foods, or nutrients as having allegedly magical qualities	No scientific basis for recommendations	
Very-low-calorie diets	Health management resources (HMR), Optavia Optifast	Less than 800 kcal/d	Requires medical supervision For clients with BMI ≥30 or BMI ≥27 with other risk factors; may be difficult to transition to regular meals	
Weight-loss online diets	Cyberdiet, DietWatch, eDiets, Nutrio.com	Meal plans and other tools available online	Recommend reasonable weight loss of 0.5–2.0 lb./week Most encourage exercise Some offer weight maintenance plans/support	

popular named diets. The benefits on cardiovascular disease essentially disappeared at 12 months, except for the Mediterranean diet.

Energy Density

The Volumetrics diet was no. 5 in the US News and World Report list of diets in 2020 [17]. It focuses on energy density as a guide to selecting foods and reducing energy intake. The diet is low in fat and rich in fruits and vegetables which give the diet a high-water content. This diet reduces calorie intake by providing bulkier foods with more water and less fat, thus enhancing satiety.

Portion-Controlled Diets

Portion control is one dietary strategy with promising long-term results. A trial in patients with diabetes using portion-controlled diets as part of the lifestyle intervention in the Look AHEAD Study found that weight loss was increased across each quartile of increased use of portion control foods [24].

Timed-Food Intake: Intermittent Fasting and Timed Meals

Intermittent fasting and time-restricted Feeding are two other strategies that may reduce energy intake and thus produce weight loss. When 11 studies of intermittent fasting or timed-energy restriction were compared to continuous calorie restriction, 9 of the studies showed no difference [25], and the 2 studies which reported benefit from these strategies were modest, at best. One study suggested that early timed-restricted feeding might improve insulin sensitivity in individuals with prediabetes even when there was no weight loss.

Behavior Modification and Lifestyle Interventions

Behavioral modification in lifestyle programs has been an important part of programs for weight loss for more than half a century with weight losses in the 5–10% range [11]. Behavior modification has a

number of components. First, it is a strategy designed to help people understand their eating behavior, from the triggers that start eating to the location, speed, and type of eating, through the consequences of eating and the rewards that can change it. In addition, it consists of strategies to help people develop assertive behavior, learn cognitive techniques for handling their internal discussions, and ways of dealing with stress. The newest innovation in the use of lifestyle intervention is to implement it over the Internet which has shown some promising results [1].

Exercise

Exercise is important for maintaining weight loss, but when used alone it does not generally produce much weight loss. A comparison of people who successfully maintain weight loss and those who do not shows a critical role of exercise. More than 200 min/week provides greater likelihood of maintaining weight loss than lower levels of exercise. Using a pedometer or wrist-activated device allows counting of steps. Working toward 10,000 steps per day is a good goal, and one that the healthcare provider should encourage.

Medications

Five medications are currently approved by the US Food and Drug Administration for long-term management of obesity along with four older drugs approved for short-term use (Table 9.7) [1, 12]. In addition there are several drugs that affect body weight but are not currently approved by the FDA for management of patients with obesity. These include leptin, amylin, oxyntomodulin, and inhibitors of glucose transport in the kidney or intestine (SGLT 1 or 2).

Noradrenergic Drugs (Many Trade Names)

Diethylpropion, phentermine, benzphetamine, and phendimetrazine were approved in the 1950s by the US Food and Drug Administration (FDA) for short-term use, based on data from clinical trials that were usually less than 3 months [1]. These drugs probably work by enhancing the availability of norepinephrine in the interneuronal space either by blocking reuptake of norepinephrine into neurons or enhancing its release. Phentermine is one of the most widely prescribed appetite suppressants [26]. The clinician is advised to use this drug and other similar drugs with care and to inform patients of the potential for abuse and the potential cardiovascular risks.

Drugs That Increase Intestinal VOLUME

Gelesis

Gelesis 100 (Plenity^{R}) was approved by the US FDA for the management of obesity in 2019 and is the latest prescription drug to be approved. It is taken with water before lunch and dinner. It is produced by cross-linking cellulose and citric acid to create a three-dimensional hydrogel matrix. The capsules release thousands of non-aggregating particles that rapidly absorb water in the stomach, creating small individual pieces of gel which have the firmness of plant-based foods, such as vegetables, but without providing calories. This product is approved for individuals with a BMI as low as 25 kg/m^2. There is also no limit on how long Gelesis100 can be used. A clinical trial with Gelesis100 produced a weight loss of 6.4% versus 4.6% for the placebo group after 6 months [27].

Table 9.7 Drugs approved by the US Food and Drug Administration for the management of obesity

Drug and mechanism of action	Trade name(s)	Dosage	Comments
Gastrointestinal fiber			
Gelesis 100 (2019) (not scheduled)	Plenity	3 capsules 20 min before lunch and dinner with 16 oz. of water	No DEA schedule Approved for BMI 25–40 kg/m^2 Composed of cellulose and citric acid
Pancreatic lipase inhibitor approved for long-term use orally			
Orlistat (1999) (not scheduled)	Xenical	1120 mg tid before meals OR 660 mg tid before meals (OTC)	GI side effects including steatorrhea, oily spotting, flatulence, fecal urgency, fecal urgency, and/or incontinence
Glucagon-like receptor-1 agonist approved for long-term use by injection			
Liraglutide (2015) (not scheduled)	Saxenda	33.0 mg/d – Dose-escalation over 5 weeks from 0.6 mg/d to 3.0 mg/d	**Boxed warning**: Thyroid C-cell tumors in mice. Nausea with some vomiting are principal side effects; acute pancreatitis or gall bladder disease can occur; hypoglycemia with some antidiabetic drugs
Combination of two drugs approved for long-term use orally			
Phentermine/topiramate extended release (2012) DEA schedule IV (combination of sympathomimetic and anticonvulsant)	Qsymia	3.75 mg/23 mg, first week; 7.5 mg/46 mg thereafter; can increase to 15 mg/92 mg for inadequate response	Contraindicated in pregnancy; fetal toxicity with monthly pregnancy test suggested; paresthesthesias and change in taste (dysgeusia); acute myopia (rare) Metabolic acidosis and glaucoma are rare; do not use within 14 days of a MAOI antidepressant
Naltrexone SR/ bupropion SR (2014) (not scheduled) Opioid receptor antagonist Dopamine and norepinephrine reuptake inhibitor	Contrave (US) Mysimba (Europe)	32 mg/360 mg tabs; take two twice daily after dose- escalation	**Boxed warning:** Suicide risk in depression; contraindicated in pregnancy, in seizures, with uncontrolled hypertension and glaucoma. Nausea, constipation, headache Avoid in patients receiving opioids, MAOI, antidepressants, and with history of seizure disorder
Noradrenergic drugs approved for short-term use			
Diethylpropion (1959) DEA schedule IV	Tenuate Tepanil	25 mg tid	Dizziness, dry mouth, insomnia, constipation, irritability Cardiostimulatory
	Tenuate Dospan	75 mg q AM	
Phentermine (1959) DEA schedule IV	Adipex Fastin	15–37.5 mg/d	Dizziness, dry mouth, insomnia, constipation, irritability Cardiostimulatory
	Oby-cap IIonamin slow release	15–30 mg/d	
Benzphetamine (1960) DEA schedule III	Didrex	25–50 mg tid	Dizziness, dry-mouth, insomnia, constipation, irritability. Cardiostimulatory
Phendimetrazine (1959) DEA schedule IV	Bontril Plegine Prelu-2 X-Trozine	17.5–70 mg tid 105 mg qd	Dizziness, dry mouth, insomnia, constipation, irritability Cardiostimulatory

Drugs That Modify Intestinal Absorption of Fat

Orlistat (Marketed Worldwide as Xenical)

Orlistat (Xenical^{R}) is a potent and selective inhibitor of pancreatic lipase and thus reduces intestinal digestion of fat. In a meta-analysis of 31 studies using orlistat, the maximal weight loss using computer modeling was −6.65 kg, and the half-time to the maximal effect occurred by 35.4 weeks [28].

Orlistat is the only FDA-approved medication for weight management in both adolescents and adults with obesity. It is available by prescription at a dose of 120 mg tid before meals and also over-the-counter at a dose of 60 mg under the trade name Alli^{R}. Small but significant decreases in fat-soluble vitamin levels may occur, and it is recommended that patients take vitamin supplements. Frequent oily bowel movements and steatorrhea often occur in patients using orlistat. Reducing dietary fat will reduce this unwanted outcome.

Lorcaserin (Withdrawn in February 2020)

Lorcaserin (Belviq^{R}) was withdrawn from the market in February 2020 due the report of 7.7% incidence of cancer in the lorcaserin arm compared to 7.1% in the placebo arm.

Glucagon-Like Peptide Receptor-1 Agonists

Drugs with this mechanism of action have been approved for the management of both diabetes and obesity. In some cases the same chemical is used for both conditions, but with different trade names and different dose recommendations. In other cases, a specific drug is only approved for one indication and not the other.

Exenatide

Exenatide (Byetta^{R}, Bydureon^{R}), approved in 1995 by the US FDA for diabetes, is a long-acting analogue of glucagon-like peptide-1. This drug delays gastric emptying and promotes a feeling of fullness after eating. In addition, some patients experience weight loss during treatment, but the drug is not approved for the management of obesity. One disadvantage of this medication is that it must be injected subcutaneously twice daily. In addition, it causes severe nausea in some patients, especially during the initiation of therapy.

Liraglutide (Marketed as Victoza^{R} for Diabetes at a Dose of 1.2 or 1.8 mg/d and as Saxenda^{R} at a Dose of 3.0 mg/d for the Management of Obesity)

Liraglutide has a 97% homology to GLP-1, which extends the circulating half-life from 1–2 minutes to 13 hours. The use in adult and pediatric patients with diabetes is limited to 1.2 mg/d or 1.8 mg/d. Weight loss is often observed in both adults and children with diabetes who are treated with liraglutide [29].

For the management of obesity, a higher dose of 3.0 mg/d (Saxenda^{R}) should be prescribed in combination with a reduced-calorie diet and increased physical activity in adult patients with obesity who have an initial BMI of ≥30 kg/m^2 or in adult patients with a BMI ≥27 kg/m^2 and who have diabetes mellitus, hypertension, or dyslipidemia. Liraglutide has not yet been approved for the management of obesity in children.

In a meta-analysis of three studies using liraglutide, the maximal computer-modeled weight loss was −7.68 kg, and half the maximal effect occurred by 12.7 weeks [28].

This drug is contraindicated in patients with a history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2. Clinicians should not prescribe liraglutide for patients with a history of pancreatitis and should discontinue liraglutide if acute pancreatitis develops. If weight loss doesn't exceed 4% after 16 weeks, liraglutide should be stopped.

There have been two cardiovascular outcome trials with liraglutide (1.8 mg/d). In patients with diabetes mellitus, liraglutide significantly lowered the rate of the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.

Combination of Two Drugs for the Management of Obesity

Two different drug combinations are currently approved by the US FDA for the management of obesity.

Combination of Topiramate and Phentermine: Extended Release

The combination of phentermine/topiramate ER (PHEN/TPM ER) (marketed as Qsymia^{R}) is approved by the US FDA, but not by the European Medicines Agency. It uses lower doses of phentermine than are usually prescribed when phentermine is used alone. Phentermine acts on norepinephrine reuptake receptors, whereas topiramate may reduce appetite through its effect on GABA receptors.

A meta-analysis of six studies using the combination of phentermine/topiramate found a maximal weight loss of −15.6 kg, and the half-time for the maximal effect was 29.8 weeks using a computer-modelled approach [28]. There were improvements in blood pressure, glycemic measures, HDL cholesterol, and triglycerides with both the middle and the top doses, which were related to the magnitude of weight loss. In patients with obstructive sleep apnea, this combination reduced the severity of these symptoms.

Topiramate, alone, in the first trimester of pregnancy may increase the risk of cleft lip/cleft palate in infants, and this combination is contraindicated in pregnancy. Glaucoma is a rare side effect of topiramate, and the drug is contraindicated in glaucoma as it is in patients with hyperthyroidism and within 14 days of treatment with monoamine oxidase inhibitors. Topiramate is a carbonic anhydrase inhibitor that often produces tingling in the fingers and may affect the taste of carbonated beverages. Other potential issues include a risk for kidney stones (associated with topiramate) and increased heart rate in patients susceptible to phentermine.

Combination of Naltrexone-Bupropion: Sustained Release

Naltrexone/bupropion (Contrave^{R} in the United States; Mysimba^{R} in Europe) is approved by the US FDA and in Europe. Bupropion, as a single agent, is approved for the treatment of depression and for smoking cessation. It reduces food intake by acting on adrenergic and dopaminergic receptors in the hypothalamus. Bupropion alone has a modest effect on weight loss, but is not approved as a separate medication for management of obesity. Bupropion stimulates the pro-opiomelanocortin (POMC) neurons in the hypothalamus to produce α-melanocyte-stimulating hormone, which reduces food intake, and β-endorphin (which stimulates feeding). Naltrexone blocks the effect of β-endorphin on appetite, thus allowing the inhibitory effects of α-melanocyte stimulating hormone to reduce food intake by acting on the melanocortin-4 receptor system.

In a meta-analysis of six studies using naltrexone/bupropion, the maximal computer-modeled weight loss was −13.2 kg, and the half-time to the maximal effect was 35.2 weeks which was probably related to the titration schedule [28]. Treatment improved fasting glucose, fasting insulin, homeostasis assessment model of insulin resistance (HOMA-IR), and HDL cholesterol, but there was a transient increase in BP.

Best Practices for the Use of Medications Approved for the Management of Obesity

Criteria for using medications approved for long-term management of obesity were agreed upon between the 2013 American Heart Association/American College of Cardiology/The Obesity Society Guideline for the Management of Overweight and Obesity in Adults [11] and the 2015 Endocrine Clinical Practice Guideline on Obesity Pharmacotherapy [12]. Clinicians may consider prescribing medications to reduce body weight in patients who (1) struggle to achieve weight loss goals, (2) meet label indications (BMI >30 kg/m^2 or > 27 kg/m^2 with comorbidities), and (3) need to lose weight for

health reasons (such as osteoarthritis, prediabetes, fatty liver, or other conditions). Furthermore, the American Association of Clinical Endocrinologists/American College of Endocrinology Comprehensive Clinical Practice Guidelines for Medical Care of Patients with Obesity from 2016 [13] indicate that clinicians may consider pharmacotherapy as a first line for weight management if patients present with one or more severe comorbidities and would benefit from weight loss of 10% or more. Those guidelines do not require that patients fail lifestyle therapy before clinicians prescribe medications.

Dietary Supplements Used to Manage Obesity

In addition to prescription medications, there are a number of agents available in pharmacies and health food stores that are touted by some to be helpful for patients with obesity [30]. Table 9.8 shows a list of some of these complementary and over-the-counter products with comments on their efficacy and safety.

Table 9.8 Complementary and over-the-counter products used by some individuals for the management of obesity

Ingredient	Proposed mechanism of action	Evidence of efficacy	Safety concerns
Chromium	Increases lean muscle mass; promotes fat loss; and reduces food intake, hunger levels, and fat cravings	Several clinical trials of varying methodological quality *Research findings*: Minimal effect on body weight and body fat	No safety concerns reported at recommended intakes (25–45 mcg/day for adults) *Reported adverse effects*: Headache, watery stools, constipation, weakness, vertigo, nausea, vomiting, and urticaria (hives)
β-Methyl-β-hydroxybutyrate	Metabolite of leucine produced in 0.3 g/d, but is taken in doses of 30–60 g/d	Used in conditions of muscle wasting and to augment muscle in athletes. A 2015 meta-analysis found HMB supplementation can preserve lean muscle mass in older adults	In humans, no adverse effects in young adults or older adults have been reported when HMB-ca is taken in doses of 3 grams per day for up to a year
Pyruvate	Increases lipolysis and energy expenditure	Few clinical trials of weak methodological quality *Research findings*: Possible minimal effect on body weight and body fat	Few safety concerns reported *Reported adverse effects*: Diarrhea, gas, bloating, and (possibly) decreased high-density lipoprotein levels
Conjugated linoleic acid (CLA)	Promotes apoptosis in adipose tissue	Several clinical trials *Research findings*: Minimal effect on body weight and body fat	Few safety concerns reported *Reported adverse effects*: Abdominal discomfort and pain, constipation, diarrhea, loose stools, dyspepsia, and (possibly) adverse effects on blood lipid profiles

(continued)

Table 9.8 (continued)

Ingredient	Proposed mechanism of action	Evidence of efficacy	Safety concerns
Calcium	Increases lipolysis and fat accumulation, decreases fat absorption	Several large clinical trials *Research findings*: No effect on body weight, weight loss, or prevention of weight gain based on clinical trials	No safety concerns reported at recommended intakes (1000–1200 mg/day for adults) *Reported adverse effects*: Constipation, kidney stones, and interference with zinc and iron absorption at intakes above 2000–2500 mg for adults
Green tea (*Camellia sinensis*) and green tea extract	Increases energy expenditure and fat oxidation, reduces lipogenesis and fat absorption	Several clinical trials of good methodological quality on green tea catechins with and without caffeine *Research findings:* Possible modest effect on body weight	No safety concerns reported when used as a beverage, contains caffeine; some safety concerns reported for green tea extract *Reported adverse effects (for green tea extract):* Constipation, abdominal discomfort, nausea, increased blood pressure, liver damage
Green coffee bean extract (*Coffea arabica*, *Coffea canephora*, *Coffea robusta*)	Inhibits fat accumulation, modulates glucose metabolism	Few clinical trials, all of poor methodological quality *Research findings*: Possible modest effect on body weight	Few safety concerns reported but not rigorously studied; contains caffeine *Reported adverse effects*: Headache and urinary tract infections
Caffeine (as added caffeine or from guarana, kola nut, yerba mate, or other herbs)	Stimulates the central nervous system, increases thermogenesis and fat oxidation	Short-term clinical trials of combination products *Research findings*: Possible modest effect on body weight or decreased weight gain over time	Safety concerns not usually reported at doses less than 400 mg/day for adults, significant safety concerns at higher doses *Reported adverse effects*: Nervousness, jitteriness, vomiting, and tachycardia
Forskolin *Plectranthus barbatus*	Activates the enzyme adenylyl cyclase and increases intracellular levels of cAMP	Oral ingestion of forskolin (250 mg of 10% forskolin extract twice a day) for a 12-week period was shown to favorably alter body composition while concurrently increasing bone mass and serum-free testosterone levels in overweight and obese men [31]	Forskolin should be used with caution or avoided altogether in women who are pregnant.
Fucoxanthin	Increases energy expenditure and fatty acid oxidation, suppresses adipocyte differentiation and lipid accumulation	Studied only in combination with pomegranate seed oil in one trial in humans *Research findings*: Insufficient research to draw firm conclusions	No safety concerns reported but not rigorously studied *Reported adverse effects*: None known

Table 9.8 (continued)

Ingredient	Proposed mechanism of action	Evidence of efficacy	Safety concerns
Garcinia cambogia (hydroxycitric acid)	Inhibits lipogenesis, suppresses food intake	Several short-term clinical trials of varying methodological quality *Research findings*: Little to no effect on body weight	Few safety concerns reported *Reported adverse effects*: Headache, nausea, upper respiratory tract symptoms, and gastrointestinal symptoms
Yohimbe (*Pausinystalia yohimbe*, yohimbine)	Has hyperadrenergic effects	Very little research on yohimbe for weight loss *Research findings*: No effect on body weight; insufficient research to draw firm conclusions	Significant safety concerns reported *Reported adverse effects*: Headache, anxiety, agitation, hypertension, and tachycardia
Hoodia (*Hoodia gordonii*)	Suppresses appetite, reduces food intake	Very little published research in humans *Research findings*: No effect on energy intake or body weight based on results from one study	Some safety concerns reported, increases heart rate and blood pressure *Reported adverse effects:* Headache, dizziness, nausea, and vomiting
Raspberry ketone	Alters lipid metabolism	Studied only in combination with other ingredients *Research findings*: Insufficient research to draw firm conclusions	No safety concerns reported but not rigorously studied *Reported adverse effects*: None known
Guar gum	Acts as bulking agent in gut, delays gastric emptying, increases feelings of satiety	Several clinical trials of good methodological quality *Research findings*: No effect on body weight	Few safety concerns reported with currently available formulations *Reported adverse effects*: Abdominal pain, flatulence, diarrhea, nausea, and cramps
Bitter orange (synephrine)	Increases energy expenditure and lipolysis, acts as a mild appetite suppressant	Small clinical trials of poor methodological quality *Research findings*: Possible effect on resting metabolic rate and energy expenditure; inconclusive effects on weight loss	Some safety concerns reported *Reported adverse effects*: Chest pain, anxiety, and increased blood pressure and heart rate
Chitosan	Binds dietary fat in the digestive tract	Small clinical trials, mostly of poor methodological quality *Research findings*: Minimal effect on body weight	Few safety concerns reported, could cause allergic reactions *Reported adverse effects*: Flatulence, bloating, constipation, indigestion, nausea, and heartburn
Glucomannan	Increases feelings of satiety and fullness, prolongs gastric emptying time	Several clinical trials of varying methodological quality, mostly focused on effects on lipid and blood glucose levels *Research findings*: Little to no effect on body weight	Significant safety concerns reported with tablet forms, which might cause esophageal obstructions, but few safety concerns with other forms *Reported adverse effects*: Loose stools, flatulence, diarrhea, constipation, and abdominal discomfort

(continued)

Table 9.8 (continued)

Ingredient	Proposed mechanism of action	Evidence of efficacy	Safety concerns
White kidney bean (*Phaseolus vulgaris*)	Interferes with breakdown and absorption of carbohydrates by acting as a "starch blocker"	Several clinical trials of varying methodological quality *Research findings*: Possible modest effect on body weight and body fat	Few safety concerns reported *Reported adverse effects*: Headache, soft stools, flatulence, and constipation

Adapted from National Institutes of Health, Office of Dietary Supplements with additions https://ods.od.nih.gov/factsheets/WeightLoss-HealthProfessional/ Accessed 2016.09.12 [30]

Table 9.9 Some features of interventional surgery for the treatment of obesity

	Gastric bypass	Adjustable gastric banding	Sleeve gastrectomy
30-day mortality	0.08%	0.11%	0.50%
Complications	21.0%	13%	13%
Reoperations	2.56%	12.23%	9.05%
BMI change from baseline at 1 year	−14.5 kg/m2	−10.5 kg/m2	−16.2 kg/m2
% excess body weight loss	72%	33.4%	69.7%
Diabetes remission	95%	73.9%	83% (obs studies)
Hypertension remission	81%	53.5%	83% (obs studies)
Dyslipidemia remission	80%	39%	–
Sleep apnea remission	95%	94%	–

Adapted from Chang, SH, Stoll CR, Song J, Varela JE, Eagon CJ, Colditz GA. The effectiveness and risks of bariatric surgery: an updated systematic review and meta-analysis, 2003–2012. JAMA Surg. 2014;149:275–87 [32]. The data from randomized controlled trials were used when available. Where they were not reported data from observational studies were used

Surgical Procedures for the Management of Obesity

Surgical strategies to treat obesity began more than 50 years ago and have now risen to over 200,000 procedures per year in the United States [1].

Surgical Procedures

There are three principal surgical procedures now widely used. Sleeve gastrectomy (SG) is the most common procedure, and Roux-en-Y gastric bypass (RYGB) is second, with laparoscopic adjustable gastric banding being less commonly used. The technically complicated biliopancreatic diversion is occasionally performed, but there is insufficient controlled data to include it. Data on the response to these three procedures are summarized in Table 9.9 [32].

Criteria for Bariatric Surgery

Criteria established in 1991 considered appropriate candidates as those with a BMI ≧35 kg/m^2 and a related comorbidity or a BMI ≥40 kg/m^2 in the absence of comorbidities as appropriate candidates for bariatric surgery. These criteria have since been modified in a joint statement by international diabetes groups indicating that bariatric or metabolic surgery is a consideration for patients with poorly controlled diabetes mellitus and a BMI of 30–35 kg/m^2. The Endocrine Society has also released pediatric guidelines for bariatric surgery based on the high rate of reversion of diabetes to normal glucose tolerance.

Outcomes of Bariatric Surgery

There is a low rate of mortality (see Table 9.9) as well as some serious complications that occur in about 4.1% of all patients. The experience of both the surgeon and the surgical center are predictors of surgical outcomes. Longer-term complications can include intestinal obstruction, marginal ulcer, ventral hernia, and gallstones. Additional metabolic complications include nephrolithiasis, osteoporosis, and hypoglycemia. Mineral and vitamin deficiencies and weight regain occur in a variable numbers of patients. Micronutrient deficiencies following gastric bypass include iron deficiency in 33 to 55%; calcium/vitamin D deficiency in 24 to 60%; vitamin B12 deficiency in 24 to 70%; copper deficiency in 10 to 15%; and thiamine deficiency in <5%. Established guidelines recommend that the healthcare provider routinely give nutrient supplementation that includes multivitamins, vitamin B_{12}, iron, minerals, calcium, and vitamin D.

There are clear benefits of bariatric/metabolic surgery that may outweigh the risks and potential complications. Weight loss is significant with most of it being retained over the long-term. The poorest weight loss following gastric bypass is comparable to the best reported weight loss for nonsurgical interventions. Changes in weight from baseline to 5 years in surgically treated groups were superior to the changes seen with medical therapy. Body weight decreased 23% with gastric bypass and 19% with sleeve gastrectomy, but only 5% with drug therapies. But like other forms of treatment for obesity, there is considerable variability of response. In a large follow-up study of patients undergoing a Roux-en-Y gastric bypass, the trajectories of initial weight loss in the first year tended to be retained for up to 7 years and varied from 12 to 45% of the initial weight. Weight loss following laparoscopic banding is similarly variable, but weight losses are only about half that seen with gastric bypass.

The single best predictors of sustained postoperative weight loss (identified by the LABS Consortium) are postoperative eating and lifestyle behaviors. Specifically, subjects who self-monitor by weighing themselves frequently and who avoid eating when full and avoid snacking between meals appear to experience the best weight loss.

The remarkable remission of T2DM following bariatric/metabolic surgery was originally noted by Pories et al. [33]. The durability of the remission was sustained for up to 7 years in many participants. There may also be a remission of dyslipidemia, sleep apnea, and hypertension following bariatric/metabolic surgery.

In the large, long-term Swedish Obese Subjects study, mortality was significantly reduced by 29% in the operated patients [34, 35] who also showed a reduction in myocardial infarction, stroke, and reduced incidence of diabetes mellitus. Cancer was significantly reduced in women.

Vagal Blockade

In addition to the major gastrointestinal procedures, there are several other surgical strategies. Vagal blockade can be produced by activating electrodes placed around the vagal trunks at the diaphragm in order to produce intermittent vagal blockade. Weight loss occurs by reducing appetite and inducing early satiety. Weight loss is modest, but superior to sham-treated controls yet less successful than conventional surgical procedures described above.

Endoscopically Placed Balloons

In 2015, the US FDA approved two intragastric balloons and a third one in 2016. The Orbera Intragastric Balloon System is filled with 400 to 700 mL of saline. The ReShape Integrated Dual Balloon System contains two connected saline-filled balloons. The Obalon Balloon System expands with air after insertion. Technical improvements to these devices have resulted in a favorable safety profile. The present protocol requires removal of these intragastric balloons after 3–6 months, which is a limitation to the long-term efficacy of this intervention. In August 2017, the US FDA sent a letter to healthcare providers noting seven deaths associated with liquid-filled intragastric balloon systems

used to treat obesity. Four of the reports involved the Orbera Intragastric Balloon System and one the ReShape Integrated Dual Balloon System. Two earlier deaths were also noted.

Another intragastric device is a specially designed percutaneous gastrostomy tube called the AspireAssist device. It allows patients to directly remove ingested food from the stomach. In a clinical trial lasting 1 year using this device, patients lost 12.1% compared to 3.6% in the control group. This aspiration technique requires available facilities to discard the aspirated food and is not for everyone.

Finally, there are two endoscopic procedures for placing a duodenal-jejunal luminal sleeve to reduce absorption of nutrients and activation of GI hormones and another which involved reducing duodenal absorptive surface by abrasion. The duodenal-jejunal luminal bypass liner shows promise. In a study that examined endoscopic ablation of duodenal mucosa, there was an enhanced glycemic control of T2DM with a reduction of HbA1c that persisted 6 months after ablation.

Liposuction

Liposuction (also known as lipoplasty or suction-assisted lipectomy) is the most common esthetic procedure performed in the United States, with over 400,000 cases performed annually. This is not generally considered a bariatric procedure, but clinicians use it to remove and contour subcutaneous fat following recovery from bariatric surgery when there is excess subcutaneous fat. The procedure involves aspiration of fat and fluid after injecting physiologic saline into fat tissue. As the technique has improved, it is now possible to remove significant amounts of subcutaneous adipose tissue. However, visceral fat and other ectopic fat deposits are unaffected. Whether this procedure improves the metabolic profile has been examined in a study by Klein et al. [36]. They studied seven women with diabetes who were also overweight and eight women with normal glucose tolerance that were overweight both before and after liposuction. The control women lost 9.1 kg of body fat, and the women with diabetes lost 10.5 kg of fat. Despite these significant reductions in body fat, there were no changes in blood pressure, lipids or cytokines, or C-reactive protein. There was also no improvement in insulin sensitivity, suggesting that the removal of subcutaneous adipose tissue without reducing visceral fat has little influence on the risk factors related to being overweight.

Conclusion

The epidemic of obesity over the past 50 years has increased by threefold the number of individuals with obesity. Since no one chooses to be fat, this has led to the search for cures for the patient with obesity. This chapter has outlined obesity as a chronic relapsing disease process for which bariatric surgery is the most effective treatment. However, many people do not want surgery, and for them there are a variety of diets, exercise programs, and behavioral programs which can be supplemented by the use of pharmacological treatment in many cases. The difficulty of reversing obesity is well recognized and poses one of the major challenges for those working on this obstinate problem.

COVID-19 Addendum

Since the time this chapter on understanding and achieving a healthy weight was completed, the world has been through the SARS-2-Cov-2 coronavirus pandemic which has affected individuals with obesity and those with diabetes more than any other group, except the elderly and nursing home residents. The impact of this pandemic on scholarly activity is shown by the fact that in March 2021, there were 337 papers, 91 of which were published in 2021, identified as related to COVID-19 and obesity in PubMed, a large medical indexing system. The impact of COVID-19 has been worldwide. This is nicely shown in the meta-analysis by Popkin et al. [37]. Individuals who were overweight/obese were 46% more likely to test positive for COVID-19, had a 113% higher risk of being hospitalized, a 74%

higher likelihood of entering an intensive care unit (ICU), and a 48% increased risk for mortality. Similar increases in hospitalization, admission to the ICU, use of ventilators, and mortality were reported by Kompaniyets et al. [38] and by Huang et al. [39]. In another meta-analysis using fully adjusted data from six studies, Hoong et al. found that the odds ratio for severe disease and mortality was more than twice that of the normal weight subjects [40]. The magnitude of the obesity also impacted outcomes. Poly et al. [41] reported that individuals with Class I obesity (BMI 30–34.9 kg/m^2) had a 27% increase in mortality, those with Class II obesity (BMI 35–39.9 kg/m^2) had a 56% increase in mortality, and those in Class III (BMI > 40 kg/m^2) had a 92% increase in mortality. The interaction of obesity and age over 65 was particularly apparent in the rate of hospitalization and death with increasing BMI [38].

Obesity affects many systems as noted earlier, and several of these systems may be involved in enhancing the risk of the coronavirus disease [1]. First, the virus enters the respiratory system where patients with obesity may express larger amounts of the angiotensin-converting enzyme-2 (ACE-2) receptors to which the coronavirus locks on in the body [42]. This in turn may activate the complement system with lysis of cytokine-containing cells followed by the often lethal cytokine storm. If there is vitamin D deficiency, this too may augment the risk. Patients with obesity often have reduced pulmonary ventilation, and this may increase their risk of ending up on a ventilator. Thus, COVID-19 in the patient with obesity and especially those who are older is a serious risk to their health.

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Medical Nutrition Therapy for the Treatment of Diabetes: Prioritizing Recommendations Based on Evidence

10

Roeland J. W. Middelbeek, Samar Hafida, and Cara Schrager

Keywords

Type 1 diabetes · Type 2 diabetes · Nutrition therapy · Glycemic index

Key Points

- Medical nutrition therapy is recognized as an essential component of diabetes self-management and education, which are crucial to the comprehensive care of people with diabetes [1].
- Medical nutrition therapy plans should be individualized, flexible, and involve principles of shared decision-making between persons with diabetes and their healthcare teams.
- Medical nutrition therapy involves delivering tools and support for adopting and maintaining healthy eating patterns focused on goal-specific outcomes with attention to promoting sustained behavioral changes over time.
- Medical nutrition therapy has been shown to be an effective method to manage weight loss, diabetes, high blood pressure, and high cholesterol levels [2, 3].

Introduction

The incidence and prevalence of diabetes has skyrocketed in the past decades, posing a significant threat to communities worldwide, with nearly half a billion people currently living with diabetes [4]. The International Diabetes Federation estimates that the prevalence will reach staggering numbers by 2045, affecting 700 million individuals globally. In the United States, the estimated prevalence of diabetes is 10.5%, affecting over 34 million people, with 7.3 million who are unaware of their diagnosis [5]. Diabetes care is complex and requires an approach that spans multiple disciplines and involves a myriad of professional services. Medical nutrition therapy is a fundamental pillar in the treatment of people with diabetes, and has the potential to prevent progression and alleviate its burden.

R. J. W. Middelbeek (✉) · S. Hafida
Joslin Diabetes Center, Boston, MA, USA

Harvard Medical School, Boston, MA, USA
e-mail: roeland.middelbeek@joslin.harvard.edu

C. Schrager
Joslin Diabetes Center, Boston, MA, USA

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Medical Nutrition Therapy (MNT) for Diabetes

Definition of MNT

The Academy of Nutrition and Dietetics defines MNT as a "specific application of the nutrition care process in clinical settings that is focused on the management of diseases," a definition distinct from nutrition counseling which is the process of supporting individuals to establish unique goals based on their priorities, in order to foster a routine of self-care, centered around healthful eating [3]. The legal definition of MNT is the evidence-based application of nutrition care delivered by registered dietitian nutritionists (RDN), where a face-to-face assessment of an intervention is conducted in accordance with nationally accepted protocols. In order to fulfill the components of MNT, an assessment, nutrition-based diagnosis, intervention, and plan for monitoring must be conducted (Fig. 10.1).

Goals of MNT

The American Diabetes Association (ADA) outlines four main goals of MNT (Table 10.1). These include encouraging healthful eating, personalizing nutrition needs, providing evidence-based food-related messaging, and offering practical tools to help with meal planning.

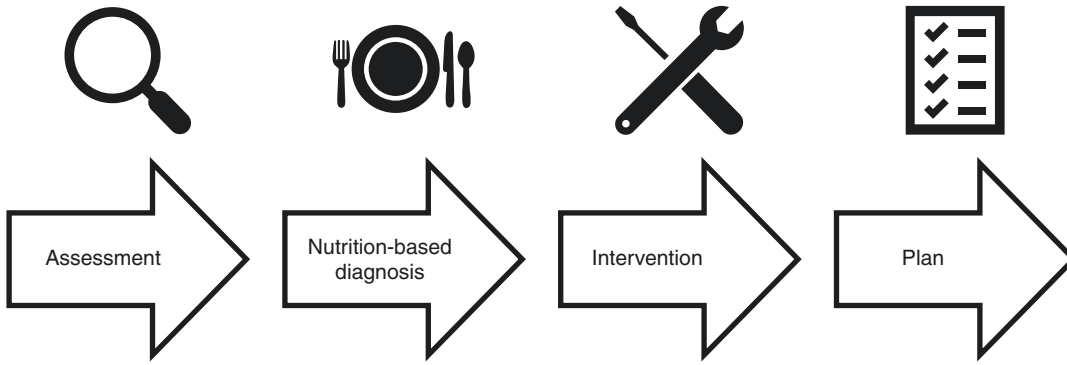

Fig. 10.1 Process of medical nutrition therapy

Table 10.1 Goals of MNT

Encourage healthful eating	**Personalize nutrition needs**
Adopt appropriate portions Choose foods dense in nutrients Achieve and maintain goals related to: Body weight A1C[a] Blood pressure Cholesterol Prevention of diabetes complications	To support personal and cultural food preferences Consider barriers to food access Assess readiness to embrace change
Provide evidence-based food-related messaging	**Offer practical tools**
To maintain the pleasure of eating Promote healthy relationship with food	To help with daily planning of meals

[a]*A1C* glycated hemoglobin

Adapted from Evert AB, Dennison M, Gardner CD, Garvey WT, Lau KHK, MacLeod J et al. Nutrition Therapy for Adults With Diabetes or Prediabetes: A Consensus Report. Diabetes Care. 2019;42:731–754 [6]

Table 10.2 Domains where MNT is effective in the management of diabetes

Glycemic control			**Cardiovascular risk factor mitigation**				
↓ A1C		↓ FPG mg/dL	↓ Total Chol Mg/dL	↓ LDL Mg/dL	↑ HDL Mg/dL	↓ TG Mg/dL	↓ SBP/DBP mmHg
T2DM	0.3–2%	18–61	8–28	8–22	2.4–6	15–153	3.2–9/2.5–5.3
T1DM	1–1.9%						
Medication use			**Weight management**				
↓ Total daily dose of insulin, medication dosages, and number of medications taken for diabetes management			↓ Weight (kg)	↓ BMI kg/m^2	↓ Waist circumference (cm)		
			2.4–6.2	0.3–2.1	1.0–5.5		

↓, reduction; ↑, increase; *A1C* glycated hemoglobin; *FPG* fasting plasma glucose; *T2D* type 2 diabetes; *T1D* type 1 diabetes; *Total Chol* total cholesterol; *LDL* low-density lipoprotein; *HDL* high-density lipoprotein; *TG* triglycerides; *SBP* systolic blood pressure; *DBP* diastolic blood pressure; *BMI* body mass index

Effectiveness of MNT in the Management of Diabetes

The Academy of Nutrition and Dietetics published evidence-based guidelines endorsed by the ADA for the management of adults with type 1 and type 2 diabetes [2, 3]. The review of the literature identified 30 diabetes-targeted nutrition practice guidelines, which demonstrated effectiveness in the following domains: glycemic control, cardiovascular risk factor mitigation, medication use, weight management, diabetes prevention, and quality of life (Table 10.2).

MNT and Glycemic Control

Intervention studies involving MNT delivered by RDNs in a series of encounters to subjects with type 2 diabetes have shown significant improvements in hemoglobin A1c (a marker of glucose control over a 3-month period), with change in A1c from −0.3% to −2% [7–9]. A1c reductions were more pronounced in those who were newly diagnosed with type 2 diabetes, and with higher baseline A1c of >8%. Similar A1c reductions were also seen in people with type 1 diabetes, who received MNT using carbohydrate counting to calculate mealtime insulin doses, resulting in A1C reductions of −1% to −1.9%. MNT intervention was delivered by a series of visits conducted by RDNs over a period of 6 months [10, 11]. In addition to hemoglobin A1C improvement, fasting blood glucose levels also showed improvements ranging between 18 and 61 mg/dL with regularly delivered MNT sessions in people with type 1 as well as type 2 diabetes [3, 10].

Cardiovascular Risk Factor Mitigation

Several studies assessing total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglyceride (TG) levels in adults with type 2 diabetes who received MNT reported mixed effects at the end of the study period. This was likely due to the prevalence of lipid-lowering agents already used by the participants during the study period. However, a number of other studies did result in improvements in LDL cholesterol, HDL, and TG levels [6]. For blood pressure control, mixed results were also reported in several randomized controlled studies and cohort studies of adults with type 1 and 2 diabetes where MNT was a component of the intervention. Some studies showed no change in blood pressure levels, and six studies demonstrated a significant lowering of systolic and

diastolic blood pressure. It is worth noting that 50–70% of the subjects were taking medications to lower blood pressure, and most had near-normal levels at the time of study entry [3, 8, 12].

Medication Use

MNT delivered by RDNs in regular intervals was associated with significant decreases in doses and number of medications required to improve glucose in people with type 2 diabetes. The favorable effect of MNT persisted for 2 years in the United Kingdom Prospective Diabetes Study (UKPDS), after which participants required escalation of therapy due to the natural progression of type 2 diabetes. MNT in the form of carbohydrate counting resulted in the improvement of A1C in adults with type 1 diabetes, without an increase in the total daily dose of insulin. Furthermore, MNT alleviated or prevented weight gain associated with initiation of basal insulin in people with type 2 diabetes [13] and insulin pump therapy in people with type 1 diabetes [14].

Weight Management

Intervention with MNT in several studies involving both participants with type 1 and type 2 diabetes demonstrated mixed results with regard to changes in body weight, body mass index (BMI), and waist circumference. Some outcomes showed no change, while others reported 2.4 to 6.2 kg weight loss and decrease in waist circumference by 1 cm to 5.5 cm [3, 14].

Diabetes Prevention

Reducing the risk for type 2 diabetes involves maintaining a healthy weight, as overweight and obesity are key risk factors for the development of type 2 diabetes. Cereal fiber and magnesium, both components of whole grains, and fruit and green leafy vegetable intake are consistently associated with lower risk of developing type 2 diabetes [15–17] with a possible protective role for low-fat dairy foods [18]. Remaining physically active is important as sedentary time is associated with an increased risk of developing type 2 diabetes [19]. A number of risk factors, both non-modifiable (genetics and aging) and modifiable (central obesity, sedentary lifestyle, and diet), have been identified as contributing to insulin resistance, a common factor in the development of diabetes and cardiovascular disease. Large clinical trials have demonstrated the role of nutrition therapy, leading to modest weight loss, combined with increased physical activity in the prevention or delay of type 2 diabetes. Examples of larger and well-designed trials include the Finnish Diabetes Prevention Study [20] and the Diabetes Prevention Program (DPP) [21].

Quality of Life

In a total of six studies where MNT was incorporated, adults with both type 1 and type 2 diabetes reported an improved quality of life. These studies included a number of RDN encounters followed by long-term follow-up with RDN visits. The improvements in the quality of life included self-perception of health status, knowledge and motivation, treatment satisfaction, and psychological well-being [3].

Recommendations for MNT Referrals and Encounters

Who Should Be Referred?

MNT is effective in improving medical outcomes and the quality of life and is cost-effective [22, 23]. Anyone who is newly diagnosed with prediabetes and/or diabetes should be referred to a RDN for MNT. Anyone with comorbidities, such as overweight or obesity, a history of disordered eating, hypertension, hyperlipidemia, and diabetic nephropathy, should also be referred to a RDN for MNT. There are four critical times in which a person with diabetes should be referred to a RDN for nutrition: (1) at diagnosis, (2) annually, (3) when a new diabetes complication occurs, or (4) when a transition in care occurs [1].

Frequency of Encounters

It is recommended there be a series of three to four encounters with an RDN, lasting from 45 to 90 minutes, starting at diagnosis of diabetes. The referral should be completed within 3 to 6 months after a diagnosis of diabetes. Follow-up appointments are recommended at least annually for ongoing monitoring and evaluation [22].

Assessment During Encounters

The RDN will assess usual food intake, the level of physical activity, current medications, current laboratory values, and anthropometric measurements, in addition to glycemic control. The goal of nutrition therapy is to promote healthy eating patterns that emphasize a variety of nutrient-dense foods and appropriate portion sizes rather than the individual micro−/macronutrients or single foods. Teaching individuals how to make appropriate food choices (including by means of carbohydrate counting) and using data from glucose monitoring to evaluate short-term effectiveness are important components of successful MNT for type 2 diabetes.

The plate method is a general guideline for healthy food distribution and emphasizes healthy portions and food choices. Persons with diabetes can benefit from basic information about carbohydrates – what foods contain carbohydrates and how many servings to select for meals (and snacks if desired). They should learn what types of carbohydrate foods have the biggest impact on glucose levels. The carbohydrate list is composed of starches, fruits, milk, and sweets; one serving or carbohydrate exchange is the amount of food that contains 15 g of carbohydrate. During the initial assessment, the RDN will guide the person with diabetes in choosing the appropriate amounts of carbohydrate servings per meal and snack. In addition, the RDN will help clarify how other macronutrients (proteins and fats) play a role in health and diabetes management.

Follow-Up

Successful self-management of diabetes is an ongoing process of problem-solving, adjustment, and support. Individuals must be able to anticipate and cope with the wide variety of decisions they face on a daily basis. Support from family and friends is important, in addition to continuing education and support from professionals. Structured programs with consistent follow-up contact assist individuals to achieve lifestyle goals and to maintain what are often challenging lifestyle changes. Technology is a helpful tool for education and diabetes management. Some apps provide data logging functions and

food databases. These help validate the successful achievement of someone's nutrition and physical activity goals. There are hundreds of mobile apps available for download, some free and some requiring a small fee.

MNT Intervention

Macronutrients

Carbohydrate

Carbohydrates are addressed first as it is the balance between carbohydrate intake and available insulin in the body that determines the postprandial glucose response and because carbohydrate is the major determinant of mealtime insulin doses. Foods containing carbohydrates – grains, fruits, vegetables, legumes, milk, and yogurt – are important components of a healthy diet and should be included in the food/meal plan of persons with diabetes. A number of studies have reported that when subjects are allowed to choose from a variety of starches and sugars, the glycemic response is similar, as long as the total amount of carbohydrate is the same. Consistency in carbohydrate intake is also associated with good glycemic control [6].

Research does not support any ideal percentage of energy from macronutrients for persons with diabetes [6], and it is unlikely that one such combination of macronutrients exists [3]. Macronutrient intake should be based on the Dietary Reference Intakes (DRI) for healthy adults. It is important to tailor carbohydrate recommendations based on the person's individual needs, preferences, and impact on glucose levels.

The ideal amount of carbohydrates recommended for healthy adults to maintain well-being is unknown. This also applies to people with diabetes, where the quality of carbohydrates outweighs the significance of how many are consumed. High-quality carbohydrates include those dense in fiber, vitamins, and minerals. Processed carbohydrates should ideally be low in sodium and added sugars.

Although different carbohydrates produce different glycemic responses (GI), there is limited evidence to show long-term glycemic benefit when low-GI diets versus high-GI diets are implemented. The benefits of a low-GI diet are complicated by differing definitions of "high-GI" or "low-GI" foods or diets. Systemic reviews related to glycemic index in people with diabetes have shown no effect of HbA1c and limited effects on fasting glucose [6].

Protein

There is no evidence to suggest that usual intake of protein (15–20% of energy intake) be changed in people who do not have renal disease [6, 22]. Although protein has an acute effect on insulin secretion, usual protein intake in long-term studies has minimal effects on glucose, lipids, and insulin concentrations.

Protein is probably the most misunderstood nutrient with inaccurate advice frequently given to persons with diabetes. Although people with diabetes are often told that 50–60% of protein becomes glucose and enters the bloodstream 3–4 h after it is eaten, research documents the inaccuracy of this statement. Although nonessential amino acids undergo gluconeogenesis in subjects with controlled diabetes, the glucose produced does not enter the general circulation [24]. If differing amounts of protein are added to meals or snacks, the peak glucose response may be affected by the addition of protein, as there may be delayed glycemic excursions [25]. However, including protein with meals and snacks can help the individual feel more satiated, thereby potentially eating less overall. Protein intake may increase the insulin response to carbohydrates, and thus carbohydrate sources with high-protein content (i.e., nuts or milk) are generally not recommended to treat hypoglycemia [6, 25].

Dietary Fat

Cardioprotective nutrition interventions recommended by the "Standards of Medical Care in Diabetes" for people with diabetes include reduction in saturated and trans fatty acids, as well as increase in plant sterols/stanols and *n*-3 fatty acids [24, 25]. It is still important to be aware that foods high in cholesterol tend to have a higher saturated fat content [26].

Nutrition goals for persons with diabetes are the same as for persons with preexisting cardiovascular disease. Thus, saturated fats <7% of total energy, minimal intake of trans fatty acids, and cholesterol intake <200 mg/day are recommended [3]. Two or more servings of fish (with the exception of commercially fried fish fillets) are recommended. In persons with type 2 diabetes, an intake of ~2 g/day of plant sterols and stanols has been shown to lower total and LDL cholesterol. If products containing plant sterols are used, they should displace, rather than be added to the diet, to avoid weight gain.

Micronutrients

There is no evidence of benefit from vitamin or mineral supplementation in persons with diabetes who do not have underlying deficiencies [3, 6]. It is recommended that health professionals focus on nutrition counseling for acquiring daily vitamin and mineral requirements from natural foods and a balanced diet rather than micronutrient supplementation. Research including long-term trials is needed to assess the safety and potentially beneficial role of chromium, magnesium, and antioxidant supplements and other complementary therapies in the management of diabetes. In select groups such as the elderly, pregnant or lactating women, strict vegetarians, or those on calorie-restricted diets, a multivitamin supplement may be needed. Routine supplementation with antioxidants, such as vitamins E and C and carotene, has not proven beneficial and is not advised because of concerns related to long-term safety [6].

Other Nutritional Considerations

Nonnutritive Sweeteners

Nonnutritive sweeteners can be used as an alternative for products sweetened by sugar. However, it is preferred to replace sugar-sweetened beverages (SSBs) with water. The use of SSB as a replacement of sugar and without compensation for reduced caloric intake may help reduce weight [27, 28]. People should be recommended to abstain from consuming additional calories from other foods when sugar substitutes are used with the goal of reducing caloric intake. SSB may have putative negative effects, including negatively modifying hunger sensation [27].

Fiber

Recommendations for fiber intake for people with diabetes are similar to the recommendations for the general public (DRI: 14 g/1000 kcal). Diets containing 44–50 g fiber daily are reported to improve glycemia, but more usual fiber intakes (up to 24 g/day) have not shown beneficial effects on glycemia. It is unknown whether free-living individuals can sustain daily consumption of the amount of fiber needed to improve glycemia. However, some research suggests that soluble fiber can decrease postprandial glucose and A1C [29]. In addition, diets high in total and soluble fiber, as part of cardioprotective nutrition therapy, have been shown to reduce total cholesterol by 2–3% and LDL cholesterol up to 7% [3]. Therefore, foods containing 25–30 g/day of fiber, with special emphasis on soluble fiber sources (7–13 g), are to be encouraged.

Alcohol

Recommendations for alcohol intake are similar to those for the general public. If individuals with diabetes choose to use alcohol, daily intake should be limited to one drink per day or less for women and two drinks per day or less for men [25]. One drink is defined as a 12 oz. beer, 5 oz. wine, or 1.5 oz. of distilled spirits, each of which contains about ~14 g alcohol. Moderate amounts of alcohol when ingested with food have minimal, if any, effect on blood glucose and insulin concentrations, and the type of beverage consumed does not appear to make a difference. However, the effect of alcohol on persons with diabetes is individualized. For individuals using insulin or insulin secretagogues, if alcohol is consumed, it should be consumed with food to prevent hypoglycemia. Moderate alcohol consumption is associated with a decreased incidence of heart disease in persons with diabetes [30]. However, chronic excessive ingestion of alcohol (>3 drinks/day) can cause deterioration of glucose control with the effects from excess alcohol being reversed after abstinence for 3 days. In epidemiological studies, moderate alcohol intake is associated with favorable changes in lipids, including triglycerides. Because the available evidence is primarily observational, it does not support recommending alcohol consumption to persons who do not currently drink. Occasional use of alcoholic beverages can be considered an addition to the regular meal plan, and no food should be omitted.

Diabetes-Related Comorbidities

Diabetic Kidney Disease

The recommendations for nutrition, in particular protein intake, in patients with diabetic kidney disease have changed over time. While previously low-protein diets were advised with the goal of reducing albuminuria and reducing the progression of kidney disease, it was found that reducing protein intake did not significantly alter the progression of diabetic kidney disease [6]. Moreover, there may be increased risk of malnutrition if protein is restricted; therefore, currently there is no recommendation to restrict protein intake in persons with diabetes and kidney disease. In persons with diabetic nephropathy, a protein intake of 1 g or less per kg body weight per day is recommended.

Gastroparesis

It is advisable to refer patients with gastroparesis for consultation to a RDN with experience in gastroparesis. An important aspect will be the selection of foods of smaller particle sizes and/or consumer smaller, more frequent meals, as this can help facilitate the transfer of food through the digestive tract [31]. In addition, foods that do not delay gastric emptying such as lower fiber and lower fat foods can be beneficial. Liquid foods may be preferred over solid foods. Acute hyperglycemia could negatively affect gastric emptying and should ideally be minimized. In people with gastroparesis, timing of insulin administration can be difficult. Continuous glucose monitoring may aid in optimizing insulin administration, and some people with type 1 diabetes or insulin-treatment in type 1 diabetes may see benefit from treatment with an insulin pump [31, 32].

Cardiovascular Disease

The incidence of cardiovascular disease in people with type 1 and type 2 diabetes is high. Thus, there is particular interest in mitigating the risks of cardiovascular disease (CVD) in diabetes. Many of the nutrition recommendations for CVD reduction in the general population also apply for people with diabetes. MNT that optimizes blood glucose control, blood pressure, and lipid profiles is a cornerstone element in the management of diabetes. This has been shown to lower the risk of CVD and stroke [3, 6]. Data from clinical trials support the role of nutrition therapy for reaching glycemic targets and decreasing markers of CVD risk [3, 6]. People with diabetes are encouraged to reduce the amount of saturated fat and replace this with unsaturated fats where possible. This has been shown to

reduce total cholesterol and LDL-C and can improve cardiovascular risk factors. In a study, which included close to 50% of people with diabetes, intakes of monounsaturated and polyunsaturated fats were associated with a lower CVD risk and death, whereas intakes of saturated fat and trans fat were associated with a higher CVD risk. Replacing saturated and trans fat with monounsaturated or polyunsaturated fat in food was inversely associated with CVD [6]. In general, replacing saturated fat with unsaturated fats, especially polyunsaturated fat, significantly reduces both total cholesterol and LDL-C, and replacement with monounsaturated fat from plant sources, such as olive oil and nuts, reduces CVD risk. However, the association between saturated fat intake and the risk of cardiovascular disease remains controversial. Replacing polyunsaturated fat with saturated or refined carbohydrate has been shown to provide cardioprotective benefits. Consumption of *n*-3 fatty acids from fish or from supplements has been shown to reduce adverse cardiovascular outcomes [3, 6]. Trans fats should be avoided as they have been associated with all-cause mortality and CVD mortality [33]. Reducing sodium to the general recommendation of 2300 mg/day demonstrates beneficial effects on blood pressure [6].

Summary and Conclusions

Over the past decades, there have been major developments in the field of medical nutrition therapy for the management of diabetes. Medical nutrition therapy (MNT) is an essential pillar of diabetes management that involves an ongoing approach to deliver effective recommendations tailored to the individual needs of the person with diabetes. Monitoring of glucose, A1C, lipids, and blood pressure is crucial to assess the outcomes of nutrition therapy interventions and/or to determine if changes in medications are necessary. It is important that all healthcare providers understand the fundamentals of evidence-based nutrition therapy to safely guide recommendations that promote adoption of healthful lifestyle practices and support each individual's unique needs and wishes.

COVID-19 Addendum

In the beginning of 2020, the world was confronted with the SARS-Cov-2 global pandemic. Infection with the novel coronavirus (SARS-CoV-2) causes the respiratory illness coronavirus disease 2019 (COVID-19), which ultimately led to the COVID-19 pandemic. In the course of the COVID-19 pandemic, it became clear that, in addition to age, people with obesity and diabetes had an increased risk of severe infection and mortality from COVID-19 [34]. Although initial data showed an increased risk of mortality in people with type 2 diabetes, there was little information on whether this also extended to people with type 1 diabetes [34].

As the pandemic progressed, reports on the increased mortality in type 2 diabetes were confirmed. However, large observational studies now also determined the effects of COVID-19 on people with type 1 diabetes. A study from the United Kingdom showed increased mortality from COVID-19 in people with type 1 and type 2 diabetes, although the number of people <50 years of age and type 1 diabetes was small [35, 36]. A study from France also underscored increased morbidity in people with type 1 diabetes [37, 38].

Taken together, the epidemiological data showed that people with diabetes, along with people with obesity, are at increased risk of morbidity and mortality from COVID-19. Improving glycemic control may be a modifiable factor in mediating risk of severe illness and mortality from COVID-19 in people with diabetes. Questions remain whether different classes of pharmacological therapy in type 1 and type 2 diabetes eventually affect mortality risk. Moreover, as vaccination efforts have taken off, future studies will also determine antibody responses to vaccination against COVID-19 in people with type 1 and type 2 diabetes.

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Bone Health: Sound Suggestions for Stronger Bones

11

Laura A. Graeff-Armas and Corrine Hanson

Keywords

Bone health · Calcium · Vitamin D · Phosphorus · Magnesium · Protein

Key Points

- Bone requires calcium, vitamin D, protein, and phosphorus for optimal growth and maintenance.
- Food is the best source for most of the nutrients required by bone.
- Many in the population are consuming diets with inadequate calcium, and the elderly may have inadequate protein as well.
- Most adults require additional vitamin D, especially if they have little sun exposure.
- Improvements in nutrition can make a significant difference to bone health, even if started later in life.

Introduction

Bone is a complicated organ made of collagen, proteins, calcium, phosphate, and cells that remodel and maintain it. It requires many nutrients obtained from the diet, or other sources, for remodeling and maintaining the bony structure. Nutrition science has identified a select few of these nutrients as particularly important for bone health. We will highlight those here. However, remember that in food, these nutrients do not occur in isolation; they are present in nature packaged in various combinations of fat, protein, carbohydrate, minerals, etc. Only in the past few decades has it been possible to consume these nutrients in isolation in the form of supplements. As is often the case, the whole is greater than the sum of its parts, and in making recommendations for bone health, we will emphasize obtaining these nutrients from food sources whenever possible.

If a patient is being treated with medication for osteoporosis, we emphasize that these nutrients are the building blocks that the medication uses to form bone. This seems a simplistic concept, but many patients think that the medications themselves contain these nutrients. All bone-active pharmacologic agents have been tested in clinical trials with additional supplemental calcium and most with vitamin D as well. Presumably, the efficacy of the pharmacologic agents depends to some extent on these supplemental nutrients.

L. A. Graeff-Armas (✉) · C. Hanson
University of Nebraska Medical Center, Omaha, NE, USA
e-mail: laura.armas@unmc.edu

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Calcium

For over 100 years, we have been aware of calcium's effects on bone health. Clinical trials using calcium supplements or dairy foods have had either positive or null effects on bone outcomes, that is, greater bone mass during growth, reduced bone loss with age, and reduced fractures. Despite this, controversy and confusion have arisen in recent years as a result of relying on placebo-controlled calcium trials (similar to drug trials). Calcium, as with all nutrients, does not lend themselves well to this type of study design, as there are no placebo diets in a free-living population. A great deal of the results of these types of trials depend on the population studied, and if one examines these trials carefully, one finds that a population of older calcium deficient women, for example, have a greater benefit from supplementation than a dietary calcium replete population. While this makes intuitive sense, some have used null studies to argue against supplementation. Common sense would tell us that adequate calcium intake is necessary and that more is not necessarily beneficial. To put this into context, the National Health and Nutrition Examination Survey (NHANES) 2009–2010 found that 42% of Americans did not meet the estimated average requirements for calcium [1], and that population would likely benefit from increased calcium intake.

The body's calcium requirements have to come from dietary sources. The *blood* level of calcium is tightly maintained despite fluctuations in dietary intake. This constancy is ensured in the face of poor dietary intake by decreasing urinary calcium output, by improving gastrointestinal calcium absorption, and, more importantly, by increasing resorption of bone tissue, thereby releasing its calcium. In brief, *blood* levels of calcium are maintained during long-term dietary calcium deprivation at the expense of the skeleton.

The body systems do not act in isolation: calcium intake and regulation of the calcium economy have effects on other body systems and diseases including hypertension, colon cancer, renolithiasis, obesity, premenstrual syndrome, and polycystic ovary syndrome. However, this review will confine itself to the skeletal effects of calcium (and of nutrition, generally).

Dietary Calcium Requirements

The gut absorbs about 30% of dietary calcium, but the mineral is also lost through gastrointestinal secretions. As a result the net intestinal absorption is only 10–15%. Additionally, calcium is lost in urine and sweat [2, 3]. These so-called obligatory losses amount to about 200 mg/day in adults. Hence, net absorption must be at least that much to maintain zero balance. That much net absorption requires a daily total intake of 1000–1500 mg (the equivalent of 3–5 dairy servings). See Table 11.1.

During growth, net absorption is more efficient, and the bones accumulate mass (and calcium), although when persons consume a low-calcium diet, the bones cannot reach their full potential. Later in life, absorption and retention are less efficient, and the bones are unable to maintain their mass. Calcium retention rises in proportion to the intake up to a certain threshold level, above which excess calcium is excreted. There is no storage mechanism for extra calcium except what is needed by the skeleton.

Table 11.1 Recommended dietary intakes for calcium [4]

Childhood	700–1000 mg
Adolescence	1300 mg
Adult 19–50	1000 mg
Adult 51–70	1000–1200 mg
Adults over 70	1200 mg
Pregnancy	1000–1300 mg
Lactation	1000–1300 mg

Because blood levels of calcium are so tightly regulated, a serum measurement tells one little about the body's calcium intake or reserve. The reserve must be severely depleted for hypocalcemia to occur.

Dietary sodium needs a brief mention here. Sodium chloride increases urinary calcium excretion (i.e., it contributes to the obligatory loss), and this could theoretically lead to bone loss on a low-calcium diet. This sodium-induced urinary calcium loss can generally be offset by consuming more calcium in the diet.

Calcium Sources

Important sources of calcium are natural foods (principally dairy, a few greens and nuts, and a few crustaceans) and calcium-fortified foods (some cereals, breads, and fruit juices). Dairy products are the richest dietary sources of calcium. In fact, it is difficult to get enough calcium on a dairy-free diet. One serving of dairy has approximately 300 mg of calcium in addition to protein, phosphorus, vitamins, and trace minerals. Even patients with lactose intolerance can "wean" themselves onto dairy foods if done slowly and milk is taken with other foods [5].

Not all food sources of calcium are equally bioavailable. For example, spinach contains 122 mg of calcium per 90 g serving, but very little (about 5%) is absorbed because the oxalate in the spinach interferes with calcium absorption. This can be a source of clinical confusion to patients who are depending on the calcium content of certain foods but are still deficient with respect to calcium stores and bone mineral density.

Calcium supplements may be needed in order to reach the recommended daily intake. Most calcium salts (citrate, carbonate, phosphate) exhibit similar bioavailability [6]. Brand name or chewable products have been shown to be the most reliable. Even relatively less soluble salts, such as carbonate, absorb well if taken with food. All calcium sources should be taken with meals and in small amounts throughout the day to ensure optimal absorption.

Vitamin D

Vitamin D is a second nutrient that is closely linked to bone health. Deficiency of this vitamin is classically associated with unmineralized bone matrix, expressed as rickets in the growing skeleton and osteomalacia in the fully formed skeleton. Vitamin D is not truly a nutrient, at least in humans, because the body makes the vitamin for itself when a precursor in the skin is exposed to ultraviolet-B light. This reaction forms pre-vitamin D, which is then spontaneously converted to vitamin D. At prevalent levels of sun exposure, vitamin D is converted almost entirely to 25-hydroxyvitamin D (25OHD) by the liver. This is the form of vitamin D that correlates best with calcium absorption in adults and is converted by the kidney and other cells to the active form of vitamin D, 1,25-dihydroxyvitamin D ($1,25OH_2D$). Like calcium, $1,25OH_2D$ is physiologically regulated, and serum measurements do not reflect vitamin D status. Although it still remains controversial, vitamin D has been implicated in the prevention of cancer and cardiovascular disease, immune response, and cell cycle regulation [7–10].

Vitamin D is essential for the active absorption of calcium. From multiple calcium absorption studies, it has been established that absorption plateaus at about 32 ng/ml [11]. Population-based studies demonstrate that bone mineral density increases in relation to 25OHD status [12]. Reduction in the risk of fracture has been reported in some clinical trials of vitamin D supplements [13]. The decrease in fractures appears to be the result of at least two mechanisms: first, vitamin D increases calcium absorption, which in turn increases bone mineral density, and second, vitamin D has an effect on muscle strength and balance. Even short-term studies show a reduction in falls [14–16]. Although large bolus doses have been associated with an increase in falls and fractures [17], indicating that large infrequent doses may not be as protective as smaller, more consistent dosing. As with calcium, the

baseline vitamin D status must be taken into account. Greater than adequate vitamin D status (which is thought to be somewhere in the range of 30–50 ng/ml) is not necessarily providing more benefit to bone outcomes.

Vitamin D Requirements

Vitamin D intake recommendations have been a source of considerable controversy in recent years. In 2011, the Food and Nutrition Board (Institute of Medicine) revised their recommendations to 600–800 IU (15–20 mcg) daily [4], but that was challenged by several groups as being too low for optimal health [18–20]. Unlike calcium and other nutrients, vitamin D is made in the skin. The total input is difficult to quantify and is dependent on many environmental factors; these are discussed below. Those of us who live away from the equator, have dark skin, and/or work indoors are at greater risk of deficiency. The simplest way to assess vitamin D status is by checking 25OHD levels. If the level is less than 32 ng/ml, supplementation with an oral vitamin D product is the simplest way for a person to get an adequate amount (see below).

Sources of Vitamin D

Food

Few foods are sources of vitamin D. The best food source is oily fish such as salmon, but there are large differences in vitamin D content between farm-raised and wild salmon. Farm-raised salmon has approximately 188 IU/3.5 oz. serving, whereas wild salmon has much more, approximately 1090 IU/3.5 oz. serving [21]. Milk in the United States and Canada is routinely fortified with small amounts of vitamin D, typically 100 IU per cup. Some cheeses, yogurt, and cereals are fortified with a small amount of the vitamin.

Sunshine

Many variables affect the skin's ability to produce vitamin D, including weather, season, latitude, altitude, pollution, clothing, age, and sunscreen. Skin pigmentation also interferes with vitamin D production as melanin acts as a natural sunscreen.

The season of the year plays a large part in determining the production of vitamin D. Those with light skin require an exposure to summer midday sun of about 15 min daily to allow adequate synthesis of vitamin D. This is with a relatively high proportion of the skin exposed and before sunscreen is applied. It is not necessary to burn or redden the skin. Those with darker skin require at least twice as much time in the sun. In the winter, UVB rays do not penetrate the atmosphere, except close to the equator. During that season, therefore, no vitamin D can be produced, and most patients will need to use supplements.

The light source used in tanning booths may be able to produce UVB rays, and this can therefore be a source of vitamin D. However, tanning booths are not regulated by the FDA, and it is difficult to know how much, if any, UVB rays are produced [22]. Moreover, the light source may also generate UVA rays which can cause skin aging and of course skin cancer; therefore, their use should be discouraged as a vitamin D source.

Supplements

Nutritional supplements for vitamin D come in two forms. Vitamin D_2 is produced by irradiating yeast, while vitamin D_3 is the animal form produced by the skin. Several studies have shown that

vitamin D_3 is between three and nine times more potent at maintaining 25OHD levels [23–25]. The question always arises as to how much to give. Rather than rely on a "one-size-fits-all" recommendation, which does not account for differences in skin pigmentation, sun exposure, age, or weight, the simplest method is to measure the patient's 25OHD level. In calculating supplement dose for a normal-weight person, a good rule of thumb is that 100–150 IU daily will raise 25OHD levels by ~1 ng/ml. In practice, this translates to between 1000 and 2000 IU daily for most patients. For an obese patient, who will have a greater volume to fill, we found the following formula is helpful: additional daily vitamin D3 dose (IU) = [weight (kg) * desired change in 25(OH)D *2.5] – 10 [26]. Occasionally, patients with malabsorption or history of gastrointestinal surgery may require substantially more vitamin D, and in this case the 25OHD level dictates the dose.

These recommendations are based on several clinical studies of different doses of vitamin D and also on clinical experience. This approach treats patients with lower vitamin D levels with higher amounts of vitamin D. Of course, empiric treatment regimens can be used, and again, 1000–2000 IU (25–50 mcg) daily seems to be adequate for many patients and is a good place to start without the risk of toxicity.

Safety

Vitamin D is a fat-soluble vitamin, and there is a valid concern that toxicity may occur at high intakes. Fortunately, there is a wide gap between the amounts of vitamin D that we typically recommend to patients and potentially toxic amounts. A review of toxicity reports and clinical trials found that doses <30,000 IU daily or achieved 25OHD levels <200 ng/ml were not associated with toxicity and concluded that the tolerable upper limit should be 10,000 IU daily [27]. The IOM used a more conservative tolerable upper limit of 4000 IU daily [4]. We find in practice that we occasionally need to give >10,000 IU daily to particular patients who have malabsorption (i.e., occurring after gastric bypass).

Other Vitamins

There are other vitamins besides vitamin D that might contribute to healthy bones. One of these is vitamin K. This vitamin may be best known for its role in blood clotting, but there is new evidence to suggest that vitamin K may play an important role in bone health. Bones contain a protein called osteocalcin, which is used as "glue" to help strengthen bones. Vitamin K is required for the production of osteocalcin, and when vitamin K is low or insufficient, these proteins will not be activated. Some recent studies have shown that vitamin K deficiency is associated with low bone mineral density and an increased risk of fractures.

There are several different types of vitamin K. The vitamin K available from our diet is found mostly in leafy green vegetables, such as spinach, broccoli, and kale (K_1). As a general rule, the darker green the vegetable, the more vitamin K it contains. Vegetable oils can also contain significant amounts of vitamin K. It is also produced by the bacteria that line the GI tract (K_2). Finally, vitamin K is also available in a synthetic form as a supplement. At this time, it is not recommended to take vitamin K supplements to prevent osteoporosis or fractures. Taking a supplement does not always have the same effect as eating whole foods that contain the same nutrient, and because of the role vitamin K plays in blood clotting, getting too much could cause problems in people at risk for blood clots.

Because of vitamin K's effects on clotting, people taking certain anticoagulation medications are often advised to limit their intake of foods high in vitamin K. Patients taking these types of medications should work with their healthcare providers to make sure that their diet contains adequate amounts of nutrients.

Protein

Bone is one of the most protein-dense tissues. When bone is remodeled and new bone is laid down, it requires fresh dietary protein. Dietary protein is known to increase urine calcium excretion, but this effect is offset by higher calcium intakes. Studies of protein intake show that, overall, it is good for bone both as a source of building materials and through effects of insulin-like growth factor. In the Framingham Study, age-related bone loss was inversely related to protein intake [28]. In a calcium intervention trial, only subjects with the highest protein intake and calcium supplementation gained bone [29]. In patients with hip fractures, mortality and recovery are improved if the patients have adequate protein intake (≈1 g protein/kg body weight/day) [30].

The general population of the United States has adequate protein intake, but the population at most risk for fracture are the ones most likely to consume a diet deficient in protein. The recommended dietary allowance (RDA) for protein for adults is 0.8 g per kg body weight per day, although this may not be adequate for a patient with a recent fracture. Animal protein foods include meat, poultry, fish, dairy products, and eggs. Plant foods include beans, nuts, and seeds.

Phosphorus

Bone mineral consists of calcium phosphate. Adequate dietary phosphorus is therefore as important as calcium for building bone. Without it, the patient will develop a form of osteomalacia; they will not mineralize the skeleton. Fortunately, phosphorus is plentiful in many plant and animal tissues, and if one has a diet with adequate protein, it also likely contains adequate phosphorus. Dairy products, meat, and fish are good sources of phosphorus.

Absorption of phosphorus is highly efficient. Net absorption is about 55–80%. Phosphorus is also efficiently retained by the body by reducing urinary phosphorus excretion. However, calcium supplements may interfere with phosphorus by acting as a binder and reducing its absorption from the GI tract. This is a good example of the general rule that food sources of nutrients are superior to a nutrient ingested in isolation. In this case, a serving of dairy food will supply phosphorus in addition to the calcium and protein needed for bone health.

The RDA for phosphorus for adults is 700 mg/day, and most of the US population obtains enough of the mineral from their diet. However, some groups may have an inadequate intake such as one-third of girls between 9 and 18 years old [31]. This group is also likely to have a diet deficient in other nutrients, including calcium and protein. Also of concern are those eating very strict vegetarian diets as these do not contain enough phosphorus in a usable form.

Magnesium

About 50% of the body's magnesium resides in the skeleton. It may serve as a reservoir for maintaining the extracellular magnesium concentration. Unprocessed foods are good sources of magnesium. Rich sources include fresh leafy vegetables, whole grains, and nuts. The body is efficient at absorbing magnesium from the diet, and about 40–60% is absorbed. The kidney is also efficient at retaining magnesium unless the patient has diabetes or alcoholism that leads to urinary magnesium loss. Measuring magnesium status can be difficult clinically because serum measurements correlate poorly with intracellular levels.

Currently, the role of magnesium in maintaining bone density and preventing osteoporosis is unclear. Cross-sectional studies have not revealed any relationship between magnesium intake and bone density. Controlled studies of magnesium supplementation show a possible increase in bone

mineral density. With the paucity of evidence for bone health, we would recommend that patients increase fruit and vegetable intake for general health, but would not make specific recommendations for magnesium supplementation.

Conclusion

In conclusion, building and maintaining bone structure require a symphony of nutrients with food being the ideal source of these nutrients. Individuals with inadequate sources of nutrients will benefit the most from supplementation.

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Coronary Heart Disease: Nutritional Interventions for Prevention and Therapy

12

Désirée Schliemann, Jayne V. Woodside, Claire McEvoy, and Norman J. Temple

Keywords

Cardiovascular disease · Cardiovascular disease risk factors · Coronary heart disease

Key Points

- Diet plays a major role in the causation of coronary heart disease (CHD), which is a major cause of morbidity and mortality.
- Replacing saturated fat with polyunsaturated fats (PUFA) helps lower risk.
- Evidence suggests that increased consumption of fatty fish and of n-3 polyunsaturated fats (n-3 PUFA) is likely to reduce CHD risk.
- A high intake of salt, *trans* fats, processed meat, and added sugar is likely to increase CHD risk.
- Diets with a generous content of fruit, vegetables, and whole grain cereals are associated with lower risk of CHD.
- Adhering to a Mediterranean diet reduces CHD risk.
- Maintaining a healthy weight and being physically active have each been shown to reduce CHD risk factors and actual risk of CHD.

Introduction

Coronary heart disease (CHD) is a major cause of morbidity and mortality in the Western world. Factors that are strongly associated with elevated risk of the disease are age, male sex, smoking, lack of exercise, hypertension, obesity, and type 2 diabetes. In addition, blood lipid levels are strong predictors of CHD risk. A pattern of blood lipids that accelerates atherosclerosis (i.e., dyslipidemia) is one where total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) are elevated and high-density lipoprotein (HDL-C) is relatively low. The strongest indicator of risk is seen for the ratio of TC to HDL-C [1].

D. Schliemann · J. V. Woodside · C. McEvoy
Centre for Public Health, Queen's University Belfast, Belfast, UK

N. J. Temple (✉)
Centre for Science, Athabasca University, Athabasca, AB, Canada
e-mail: normant@athabascau.ca

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A large body of evidence collected over several decades from observational epidemiological studies and randomized controlled clinical trials (RCTs) strongly supports a major role for diet in the prevention and treatment of CHD. Observational epidemiological studies refer mainly to prospective cohort studies and case-control studies. Dietary factors that have been proposed to have a clinically important impact on the risk of CHD include saturated fats (SFA), *trans* fats (TFA), polyunsaturated fats (both n-6 and n-3 PUFA), sugar, dietary fiber, salt, and alcohol. This chapter examines how each of these food components may affect the risk of CHD. The chapter also discusses the possible importance of meat, fruit, and vegetables, as well as whole dietary patterns. Finally, this chapter examines the relationship between obesity and exercise and CHD risk. Early studies focused on the effect of diet on blood lipids, but it is now accepted that diet affects CHD etiology through multiple mechanisms, including insulin resistance, blood pressure, endothelial function, inflammation, and thrombosis.

Dietary Fat and CHD

Fat Intake

For many years, it was widely believed that a relatively high intake of dietary fat (around 35–42% of energy intake) increases the risk of CHD and other chronic diseases of lifestyle. This topic is also discussed in greater detail in Chap. 29. A major reason for this belief is that the populations of Westernized countries typically eat a diet relatively rich in fat and also have a high frequency of CHD. In addition, it was long believed that an increased intake of fat can lead to a positive energy balance and contribute to obesity. Because of these widely held beliefs, populations were strongly advised to reduce their fat intake. Starting in 1980, a common recommendation was that fat intake should be "less than 30%" of energy intake. However, accumulated research has left no doubt that the quantity of fat intake has very little association with the risk of CHD. There is no good evidence that low-fat diets reduce mortality rates from CHD. As a result of this realization, the recommendation regarding fat intake shifted in 2005 to a more liberal 20–35% of energy intake.

It must be borne in mind that when intake of fat is reduced, intake of carbohydrates inevitably rises in compensation. It is a serious error to look at the quantity of dietary carbohydrate without also paying careful attention to the food source of the carbohydrate. This is because different carbohydrate-rich foods vary greatly in their impact on the risk of CHD. This topic is discussed further when we look at refined carbohydrates, sugar, dietary fiber, and whole grains.

A critical aspect of fat intake with regard to the risk of CHD is the type of fat. Different fats have very different effects on blood lipid levels, and this is the key mechanism that explains how fat affects the risk of CHD [2]. Common dietary recommendations for fat intake are shown in Table 12.1.

Saturated Fat and Dietary Cholesterol

Many studies over the past 40 years have established that saturated fats (SFA) are positively correlated with the blood levels of total cholesterol and LDL-C. Dietary cholesterol also increases total cholesterol and LDL-C levels but to a much lesser degree than SFA. RCTs have demonstrated that diets low in SFA (<7% of energy intake) and cholesterol (<200 mg/day) bring about reductions in LDL-C levels of approximately 10%. This evidence is strongly suggestive that a reduced intake of SFA (and perhaps of dietary cholesterol) will lower the risk of CHD.

But this evidence is contradicted by the findings from cohort studies, many of which have investigated the relationship between intake of SFA and the risk of CHD. Meta-analyses of these studies have revealed that the intake of SFA has only a weak, nonsignificant association with the risk of CHD

Table 12.1 Common recommendations for dietary fat modification in order to modify blood lipids and prevent CHD

Dietary fat	Recommendation[a]	Major dietary sources
Total fat	20–35% energy intake	As below
Saturated fats (SFA)	<7% energy intake	Animal products (fatty meat, processed meat, cheese, butter, cream, lard, shortening, full-fat milk, ice cream), cocoa butter, chocolate, coconut oil, palm oil, cakes, pastry products, cookies
Trans fats (TFA)	<1% energy intake	Stick margarine (hard margarine made with hydrogenated oils), cakes, pastry products, cookies, chips, many fast foods. This fat has been almost entirely removed from foods sold in the USA
Cholesterol	<200 mg/day	Liver, kidney, egg yolk, shellfish
Polyunsaturated fats (PUFA)	4–10% energy intake	Soft margarines, vegetable oils (corn, safflower, soybean, sunflower)
Monounsaturated fats (MUFA)	<20% energy intake	Olive oil, canola oil, peanut oil, avocados, olives, almonds, cashews, peanuts
n-3 PUFA	0.5–2% energy intake	Sardines, mackerel, herring, pilchards, salmon, tuna Walnuts, flaxseed oil, soybean oil, canola oil

[a]Different health agencies make different recommendations. The recommendations shown are not necessarily ideal for minimizing the risk of CHD but are the most common ones currently given

(risk ratio [RR]: 1.06 for total CHD; 1.15 for CHD mortality when comparing the extreme quintiles) [3]. These findings call into question whether intake of SFA is indeed a major factor in the causation of CHD [4]. The same is true for intake of eggs, the main dietary source of cholesterol. Cohort studies point to a lack of association between the quantity of eggs that people eat and their risk of CHD [5]. This is an important finding because many persons avoid eating eggs, which are an excellent source of nutrients, because they are concerned about their cholesterol content, but for most people this concern is unwarranted.

Trans Fats

Trans fats (TFA) raise total cholesterol (TC) and LDL-C levels. In that respect they are similar to saturated fats (SFA); whereas SFA tend to increase HDL-C, TFA lower it. The net result is that *trans* fats cause an increase in the ratio of TC to HDL-C which, as noted earlier, is the strongest predictor of the risk of CHD. This strongly suggests that TFA are likely to increase the risk of CHD. Evidence from cohort studies adds much weight to this belief: A recent meta-analysis of these studies reported that TFA intake is associated with a 16% increase in CHD risk when comparing the top and bottom thirds of intake [3].

These findings have led to public health initiatives directed at removing as much TFA as possible from the food supply. These efforts have met with much success. TFA have been almost entirely removed from foods sold in the USA and Canada.

N-6 Polyunsaturated Fats and Monounsaturated Fats

Polyunsaturated fats (PUFA) and monounsaturated fats (MUFA) are the major unsaturated fats. PUFA fall into two main groups: n-6 PUFA and n-3 PUFA. n-6 PUFA are found in abundance in vegetable oils. Two especially rich sources of MUFA are olive oil and canola oil. The different types of fat have very different effects on the blood lipid levels. The change in blood lipids is closely associated with the change in the risk of CHD. MUFA tend to have a neutral effect on total cholesterol (TC) and

LDL-C levels. Consistent with this there is little association between intake of MUFA and risk of CHD [2]. An increased intake of PUFA, by contrast, lowers TC and LDL-C levels. Not surprisingly, therefore, people with a higher intake of PUFA are at reduced risk of CHD [6].

What is especially noteworthy is that when SFA is partly replaced with PUFA, the LDL-C is lowered but without lowering the HDL-C. The overall result is a decrease in the ratio of TC to HDL-C. We can predict that these favorable changes in blood lipids will help prevent CHD. Supporting evidence has come from cohort studies which indicate that making this dietary change does indeed lead to a significantly reduced risk of CHD [6].

Let us now summarize the key points. The evidence is quite weak that SFA plays an important role in the causation of CHD. However, adding extra PUFA (i.e., n-6 PUFA) to the diet at the expense of SFA leads to favorable changes in blood lipids and a lower risk of CHD. In general, dietary changes that bring about favorable changes in blood lipids induce a greater fall in TC and LDL-C in persons with hypercholesterolemia.

N-3 Polyunsaturated Fats

Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are long-chain n-3 polyunsaturated fats (PUFA) that are found in fatty fish (**Table 12.1**). Alpha-linolenic acid (ALA) is a n-3 PUFA with a slightly shorter chain length (number of carbons). It is found in some plant oils, namely, flaxseed (richest source), soybean, and canola oil (poorest source). Walnuts are another source. ALA can be converted to a limited extent in humans to EPA but almost not at all to DHA [7].

n-3 PUFA from fatty fish exert several different cardioprotective actions. These include improving endothelial function and reducing the risk of inflammation and arrhythmias [7].

Most prospective cohort studies have demonstrated inverse associations between fish consumption and the risk of CHD. These studies indicate that eating fish between twice and four times per week reduces the risk of death from CHD by around 21% [8].

The *consensus opinion among experts is* that this benefit is mainly accounted for by n-3 PUFA from fatty fish. It logically follows that supplements of fish oil should be protective against cardiovascular disease. This possibility has been tested in many RCTs. The large majority of the subjects in these studies have existing CHD or are at high risk of the disease. Reductions in cardiac death have been reported in several of these studies, but findings are often conflicting [9].

The benefits of n-3 PUFA from plant sources (ALA) have been less well researched. However, a meta-analysis suggests that these fats do bring about a moderate risk reduction of fatal CHD [10].

The overall picture that emerges from this research is that fish, especially fatty fish, is clearly protective against CHD. For this reason, fish is widely recommended as a part of a healthy diet. However, the extent to which fish oil and ALA provide similar benefits is still unclear. Current recommendations for n-3 PUFA are shown in Table 12.1.

Foods Rich in Carbohydrates

Refined Carbohydrates

It was pointed out earlier that intake of saturated fats (SFA) has only a weak association with the risk of CHD. This has for many years been a cause of much confusion. It has been claimed countless times that diets with a relatively high content of SFA lead to a high blood cholesterol, which then leads to atherosclerosis and finally to CHD. But the story is more complicated. SFA is a macronutrient. It is an oversimplification to describe a diet as simply high or low in SFA. If the diet is rich in SFA, then

another macronutrient will be displaced. Conversely, if the diet is low in SFA, then another macronutrient will replace it. It is a bad mistake to focus only on the quantity of SFA in the diet while ignoring the other macronutrients. PUFA provides one example of this. As was explained above, if SFA is replaced by PUFA, then there is a decrease in the risk of CHD. But what about carbohydrates?

Starting around 1980, the populations of most Western countries were advised to cut down on fat, in general, and SFA, in particular. Millions of people heeded this advice and, for example, switched from full-fat milk to low-fat milk and from regular meat to lean meat. Something had to replace the lost calories. The inevitable result was that the average American consumed more carbohydrate [11]. The large majority of this extra carbohydrate came from heavily refined foods, such as foods made with white flour. A major goal of this dietary advice was to help prevent CHD and obesity. Did it work?

Replacing dietary SFA with refined carbohydrates lowers the total cholesterol (TC), the LDL-C, and the HDL-C, resulting in little change in the ratio of TC to HDL-C [12]. However, this dietary change does cause a rise in the blood level of triglycerides [12], and this may cause some elevation in risk. Overall, the changes in blood lipids are unlikely to have any benefit on the risk of CHD. Consistent with these observations, cohort studies have shown no evidence that replacing SFA with refined carbohydrates reduces the risk of CHD [13].

Sugar

Much of the refined carbohydrates found in the diet are present as sugar. Here we are referring to two distinct types of sugar. Sucrose is added to many foods. High-fructose corn syrup is added to many sugar-sweetened beverages (SSB) and other foods. SSB are a major diet source of sugar. Very little of these sugars occur naturally.

Many studies have been made concerning the relationship between sugar and CHD. Experimental studies have revealed that sugar causes an increase in the blood pressure and the blood level of triglycerides, TC, and LDL-C [14]. These changes in risk factors allow us to predict that a relatively high intake of sugar will be associated with an elevated risk of CHD. The confirmation of this comes from a meta-analysis of cohort studies. Intake of SSB was found to be associated with the risk of CHD [15]. A 22% greater risk of myocardial infarction was seen for each additional daily serving.

Unrefined Cereals

The findings summarized above strongly indicate that consumption of refined carbohydrates increase the risk of CHD. This relationship is especially strong for SSB. Whole grains present an altogether different picture. A meta-analysis of cohort studies concluded that persons whose intake of whole grains is relatively high have a 21% lower risk of CHD in comparison with people whose intake is low [16]. Similar findings were seen in cohort studies that estimated the intake of cereal fiber [17]. Intake of cereal fiber is a proxy measure for whole grains.

Meat

Meat falls into three distinct groups: red meat (beef, pork, and lamb), processed meat (ham, sausages, bacon, salami, etc.), and poultry (chicken and turkey). Until a few years ago, any consideration of a relationship between meat and CHD was viewed as being a reflection of the fat content of the meat. Accordingly, meat with a high content of SFA was seen as posing considerably more risk of CHD than

is the case for lean meat. However, meat is now seen as being intrinsically harmful to cardiac health irrespective of its SFA content.

Our strongest evidence has come from studies on cardiovascular disease rather than on CHD. A summary of cohort studies concluded that each additional 100 grams per day of red meat increases the risk of cardiovascular disease by 15%, while an extra 50 grams per day of processed meat increases risk by 22% [18]. Clearly, processed meat is more unhealthy for cardiovascular health than is red meat. Studies on poultry indicate that this type of meat neither increases nor decreases risk. As mentioned earlier, fish is strongly protective against CHD.

The most likely reason why processed meat is so unhealthy is because of the considerable amounts of preservatives used in meat processing including large amounts of sodium.

Fruit and Vegetables

Fruit and vegetables are complex foods and contain a great many bioactive substances that have a positive effect on health, including folate, potassium, magnesium, dietary fiber, and hundreds of phytochemicals, while also having a negligible amount of fat. By virtue of their high content of fiber and low energy density (i.e., a low-calorie content per 100 g), a generous intake of fruit and vegetables helps counter the development of obesity. For these reasons it is not surprising that cohort studies have shown that consumption of fruit and vegetables has a strong protective association with the risk of CHD. A meta-analysis of these studies reported that the RR for each additional 200 g per day is 0.90 for fruit and 0.84 for vegetables [19]. This suggests that vegetables are more potent than fruit in their protective benefit.

There is mixed evidence regarding the relationship between consumption of potatoes and health. Findings from cohort studies suggest that potatoes have no association with risk of CHD [20]. Overall, boiled and baked potatoes have fairly little effect on health in contrast to the strongly beneficial effects of most other vegetables. But potatoes may pose some health risk when eaten as French fries as they appear to increase the risk of type 2 diabetes and hypertension [20]. Based on these findings, potatoes, especially French fries, are generally excluded from recommendations to eat more vegetables.

Salt

There is a well-established link between salt and hypertension (see Chap. 13). As hypertension is a major risk factor for CHD, a reduction in salt/sodium intake is strongly recommended. A meta-analysis of cohort studies that included 177,000 people showed that higher salt intake is associated with a significantly greater incidence of cardiovascular disease; there is a dose-dependent association [21]. Conversely, RCTs have shown a lower risk of cardiovascular disease when subjects with prehypertension were placed on a diet with a reduced salt content [22].

Alcohol

The relationship between alcohol and health is explored in Chap. 32. Here we briefly discuss this with a particular focus on CHD.

The findings from many cohort studies indicate that drinking alcoholic beverages in moderation—one or two drinks per day—affords some protection against CHD. However, there has been much controversy regarding whether these findings are real or are due to inherent flaws in the data. We need to remind ourselves of the golden rule: Epidemiology shows association, not causation.

Based on the totality of the evidence, we can conclude as follows. The lowest risk of CHD is seen at an alcohol intake of about one drink per day, but possibly less. This is also true for cardiovascular disease in general. There is no dispute that as alcohol intake climbs above four drinks/day, so does the risk of cardiovascular disease, especially stroke and heart failure.

There has been much speculation that red wine is more potent than other forms of alcoholic beverages for the prevention of CHD. But when the epidemiological evidence is looked at as a whole, especially cohort studies, then a different story emerges: It appears that all forms of alcoholic beverages – beer, spirits, and wine, both red and white – are similarly protective. However, it is premature to completely dismiss the possible health benefits of red wine.

Should We Recommend Dietary Supplements?

Many RCTs have been carried out that have investigated the possible benefit of various dietary supplements in the prevention of CHD. Most attention has focused on antioxidant supplements (beta-carotene and vitamins C and E) as well as vitamin D and CoQ (also known as CoQ10 or coenzyme Q10). The findings generated by these studies have been mostly disappointing. As a result none of these supplements can be recommended for CHD risk reduction. The possible value of these supplements on other aspects of health is further discussed in Chap. 42.

Whole Diet Approaches to CHD Risk Reduction

The above discussion provides strong evidence that dietary supplements have very limited value in the prevention or therapy of CHD. This realization was an important factor in persuading investigators that a more fruitful strategy was to move beyond food components and focus on the potential value of whole diets. A number of studies have investigated the efficacy of a whole diet approach for CHD prevention and therapy [23].

The star of the show is the Mediterranean diet. The diet varies from one country to another around the Mediterranean Sea, but typical features include a high content of plant foods (i.e., fruit, vegetables, cereals, legumes, nuts, and seeds); moderate amounts of fish, poultry, milk, and other dairy products; and small amounts of red and processed meat. The diet includes olive oil as the main fat in food preparation and low to moderate alcohol consumption (especially red wine consumed mainly at meals). Meta-analyses of cohort studies have consistently reported significant inverse associations between adherence to the Mediterranean diet and CHD risk [24].

We now have strong evidence that the Mediterranean diet is much healthier than the diets commonly eaten in most of the Western world, including the USA. The benefits go well beyond CHD. But the diet is not perfect. The cereals typically consumed in the Mediterranean diet are refined; for reasons explained above, it is highly preferable if people eat whole grains. Another important point is that extra virgin olive oil is preferable to regular olive oil as it appears to achieve a greater reduction in CHD risk [25]. The presumed explanation for this is that extra virgin olive oil is a rich source of phytochemicals. The health benefits of the Mediterranean diet are further discussed in Chap. 15.

Another dietary pattern that can be recommended is the Dietary Approaches to Stop Hypertension (DASH) diet. This was originally developed with the goal of lowering elevated blood pressure but is now recognized as being a heart-friendly diet. It is described in more detail in Chap. 16.

Obesity

Obesity is strongly associated with the risk of various types of cardiovascular disease, including CHD, as well as with type 2 diabetes and hypertension. This association becomes weaker after age 65. Much of the association between obesity and CHD can be accounted for by the frequent presence of established CHD risk factors in obese people, notably hypertension, elevated LDL-C, low HDL-C, and insulin resistance (including glucose intolerance and diabetes) [26].

BMI is the most widely used measure to determine if a person is obese. However, the distribution of body fat is also important when assessing disease risk. Excess abdominal visceral body fat seems to be a risk factor, independent of BMI. Waist circumference, a measure of abdominal adiposity, appears to have a stronger association with CHD risk than does BMI [26]. For the practicing physician and healthcare professional, waist circumference offers a quick and useful tool to assess the degree to which a patient is carrying excess abdominal fat and its threat to cardiac health. While cut points for BMI for overweight and obesity are well-established and accepted, further research is required to determine analogous cut points for waist circumference in different sex, age, and ethnic groups. However, commonly used cut points are waist circumferences of >90 cm (>35.4 in) for men and > 80 cm (>31.5 in) for women in some countries and > 102 cm (40 in) for men and > 85 cm (>35 in) for women in the USA.

Physical Activity

Physical activity, by which we mean aerobic exercise, has consistently been associated with a reduction in CHD events in both primary and secondary preventions [27]. Indeed, a sedentary lifestyle is now recognized as one of the big four risk factors, alongside dyslipidemia, smoking, and hypertension (five, if we include diabetes). Much of the benefit of physical activity can be explained in terms of its favorable effects on several factors associated with CHD, namely, body weight, blood pressure, the blood lipid profile (including a rise in HDL-C), insulin resistance, and glucose tolerance [28]. To paraphrase Newton, physical activity is equal and opposite to obesity.

There is widespread agreement among medical organizations that everyone should be encouraged to engage in an exercise program. Typical recommendations are for at least 30 min of moderate-intensity physical activity, such as walking at a speed that induces mild exertion, on at least 5 days per week. As the benefits are cumulative, the exercise can be done as several short activities every day or as one or two long activities at the weekend. The relationship between the quantity of exercise and the degree of risk reduction seems to be dose-dependent. Carrying out 300 min of moderate intense exercise per week has been suggested to decrease CHD risk by 20% compared to 14% for individuals engaging in 150 min per week [27]. Engaging in vigorous intensity exercise, such as jogging, is likely to produce further benefits.

A major challenge in this area is to determine what behavioral strategies will motivate individuals to engage in a long-term program of physical activity.

Conclusion

We now have compelling evidence that diet and lifestyle changes can substantially reduce the risk of CHD.

A strong predictor of risk of CHD is the ratio of total cholesterol to HDL-C in the blood. Dietary changes that raise this ratio increase the risk of CHD, and vice versa. The key determinant is the type of fat, not the amount. For that reason simply lowering the percentage of energy from dietary fat has

little effect on the ratio and therefore on risk of CHD. *Trans* fats are the worst type of fat. Fortunately, these fats have been almost eliminated from the diet in the USA and much reduced in many other countries. It is a mistake to focus on reducing the intake of saturated fats (SFA) without simultaneously advising consumers what should be added to the diet to replace the lost calories. Replacing SFA with polyunsaturated fats (PUFA) lowers the ratio of total cholesterol to HDL-C (and therefore helps prevent CHD), while replacing it with refined carbohydrates achieves little or nothing. Likewise, monounsaturated fats have a neutral effect. These contrasting effects that are seen when SFA is replaced with different macronutrients and foods help explain why cohort studies have commonly failed to see a direct association between intake of SFA and risk of CHD.

In recent years, the focus of CHD prevention has shifted away from individual food components and toward foods and dietary patterns. We can state with a high degree of confidence that the risk of CHD can be greatly reduced by a diet that contains generous amounts of fruit, vegetables, whole grains, and nuts, plus at least two servings per week of fish, preferably fatty fish. The diet should also be low in salt, red meat, processed meat, and refined carbohydrates, especially SSB. This dietary pattern has much in common with that found in the traditional Mediterranean diet.

Two other critically important factors in the prevention of CHD are the avoidance of excess weight gain and engaging in regular exercise. These factors are key components of a healthy lifestyle that together with a healthy diet have the potential to substantially reduce the burden of CHD. This was convincingly demonstrated in the following study. The Nurses' Health Study is a particularly large cohort study [29]. The researchers enrolled 84,000 female American nurses. They identified the nurses who led a low-risk lifestyle based on body weight, exercise, smoking, and seven dietary variables. The findings revealed that the 3% of nurses who were at the lowest risk had six times less risk of CHD than the other nurses.

The focus of this chapter has been CHD. We can conclude with some comments on other types of cardiovascular disease. While the relative importance of different risk factors varies from one form of cardiovascular disease to the next, the general recommendations made here will go far to achieving the prevention of all types of cardiovascular disease. This is certainly true for stroke.

The take-away message from this chapter is that physicians and other healthcare professionals need to encourage their clients to consume a healthy diet as a key part of a healthy lifestyle.

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Dietary Influences on Blood Pressure

13

TanYa M. Gwathmey and Jamy D. Ard

Keywords

Nutrition · Blood pressure · Hypertension · Nutraceuticals · Dietary supplements · Dietary patterns

Key Points

- Hypertension is a major risk factor for heart disease and stroke, affecting ~50% of the US population.
- Obesity can lead to hypertension, but weight loss can help to reduce blood pressure.
- High levels of dietary sodium will increase blood pressure for some individuals; reductions in sodium intake can lower blood pressure and the risk of hypertension.
- Reductions in alcohol consumption may help to decrease blood pressure.
- Dietary patterns play an important role in helping to achieve/maintain a healthy blood pressure.

Introduction

High blood pressure (hypertension) is one of the major risk factors for cardiovascular and cerebrovascular disease, contributing to almost 50% of these conditions [1]. Moreover, chronically high blood pressure (BP) affects >1.13 billion people worldwide, is associated with both renal failure and dementia, and is therefore recognized as a major global health threat[1]. Nearly 1 out of 2 adults within the US population has hypertension (108 million people), and ~ 82 million of those individuals do not have their hypertension under control [2]. Ninety-five percent (95%) of individuals with high BP have *essential* or *primary hypertension* (unknown cause) [2]; however, the principal causes of *secondary hypertension* include obstructive airways, hormonal abnormalities, thyroid disease, and high dietary salt or alcohol intake. Approximately 20–30% of individuals with high BP are characterized by *resistant hypertension* and require at least three different types of antihypertensive medications to achieve BP control [2]. Resistant hypertension is generally more prevalent in individuals who are older, obese, female, African American, or have an underlying illness such as diabetes or renal disease [2]. Table 13.1 provides the classification of BP categories, as defined by the American Heart Association.

T. M. Gwathmey (✉) · J. D. Ard
Wake Forest School of Medicine, Winston Salem, NC, USA
e-mail: tgwathme@wakehealth.edu; jard@wakehealth.edu

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Table 13.1 Classification of hypertension

Blood pressure category	Systolic (mmHg)		Diastolic (mmHg)
Normal	<120	And	<80
Elevated	120–129	And	<80
High blood pressure (hypertension stage 1)	130–139	Or	80–89
High blood pressure (hypertension stage 2)	>140	Or	>90
Hypertensive crisis (requires immediate care)	>180	And/or	>120

Treatment for hypertension primarily includes antihypertensive medications that fall in the categories of thiazide diuretics, calcium channel blockers, beta blockers, and therapeutic targets of the renin-angiotensin-aldosterone system (RAAS), which is responsible for the regulation of BP and fluid volume. RAAS blockade is largely represented by angiotensin-converting enzyme (ACE) inhibitors and angiotensin II (Ang II) receptor blockers (ARBs).

In addition to the primary treatment strategy of antihypertensive drugs, alternative or complimentary approaches to BP control include changes in physical activity, modifications of diet, and the use of nutraceuticals (whole foods or components of foods that provide health benefits in addition to their nutritional value), or dietary supplements. Therefore, the current chapter focuses on the impact of nutrition on BP control.

Blood Pressure and the Blood Glucose Relationship

Approximately 50% of patients with essential hypertension display insulin resistance [3]. In addition to its role in the regulation of BP, the RAAS also plays a key role in the pathophysiology of insulin resistance through the actions of angiotensin II (the primary bioactive peptide of the RAAS) in the dysregulation of insulin secretion, adipogenesis, and microvascular blood flow to the muscle [3, 4]. Furthermore, angiotensinogen, the primary precursor to the production of angiotensin peptides, along with ACE, is found in adipocytes, suggesting the production of local−/tissue-generated Ang II to mediate these actions [4]. Indeed, a vast number of clinical trials comparing the effects of ACE inhibitors or ARBs versus other antihypertensives (thiazides, β-blockers, and calcium channel blockers) have consistently demonstrated that greater improvements in insulin sensitivity are achieved by RAAS blockade [4]. Insulin resistance is a primary risk factor for the development of type II diabetes and is associated with the dysregulation of blood glucose levels/hyperglycemia, abnormalities in carbohydrate, fat and protein metabolism, accumulation of visceral fat, and increased body weight.

Body Weight

There is a linear relationship between higher body mass index (BMI) and BP, with no apparent threshold. Individuals with obesity (BMI $\geq$ 30 kg/m^2) have 3.5 times greater likelihood of developing hypertension, and the population attributable risk due to obesity for hypertension is estimated to be 60–70% [5]. While BMI is generally related to BP, the distribution of excess body fat is a more specific marker of risk for elevated blood pressure. For example, waist-to-hip ratio, a marker of central distribution of adiposity, is associated with higher blood pressure independently of BMI [6]. Abnormal adipocyte function in high-risk fat depots may be one of the central links between obesity and the development of elevated blood pressure. The adipocyte plays a role in the regulation of vascular tone via the secretion of adipokines including leptin, adiponectin, resistin, chemerin, and visfatin that interact directly

with the vascular smooth muscle and endothelium. Once the adipocyte is functioning abnormally, the cascade of responses that happen as a result include recruitment of circulating macrophages that support low-grade inflammation, increased insulin resistance, compensatory hyperinsulinemia, sodium retention, and increased intravascular volume [5].

Weight loss has a significant effect on reducing blood pressure. A weight loss of 3–5% of initial body weight has been associated with reductions in blood pressure [7]. Per kg of weight lost, the mean reduction in SBP is 1 mm Hg and 0.9 mm Hg DBP. Blood pressure reduction can be achieved as a result of lifestyle behavioral therapy (LBT), anti-obesity pharmacotherapy, or bariatric surgery. Each approach may have limitations that can impact treatment response or applicability. LBT is broadly applicable, but when used alone, the typical weight loss (5–8% of initial weight) and overall response rates are lowest compared to pharmacotherapy and surgery [7]. Pharmacotherapy can be a useful adjunct to LBT, but for some medications, poorly controlled blood pressure is a contraindication due to potential short-term increases in blood pressure. Bariatric surgery provides the largest and longest sustained weight loss response but is only indicated for those with a BMI $\geq$ 40 kg/m^2 or those with a BMI $\geq$ 35 kg/m^2 with associated complications of obesity that are not well controlled [7].

Dietary Components and Their Effects on Blood Pressure

The relationship between individual dietary components, such as macronutrients, micronutrients, and minerals, and BP is important to understand but does not capture the interactions of the food matrix that affect BP. To guide patients, we need to understand how blood pressure is influenced by the pattern of foods that we eat in varying combinations. The Dietary Approaches to Stop Hypertension (DASH) dietary pattern is an example of this optimal combination of foods. The DASH dietary pattern was developed based on an understanding of some of the relationships between individual nutrients and blood pressure; the pattern was then synthesized based on combining foods that provided higher levels of those key nutrients into a menu plan that guaranteed achievement of the nutrient targets with consumption of the appropriate foods and amounts [8]. In this section of this chapter, we will review the relationship between key nutrients and blood pressure, but ultimately point back to how this informs a pattern of food intake that might be optimal for controlling blood pressure.

Macronutrients

Protein

Protein intake may affect BP via several mechanisms including ACE inhibition by bioactive peptides, increases in key amino acids that have vasodilatory actions, and improvements in insulin sensitivity [9, 10]. In US populations, the average protein intake per 2000 kcal is approximately 15% of calories or 75 g of protein. Table 13.2 shows the protein intake prescribed in the DASH and the OmniHeart dietary patterns [11]. The source and quality of protein may also have an impact on the BP effects of protein. Observational data suggest that plant protein may be more beneficial for BP, but clinical trials have not demonstrated major differences between plant and animal protein with regard to BP-lowering effects [10]. One systematic review suggests that intake of soy protein associated with isoflavones can reduce the risk of developing hypertension [12]. These effects are not seen when protein is consumed as a supplement.

Fat

Total fat intake may not be a defining factor for BP control; however, fat sources and the ratio of unsaturated to saturated appears to be more relevant. Saturated fat has generally been targeted for replacement, using unsaturated fat options such as mono- and polyunsaturated fatty acids (MUFA and

Table 13.2 Comparison of three dietary patterns for blood pressure reduction

Nutrient/food component	DASH diet	OmniHeart protein	OmniHeart unsaturated fat	Key food sources	Key notes, patient guidance
Protein, % kcal	18	25	15	Poultry, fish, lean meat, beans, legumes, grains, nuts, seeds	Red and processed meat limited; nearly 50% of protein from plant sources
Fat, % kcal	27	27	37	Unsaturated oils like olive, canola, safflower, nuts, seeds	Saturated fat 6% in all patterns
Monounsaturated, % kcal	13	13	21		
Polyunsaturated, % kcal	8	8	10		
Carbohydrates, % kcal	55	48	48	Fruit, vegetables, whole grains, beans, legumes	Added sugar from sweets and beverages limited
Fiber, g/1000 kcal	14.7	14.3	14.3	Fruit, vegetables, whole grains, beans, legumes, nuts, seeds	Patients may have bloating with increased fiber intake. Decreasing sodium may mitigate bloating
Potassium, mg/2100 kcal	4700	4700	4700	Fruits, vegetables, beans, legumes, nuts, and whole grains	
Calcium, mg/2100 kcal	1200	1200	1200	Low-fat dairy	Recommend nuts, seeds, beans, leafy greens, and fortified foods to get dietary calcium in those with significant lactose intolerance
Magnesium, mg/2100 kcal	500	500	500	Nuts, seeds, legumes, whole grains, and green leafy vegetables	

PUFA). DASH is lower fat but emphasizes MUFA and PUFA as the primary fat source (Table 13.2) [8]. In the OmniHeart trial, despite a higher fat intake, the unsaturated fat arm had a similar BP effect as the DASH-based diet [11].

Omega-3 fatty acids (n-3 FA) primarily derived from marine sources have been associated with lower BP in observational and randomized clinical trials [13]. While fish is the primary source of n-3 FA like eicosapentaenoic acid and docosahexaenoic acid, the amounts of n-3 FA associated with BP reduction have typically come in the form of supplements in the range of 3–4 g daily of fish oil supplements. Plant-based n-3 FA such as alpha-linolenic acid, derived from sources like flaxseed, do not appear to have the same associated BP reduction [13].

Carbohydrates

The DASH diet is a carbohydrate-rich diet (Table 13.2), suggesting that a high carbohydrate intake can be part of a pattern that lowers BP. Like the other macronutrients, carbohydrates are not uniform in quality, structure, or effect, so further examination of the type of carbohydrates associated with lower BP is warranted. Fiber intake may be one of the best indicators of carbohydrate quality. A recent meta-analysis of 15 randomized trials suggests that higher intakes of fiber (25–29 g/d) compared with lower intakes lead to a mean difference of −1.27 mm Hg (−2.5 to −0.04) in SBP [14]. Similar estimates of effects are seen with whole grain intakes. Sugars, on the other hand, represent energy-dense, low-nutrient versions of carbohydrates that appear to have an adverse effect on BP and are therefore

limited in the DASH diet. The effects of sugar on BP may depend on an interaction with sodium. Evidence from the INTERMAP study showed that in individuals above the median for 24-hour urinary sodium excretion, fructose intake higher than 5.6% of kcal/day was associated with higher BP of 2.5/1.7 mm Hg [15].

Micronutrients

Sodium

Sodium is often the primary intervention target in clinical practice for reducing BP. The omnipresence of sodium in the food supply, especially in processed food, means that reducing sodium in industrialized countries requires an individual to significantly reduce processed food and food away from home. Individuals can expect a mean reduction in SBP/DBP of 2/1 mm Hg when reducing sodium from ~3300 to 2400 mg per day [16]. Further reduction in BP could be achieved (7/3 mm Hg) when reducing sodium to 1500 mg per day. In general, for someone consuming a higher sodium intake, counseling to reduce sodium by 1150 mg per day (~1/2 teaspoon salt) would be expected to achieve 3–4/1–2 mm Hg reduction in BP. It should be noted that reducing sodium intake while also implementing the DASH dietary pattern has been shown to be more effective than doing either intervention alone [16].

Potassium

Potassium is thought to play a protective role in blunting the hypertensive effects of higher sodium intakes. Low dietary potassium intake is associated with salt-sensitive hypertension [17]. Potassium may also have direct vascular effects and is involved in natriuresis. Dietary potassium interventions have typically failed to demonstrate an independent effect of dietary potassium. The use of potassium supplements for lowering BP has a slightly stronger evidence base. A meta-analysis of RCTs using potassium supplementation suggested BP-lowering effects of 4.7 mm Hg SBP (95% CI, 2.4–7) and 3.5 mm Hg DBP (95% CI, 1.3–5.7). The effect was noted to be greater in those who had hypertension (6.8/4.6 mm Hg) [18].

Calcium

Prospective cohort studies have shown that individuals with higher dietary calcium intake have lower incidence of hypertension and lower BP. For example, a recent meta-analysis found the risk of developing hypertension in the general population was lower for the highest levels of calcium intake (relative risk = 0.89, 95% CI 0.86, 0.93) and for each 500 mg/d increment (relative risk = 0.93, 95% CI 0.9, 0.97) [19]. The evidence for effects of calcium supplementation on BP is mixed however. A 2006 Cochrane review of 13 RCTs showed significant effects of calcium supplements on SBP (−2.5 mm Hg) and no effect on DBP in individuals with elevated blood pressure at baseline. The evidence was graded as weak due to poor-quality trials and significant heterogeneity [20].

Magnesium

Dietary magnesium intake has been associated with lower BP. A systematic review and meta-analysis of ten prospective cohort studies showed an inverse association between magnesium intake and the risk of hypertension (relative risk = 0.92, 95% CI 0.86, 0.98) [21]. A 100 mg/d increment in magnesium intake was associated with a 5% lower risk of developing hypertension. There is no association between serum magnesium levels and the risk of hypertension. Supplementation of magnesium has been shown to produce small decreases in BP [22]. A 2016 meta-analysis of 34 trials showed a statistically significant reduction of SBP (−2.0 mm Hg) and DBP (−1.78 mm Hg). The authors of this study estimated that a 300 mg/d dose for at least 1 month would be sufficient to lower BP.

Other Food Components

Caffeine

Caffeine is a stimulant alkaloid that affects the central nervous system and is the most commonly consumed pharmacologically active food substance [23]. In the USA, the mean intake of caffeine from all beverages is about 165 mg per day. Intakes ranging between 100 and 400 mg have been widely studied and consistently shown to increase both SBP and DBP acutely in the majority of instances [24]. However, observational studies of long-term daily coffee consumers have not identified an association between coffee consumption at various levels and long-term BP. In populations of people without hypertension, prospective cohort studies have not identified an increased risk of developing hypertension with increasing levels of intake of caffeine, primarily as coffee [24].

Alcohol

It has been recommended by the Joint National Commission on Blood Pressure that daily alcohol intake be limited to two drinks for men and one drink for women. It is estimated that nearly 10% of the population burden of hypertension in the USA is due to alcohol [25]. Reducing alcohol intake from high levels leads to decreases in blood pressure in a dose-dependent fashion. A 2017 meta-analysis of 36 trials of alcohol reduction interventions showed that reducing alcohol for those who drank less than two drinks per day was not associated with reduced BP [26]. However, for those who drank more than two drinks per day, the effects were clear—reducing alcohol intake to near abstinence decreased blood pressure. For those who drank larger quantities of alcohol on a regular basis (e.g., >6 drinks/day), reducing alcohol by 50% was associated with a decrease in SBP of −5.5 mm Hg (95% CI, −6.7 to −4.3) and DBP of −3.97 mm Hg (−4.7 to −3.25).

Grapes, Wine, and Other Polyphenols

Resveratrol, a member of the stilbenoids group of polyphenols, is commonly found in the skin and seeds of red grapes, red wine, berries, pomegranate, and cherries and exhibits a wide range of beneficial properties, including antioxidant and anti-inflammatory activities. Resveratrol and other polyphenols such as flavonoids exhibit cardioprotective activity and blood pressure-lowering effects by increasing nitric oxide (NO) availability and improving insulin sensitivity [27]. A systematic review and meta-analysis of randomized, control, clinical trials demonstrated that long-term supplementation with resveratrol (300 mg daily) markedly reduced SBP (−9.4 mm Hg), DBP (−6.2 mm Hg), and mean arterial pressure (−7.3 mm Hg) compared to those subjects receiving placebo [27], indicating that resveratrol may serve as a potent vasorelaxant.

Tea, the second highest consumed beverage in the world, and cocoa are both rich in flavanols, a subgroup of flavonoids, whose consumption is associated with increased NO levels and improved elasticity of blood vessels. Green tea is especially enriched with the catechin flavanol, epigallocatechin-3-gallate (EGCG), which upregulates eNOS (endogenous nitric oxide synthase) expression, resulting in enhanced NO production and improved endothelial function through modulation of prostaglandin E1 [28]. Moreover, EGCG acts as a potent ACE inhibitor, increases gamma-aminobutyric acid (GABA), and alters sympathetic nervous system activity to modulate BP [29]. A number of systematic reviews and meta-analyses have shown improvements in BP following consumption of EGCG, including a meta-analysis of 14 randomized clinical trials (including 971 participants) where green tea/green tea extract supplementation resulted in reductions in both systolic and diastolic BP compared to placebo in overweight/obese subjects [28].

Beet Root Juice

Beet root juice is a natural source of NO through its metabolism from nitrate. Beet root is rich in betacyanins, betaine and betalain, and functions to improve NO availability in the endothelium,

promoting vasodilation and reducing levels of oxidative stress and inflammation. A meta-analysis of 18 randomized clinical trials evaluating the consumption of beetroot juice reported a significant decrease in systolic BP [30], while a systematic review of 9 cross-over studies with a beetroot juice intervention for up to 28 days resulted in significant improvements in vascular and endothelial function and a reduction in BP [31].

Dietary Supplements

A number of dietary supplements tout cardiovascular benefits, including reductions in BP. While many may be anecdotal, few show clinical relevance as evidenced in clinical trials, or demonstrate significant reductions in BP compared to lifestyle modifications [32]. Supplements that show some evidence of benefit include fish oil, L-arginine, and allicin [32]. *Fish oils*, rich in omega-3 polyunsaturated fatty acids, are reported to substantially lower blood pressure through reductions in aldosterone levels, alterations in sodium transport, and increased vasodilatory activity through stimulation of prostaglandins E1 and G1 and eNOS/NO production [32]. RCTs evaluating the effects of fish oil supplementation (180 mg eicosapentaenoic acid and 120 mg docosahexaenoic acid, daily) for 13 days up to 2 months report reductions in BP ranging from −6 to 12 mm Hg for systolic and − 5 to −8 mm Hg for diastolic BP [32]. *L-arginine*, commonly used in the DASH diet, is a nonessential amino acid, which acts as a precursor of NO to promote relaxation of the endothelium, while also acting as a strong antioxidant and anti-inflammatory agent. A comprehensive meta-analysis of 11 RCTs, including 387 participants, reported that oral intervention with L-arginine (4–24 g daily) for up to 12 weeks lowered SBP (−5.39 mm Hg) and DBP (−2.66 mm Hg) [33]. *Allicin* (abundant in garlic) enhances NO synthesis to promote vasodilation and is a strong inhibitor of ACE activity. A meta-analysis and systematic review of 20 RCTs, including 970 subjects, demonstrated that supplementation of garlic extract (600–900 mg daily for 8–12 weeks) resulted in lower SBP (−5.1 mm Hg) and DBP (−2.5 mm Hg) when compared to placebo [34].

Summary/Conclusion

Control of BP through pharmacotherapy remains the primary approach for individuals with hypertension; however, behavioral/lifestyle modifications, including specific dietary patterns, may play an important role in achieving BP control. The precise balance of macronutrients, micronutrients, and minerals must be optimized to fit individual dietary needs and health conditions. Inclusion of nutraceuticals and dietary supplements that promote a healthy blood pressure should be considered when developing an ideal meal plan; however, the efficacy of dietary supplements suggests an adjuvant role as therapy for the reduction of BP in hypertension.

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Suggested Further Readings

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Diet, Physical Activity, and Cancer Prevention

14

Rachel A. Murphy

Keywords

Cancer · Diet and cancer prevention · Body weight · Alcohol · Meat · Exercise

Key Points

- Healthy behaviors track through life and should be encouraged starting at an early age.
- To reduce cancer risk, maintain a healthy weight throughout life; eat a diet high in wholegrains, non-starchy vegetables and fruits, and beans; limit consumption of red meat and eat little, if any, processed meat; avoid alcohol; be physically active every day; and limit time spent sitting and in other sedentary behavior.
- As best as they are able, cancer survivors should follow recommendations for cancer prevention.

Introduction

The burden of cancer worldwide is substantial; an estimated 18.1 million new cancers were diagnosed, and 9.6 million cancer deaths occurred in 2018 [1]. Cancer is among the leading causes of death in the United States, and more than one in three Americans will be diagnosed with the disease in their lifetime [2]. As the burden of cancer continues to grow due to population growth, exposure to carcinogens, and aging, it has become apparent that "we cannot treat our way out of the cancer problem" [3]. Although some factors that affect cancer risk cannot be modified, such as genetics and age, various important influences can be modified. Prevention strategies that target modifiable factors are therefore needed to reduce the current and future burden of cancer.

A large body of evidence has shown that nutrition, body weight, and physical activity are major modifiable risk factors for cancer in addition to playing roles in cancer progression and survival. Evidence on the relationship between diet and cancer dates back to the 1980s when Doll and Peto [4] estimated that ~35% of cancer deaths could be attributed to diet. Subsequent reports, such as "Diet, Nutrition, and Cancer," by the US National Academy of Science [5]; the 1988 *Surgeon General's Report on Nutrition and Health* [6]; and the US National Research Council of the National Academy of Sciences, *Diet and Health: Implications for Reducing Chronic Disease Risk* [7], contributed to the now

R. A. Murphy (✉)
Cancer Control Research, BC Cancer, and the School of Population and Public Health, University of British Columbia, Vancouver, BC, Canada
e-mail: rachel.murphy@ubc.ca

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widely accepted importance of nutrition and dietary components for determining cancer risk. In 2018, the Third Expert Report from the World Cancer Research Fund International (WCRF) and the American Institute of Cancer Research (AICR) were released, providing the most comprehensive, evidence-based recommendations for how people can reduce their risk of cancer through healthy living [8]. The WCRF International Continuous Update Project provides an ongoing review and synthesis of evidence from nearly 10,000 studies [9] to ensure public access to up-to-date information on cancer prevention.

Despite considerable evidence supporting the critical role of diet for reducing the risk of cancer, inconsistencies exist, and the strength of the evidence linking foods, nutrients, and eating patterns with cancer varies. Variation in evidence reflects challenges in the field of nutrition including bias of self-reported dietary assessment, the limited number of biomarkers of dietary intake, heterogeneous analysis, and reporting of results as well as known variation in the response to diet due to factors such as genetic and metabolic variation. Although inconsistencies and gaps exist in nearly all fields of research, it has disproportionately skewed the perception of nutrition research and particularly relationships between diet and cancer. This has resulted in confusion among the general public regarding cancer preventive behaviors who may subsequently seek information from sources that lack credibility. Physicians and health professionals can therefore play an important role in conveying credible information and strategies to encourage healthy behaviors.

Most cancer prevention guidelines are framed toward adults since nine in ten cancers are diagnosed in people aged 50 and older [10]. However, in general, cancers have a long latency period; hence, the exposures that contribute to a cancer diagnosis at age 55 years were likely accumulated earlier in life. In addition, many health habits are formed early. Children and adolescents who have a healthy diet, are physically active, and have a healthy body weight are more likely to continue those behaviors into adulthood. As such, interventions aimed at disrupting the persistence of obesity, poor diet, and physical inactivity in childhood are critical. On the other hand, older adults, those aged 65 and older, should also be included in prevention efforts rather than the current focus on the management of cancer after diagnosis [11]. The life expectancy for many adults over age 65 exceeds 10 years, and studies suggest that older age is still an etiologically relevant time period for efforts to prevent cancer [12, 13]. The evidence and strategies presented in this chapter are therefore applicable to the broader population seen by physicians and healthcare practitioners.

Overweight and Obesity

Overweight and obesity are most commonly assessed using body mass index (BMI). BMI is readily measured in a clinical and research setting from weight in kilograms divided by height in meters squared (kg/m^2). BMI categories established by the World Health Organization (WHO) are underweight, <18.5 kg/m^2; normal, 18.5–24.9; overweight, 25.0–29.9; obese, 30.0–39.9; and severely obese, ≥ 40.0. Obesity is discussed in greater detail by Bray and Champagne in Chap. 9.

In the United States, 18.5% of children and adolescents aged 2 to 19 years (approximately 13.7 million individuals) are obese [14]. The prevalence of obesity in adults was 42.4% in 2017–2018, a considerable increase from 30.5% in 1999–2000 [15]. Obesity disproportionately affects some populations more than others. African Americans have the highest prevalence of obesity (49.6%), followed by Hispanics (44.8%), non-Hispanic Whites (42.2%), and Asians (17.4%). The prevalence of obesity is greater among middle-aged adults (40–59 years, 44.8%) than in adults aged 20–39 (40.0%) or over 65 (42.8%) [15].

Excess body weight contributes to many of the most common types of cancer. Accordingly, one of the most important things a person can do to reduce their risk of cancer is to maintain a healthy weight throughout life. There is consistent evidence indicating that higher body fat is associated with increased risk of many types of cancer including the endometrium, esophagus, gastric cardia, liver,

kidney, pancreas, colon/rectum, gallbladder, ovary, breast (in postmenopausal women), and thyroid [16]. The mechanisms by which overweight and obesity increase the risk of cancer are complex and interrelated, including chronic low-grade inflammation, production of excess estrogen in adipose tissue, increased levels of insulin and insulin-like growth factor-1, and production of hormones from fat cells, as well as direct and indirect effects on the regulation of cell growth and altered immune response [17].

Among people who are overweight or obese, weight loss can reduce the risk of cancer. A study of intentional weight loss in the Women's Health Initiative (WHI) study reported that, compared to women with stable weight, women who lost weight had an approximately 30% lower risk of endometrial cancer. The reduction in cancer risk was even greater among women who were initially obese (~56% lower risk). Conversely, weight gain of 10 pounds or more was associated with a higher endometrial cancer risk [12]. A study of 181,000 women reported that even modest (>4 lbs) sustained weight loss is associated with lower risk of breast cancer [18]. These findings suggest that women over the age of 50 can lower their risk of cancer through weight loss.

At the most basic level, weight maintenance occurs when energy intake equals energy output. Physical activity and appropriate dietary intake are critical for maintaining and/or achieving a healthy body weight. To support a healthy body weight, the following actions are encouraged.

- Eat a healthy diet with an appropriate caloric level that supports nutrient adequacy. A healthy dietary pattern includes a variety of vegetables, whole fruits, grains (at least half as whole grains), dairy products or alternatives, a variety of protein-rich foods, and oils and minimal consumption of saturated and *trans* fats, sodium, and added sugar.
- Choose water and nutrient-dense beverages. Avoid sugary drinks and alcoholic beverages. If alcohol is consumed, then drinks should be limited to up to one drink per day for women and up to two drinks per day for men.
- Be mindful of eating habits—how, why, what, when, where, and how much is eaten.
- Be physically active and limit time spent sitting, based on the guidelines below.

Physical Activity

The American Cancer Society publishes guidelines on Nutrition and Physical Activity for the prevention of cancer [19]. Children and teenagers should engage in at least 1 h of moderate- or vigorous-intensity activity each day, with vigorous activity on at least 3 days each week. This may help form healthy habits that persist into adulthood when most chronic diseases occur, including cancer. Adults should engage in at least 150 min of moderate-intensity or 75 min of vigorous-intensity activity each week, or a combination of these, preferably spread throughout the week. Strong evidence has shown that increased physical activity and achieving recommended physical activity levels is associated with reduced risk of breast, colon, endometrium, kidney, liver, myeloma, non-Hodgkin lymphoma, and advanced prostate cancer [19, 20]. There also appears to be a dose-response relationship, whereby more physical activity leads to a greater lowering of cancer risk [20]. Physical activity may also be beneficial for reducing the risk of other types of cancer, but additional evidence is needed.

Sedentary behavior is another important issue. This is defined as waking behavior with an energy expenditure ≤1.5 metabolic equivalents (METs), including time spent sitting, reclining, or lying down [21]. Shifts in occupation over the past decades, coupled with changes to the structural environment, have contributed to decreases in physical activity and greater time spent in sedentary activities. Even among people who are physically active, greater sedentary time may increase the risk of cancer [21] as the deleterious effects of sedentary behavior may impact cancer risk via different biological processes than physical activity [22]. A deeper understanding of the mechanisms, and dose-response

relationship with cancer, is needed. Advice to limit sedentary behavior has now been incorporated into physical activity guidelines. The current recommendations are general: "Sit less, move more," and break up periods of sedentary time with physical activity when possible [19, 23].

Dietary Intake

Recommendations

In addition to weight and physical activity, the WCRF International/AICR report provides recommendations on six simple dietary habits that can promote cancer prevention: (1) eat a diet rich in wholegrains, vegetables, fruits, and beans; (2) limit "fast foods" and other processed foods high in fat, starches, or sugars; (3) limit red and processed meat; (4) limit sugar-sweetened beverages; (5) limit alcoholic drinks; and (6) do not rely on dietary supplements including vitamins. The report provides summaries for each of these recommendations, namely, details on the exposure (e.g., fruit, citrus fruit, non-starchy vegetables), the specific cancer site(s) associated, and the strength of the evidence [8]. Individual and public health goals related to each recommendation are also provided. For example, individual goals include consuming a diet that provides at least 30 g/day of fiber; consuming at least five portions per day of a variety of non-starchy vegetables and fruit; and, if you eat red meat, limit consumption to less than three servings per week and consume little, if any, processed meat. Diet-specific recommendations with evidence considered to be "convincing" (the strongest category of evidence as graded by the WCRF International/AICR) are summarized in Fig. 14.1 and discussed below. While most of these goals are generally attainable, many Americans fall far short of the recommended fiber intake. Careful meal planning, including high-fiber food substitutions, may be needed.

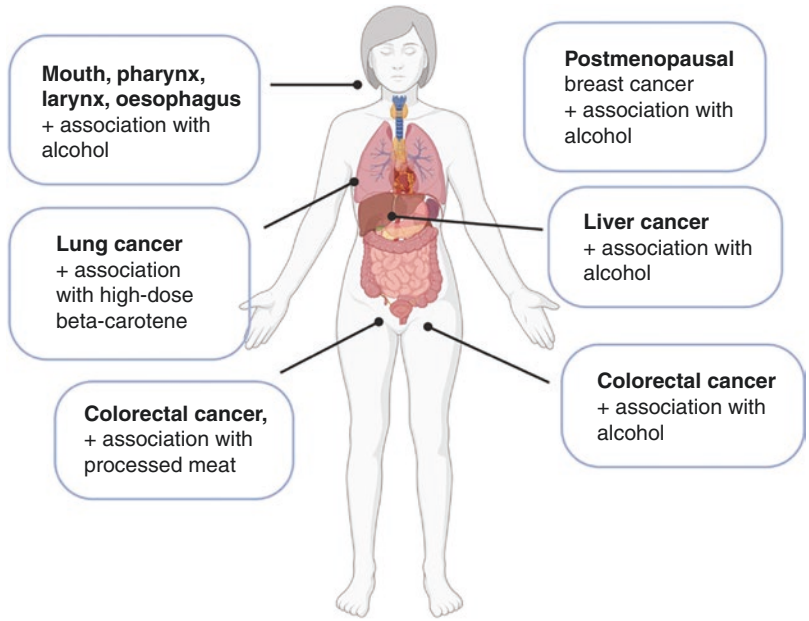

Fig. 14.1 Summary of convincing evidence on dietary components and cancer risk. Evidence considered convincing by the WCRF International/AICR Continuous Update Project [9]. (Created with Biorender.com)

A resource that supports building healthy habits is provided in the "Suggested Further Reading" at the end of the chapter.

Recently, the recommendations have been operationalized into a standardized score that provides points for each recommendation [24]. This simplified approach will facilitate comparability across research studies. However, there are limitations to consider. There is no clinical guidance on the relative importance of recommendations; this can lead to subjectivity in scoring that can lead to confusion for clinician and patient alike. For example, recommendations that encompass multiple components (e.g., eat a diet rich in whole grains, vegetables, fruit, and beans) have points split by the components. There is also no prescriptive guidance for some categories such as "limit" consumption of fast foods. Nonetheless, the score enables researchers and healthcare professionals to assess a given population or individuals for the risk of cancer based on these commonly captured measures (Fig. 14.2).

Meat Consumption

Meat can be broadly categorized as white meat, red meat, and processed meat. The nutritional profile of fish is quite different than meat and tends to be considered separately. White meat refers to poultry, while red meat includes beef, veal, pork, lamb, mutton, and goat. Processed meat refers to meat that has been preserved with salting, curing, fermentation, smoking, or other processing/preservation such as ham, sausages, corned beef, beef jerky, and canned meat. The recommendation to limit consumption of red meat to three servings or less per week and avoid processed meat is based upon strong preclinical and epidemiologic evidence that consumption of either red or processed meat increases the risk of colorectal cancer [25, 26]. In 2015, the International Agency for Research on Cancer (IARC) classified red meat as a grade 2A carcinogen, probably carcinogenic to humans, while processed meat was classified as group 1, carcinogenic to humans. Group 1 is the strongest classification, the same

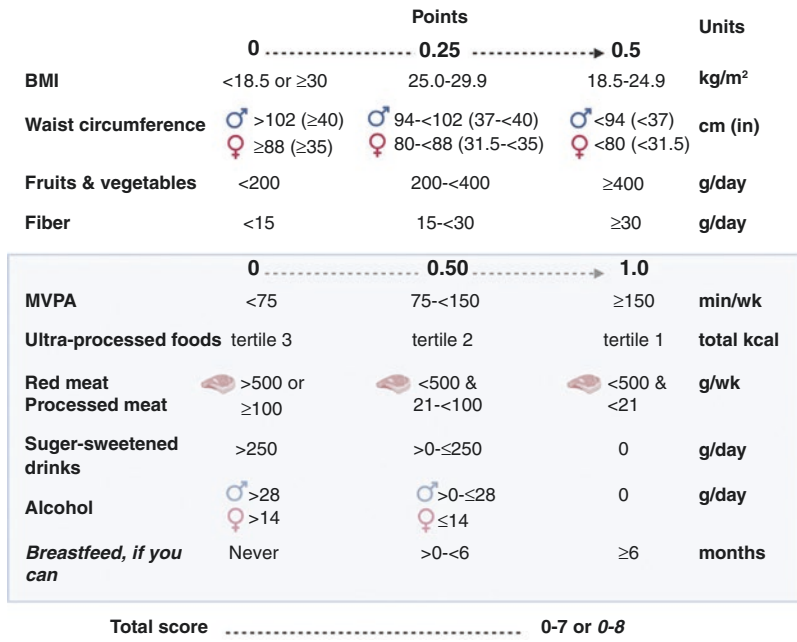

Fig. 14.2 Operationalization of cancer prevention recommendations into a standardized score. Abbreviations: MVPA, moderate-vigorous physical activity. Italic font represents optional criteria. Shaded box represents criteria with different scoring system (0–1 vs. 0–0.5). (Adapted from Shams et al. [24]. Created with Biorender.com)

group as asbestos and tobacco smoke. Group 2A reflects limited evidence from epidemiological studies and strong mechanistic evidence from preclinical or clinical studies.

There are several mechanisms by which red meat and processed meat may increase the risk of colorectal cancer. One suggested mechanism is that cooking methods that use high temperatures, grilling, for example, produce potential carcinogenic substances such as polycyclic aromatic hydrocarbons (PAHs) [27]. These compounds have been identified as potentially carcinogenic by the IARC. Another proposed mechanism involves heme, the cluster of myoglobin and hemoglobin, which gives meat its red color. Heme can induce lipid peroxidation in the colon, leading to the formation of cytotoxic and genotoxic aldehydes which can promote cancer progression [27].

While the WCRF International/AICR recommendations and classification of red meat and processed meat reflects associations with colorectal cancer, there are also suggestive associations with other types of cancers. Evidence has linked greater red meat consumption to risk of cancer of the pancreas [28] and prostate [29], while a higher intake of processed meat is linked to stomach cancer [30]. The recommendations have been misinterpreted by some as being "anti-meat" or encouraging people to avoid meat altogether. However, meat is an important source of nutrients including protein, iron, zinc, selenium, and vitamins B6 and B12. A number of studies have also shown that the Mediterranean diet, which contains moderate to low amounts of poultry (along with little red meat), is associated with lower risk of some types of cancer [31].

Lung Cancer and Beta-Carotene Supplements

Guidelines for cancer prevention as well as national dietary guidelines in the USA and Canada recommend that individuals meet their nutritional needs through food as much as possible [9, 19, 32]. Fruits, vegetables, and other whole foods contain a combination of nutrients and other substances that are important for health such as fiber, micronutrients, and antioxidants. It is unclear whether the health benefits that may be provided by supplements are comparable to the benefits provided by nutrients in food. Caution is also warranted given evidence that high-dose supplementation of some micronutrients, beyond levels attained in the diet, may be harmful.

Epidemiologic evidence suggests that consumption of fruits and vegetables rich in carotenoids are associated with reduced risk of lung cancer. In contrast, chemoprevention trials unexpectedly found higher lung cancer risk with high-dose beta-carotene supplementation [33, 34]. The Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study was a randomized, double-blind, placebo-controlled trial aimed at reducing the risk of lung cancer and other cancers [34]. Male smokers aged 50–69 years were assigned to supplementation with one of alpha-tocopherol (50 mg/day), beta-carotene (20 mg/day), both substances, or a placebo. No reduction in lung cancer risk was found over the follow-up period for men who received alpha-tocopherol or alpha-tocopherol with beta-carotene. Men who received beta-carotene had an 18% higher risk of lung cancer compared to those who did not, raising the possibility of potential harmful effects. The Beta-Carotene and Retinol Efficacy Trial (CARET) randomized participants with a history of smoking or asbestos exposure to beta-carotene (30 mg/day) and retinyl palmitate (25,000 IU/day) or placebo [35]. The study was stopped prematurely due to observations of a 28% increase in lung cancer, 17% increase in death, and a greater rate of death from cardiovascular disease among participants assigned to beta-carotene and retinyl palmitate supplementation compared to the placebo.

In addition to lung cancer, beta-carotene supplementation may increase the risk of stomach cancer [36]. Findings from a meta-analysis of nine randomized controlled trials reported no apparent benefit from beta-carotene supplementation on pancreatic cancer, colorectal cancer, prostate cancer, breast cancer, melanoma, and non-melanoma skin cancer [36]. The reasons why high-dose

beta-carotene supplementation may increase the risk of cancer in some populations are incompletely understood.

Alcohol

Although modest consumption of alcohol may have protective effects on cardiovascular disease, ethanol has been classified by IARC as a group 1 carcinogen [37]. Strong evidence suggests that any amount of alcohol consumed is associated with increased risk of cancers of the mouth, pharynx, and larynx, esophagus (squamous cell carcinoma), and breast (both premenopausal and postmenopausal) [9]. Colorectal cancer risk is elevated among people who consume two or more alcoholic drinks per day (~30 grams or more), while three or more alcoholic drinks per day (~45 g or more) are associated with increased risk of stomach and liver cancer [9]. There also appears to be a dose-response relationship meaning that the risk of cancer increases as alcohol consumption increases. As such, *any reduction* in alcohol consumption may be beneficial for reducing the risk of cancer.

Alcoholic drinks contain a mixture of carcinogenic compounds. IARC has identified a total of 15 known and suspected human carcinogens in alcoholic drinks including ethanol, acetaldehyde, aflatoxins, and ethyl carbamate. Beer, wine, spirits, and other alcoholic drinks all contain carcinogens, and there is no indication that a given type of alcoholic drink has more or less carcinogens. The main mechanisms through which alcohol increases cancer are thought to be via a genotoxic effect of acetaldehyde, induction of cytochrome P450 2E1, elevated oxidative stress, increased estrogen, altered folate metabolism, and effects on DNA repair and stability [38]. Depending on the cancer site, different biological processes may link alcohol consumption to cancer. For example, acetaldehyde is a metabolite of alcohol that may be causally related to upper digestive tract cancers [37]. Alcohol consumption can increase estrogen levels and stimulate cell proliferation in mammary glands which may contribute to breast cancer [37].

Dietary Patterns

The guidelines for cancer prevention are generally centered on individual components of the diet. However, over the past decades, there has been a move away from the reductionist approach of focusing on specific foods or single nutrients toward a holistic approach which describes the overall diet. Dietary patterns refer to the foods, food groups, and nutrients; their combination and variety; and the frequency and quantity in which they are consumed. This shift recognizes the complexity of diet; foods are not eaten in isolation; nutrients and other diet components are interrelated and may interact with each other to influence cancer risk. Dietary patterns are now included in the latest Dietary Guidelines for Americans (2015–2020) [32] and the WCRF International/AICR Third Expert Report (2018) [8]. This growing field of research holds promise for identifying results that can be more easily incorporated into dietary recommendations for cancer prevention.

The number of epidemiologic studies of dietary patterns and cancer is rapidly expanding. However, at present, evidence on the "best" dietary pattern or patterns for cancer prevention are unclear. Heterogeneity in dietary assessment, and particularly methods to derive dietary patterns, makes it difficult to compare cancer risk across studies and identify the best practice. Despite these limitations, general themes have emerged. Most people have a Western or "unhealthy" dietary pattern characterized by high intake of snacks, sweets, red meat, processed meat, and potatoes. While this is a representation of our collective cultural habits, it also represents a cancer risk. Conversely, a prudent or "healthy" dietary pattern is typically characterized by greater intake of fruits and vegetables, legumes, and poultry and is associated with lower cancer risk.

A meta-analysis of 93 studies reported that high adherence to a healthy diet was associated with reduced risk of colorectal, lung, and breast cancer, particularly postmenopausal, hormone receptor-negative. Conversely, high adherence to an unhealthy diet was associated with increased risk of colorectal cancer [38]. The findings with colorectal cancer and breast cancer were confirmed in other systematic reviews and meta-analyses [39, 40]. Associations with other types of cancers suggest similar relationships—lower risk with a healthy or prudent dietary pattern and increased risk with a Western or unhealthy pattern—but results are not consistent and vary by study design (case control vs. prospective study). Relatively consistent associations have also been found between higher adherence to national dietary guidelines and lower risk of cancer [41].

Conclusion

A large body of evidence has shown that a healthy diet, physical activity, and maintaining a healthy body weight can reduce the risk of many of the most common types of cancer by upward of 30%. The health benefits of this lifestyle strategy extend well beyond cancer: As emphasized in other chapters, research studies have confirmed that following public health recommendations for the prevention of cancer also reduces the risk of cardiovascular disease and all-cause mortality. However, a number of challenges remain. Currently, recommendations are a "one-size-fits-all" approach, despite variations in risk for subgroups of the population (e.g., family history, genetic mutation, sex, and age), and the over 100 types of cancer that differ in etiology. Tailored prevention approaches may be more effective and resonate more with people. Advances in systems biology approaches (e.g., metabolomics, genomics, proteomics, metagenomics, and transcriptomics) may help to characterize how individuals respond to foods and nutrients as well as improving measurement of dietary exposures. But much more research is needed to translate findings into personalized or precision nutrition approaches, especially when interventions are targeted toward a health outcome like cancer. Another key question is how to better engage people to renew confidence in the relationship between diet and cancer. Physicians and healthcare practitioners can play a key role through increasing the awareness of the importance of diet, physical activity, and body weight among patients, providing evidence-based information, identifying those most in need of behavior change, and supporting those changes when possible.

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Suggested Further Readings

An interactive resource for food planning: ChooseMyPlate. U.S. Department of Agriculture. Available at https://choosemyplate.gov.

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Part IV

Dietary Patterns

The Mediterranean Diet: A Healthy Dietary Plan

15

George A. Bray and Catherine M. Champagne

Keywords

Healthy fat · Olive oil · Moderate alcohol intake · Fish and chicken

Key Points

- The Mediterranean diet is a name encompassing foods that are typically eaten in countries surrounding the Mediterranean basin.
- Olive oil is the principal source of fat in this dietary pattern. This dietary pattern also includes generous amounts of nuts and legumes as well as fruits and vegetables. Moderate intake of red wine is characteristic, but not mandatory. Fish is a primary protein source.
- The Mediterranean diet significantly reduces the risk of cardiovascular disease as shown in the PREDIMED Trial (PREvencio'n con DIeta MEDiterra'nea).
- Substituting the Mediterranean diet for Western-diet foods reduces body weight gain.
- Individuals consuming the Mediterranean diet may also have a reduced risk of developing type 2 diabetes mellitus.
- The Mediterranean diet also improved components of the metabolic syndrome.

Introduction

A separate chapter on the Mediterranean diet is included in this edition of *Nutrition Guide for Physicians and Related Healthcare Professionals*, along with chapters on the DASH diet and the vegetarian/flexitarian diet because these were the top-three-rated diets overall in the US News and World Report survey in 2019 and again in 2020 [1, 2].

Prior to the discovery of the "New World" by Christopher Columbus in 1492, European diets were very different than today. Important food components that are native to the Americas included tomatoes, squash, potato, avocado, the common bean, lima beans, and cacao. What an addition to the European diet! Can you imagine Italian food without tomatoes? The introduction of these foods led to a change in the dietary patterns in countries around the Mediterranean basin. But, even with these foods, there is considerable variation between the types of foods that are eaten in the eastern Mediterranean, in Greece,

G. A. Bray (✉) · C. M. Champagne
Pennington Biomedical Research Center, Baton Rouge, LA, USA
e-mail: George.bray@pbrc.edu

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in Italy, in Spain, and in North Africa. Because of the variability in diet by country, there is no single Mediterranean diet, but rather a Mediterranean dietary pattern involving certain foods.

Ancel Keys played a major role in highlighting the importance of a healthy Mediterranean diet [3]. In his famous Seven Countries Study, he noted a lower incidence of heart disease in people living in Southern Europe [4]. In a review in 1995, Dr. Keys stated it this way: "My concern about diet as a public health problem began in the early 1950s in Naples, where we observed very low incidences of coronary heart disease associated with what we later came to call the 'good Mediterranean diet'." The heart of this diet is mainly vegetarian and differs from American and Northern European diets in that it is much lower in meat and dairy products and uses fruit for dessert. These observations led to our subsequent research in the Seven Countries Study, in which we demonstrated that saturated fat is the major dietary villain. Today, the healthy Mediterranean diet is changing, and coronary heart disease is no longer confined to medical textbooks. "Our challenge is to persuade children to tell their parents to eat as Mediterraneans do." [3, 4]. Since these early reports, there have been many papers summarizing aspects of the Mediterranean diet, and a few recent reviews are listed here [5–8].

What Is a Mediterranean Diet?

As noted above, there is considerable variability in what we call the "Mediterranean diet." Having said this, there are a few features that are common to most of them. These diets are generally not restricted in the amount of fat that is eaten, but emphasize healthy fats. In addition, a Mediterranean diet would generally contain two or more specific components. Olive oil is the main cooking oil as well as olive oil used on dressings for salads. There would be generous consumption of nuts and legumes as well as significant intakes of fruits and vegetables. Moderate intake of red wine is also a characteristic of this dietary plan, though not mandatory. Consumption of fish is a primary protein source, and consistent with this, there is limited consumption of red meat. Finally, there is limited consumption of dairy products. Panagiotakis et al. [9] included the following feature in their Mediterranean diet: 30–40% of total calories from fat using olive oil (and other monounsaturated fats such as canola oil). Also included are unrefined cereals and products with the emphasis on whole grain bread, whole grain pasta, and whole wheat. Vegetables at 2–3 servings/day and fruits at 4–6 servings/day were central elements of the diet. Fish as a major source of protein was included at 4–5 servings/week. Nuts at more than four servings/week were a second source of protein. Finally moderate consumption of wine was included in the diet.

The elements of this dietary plan can be used to assess the degree of adherence to the Mediterranean diet. A Mediterranean diet score can be calculated and used in evaluating the effect of this diet on markers of health. There are different ways the Mediterranean diet can be evaluated. This usually involves assigning points to whether a behavior was adhered to or not and sometimes, for example, red meat, when a behavior was avoided. The scores are then summed and a final score is derived. This often has a maximum point value of 9 with tertiles consisting of 0–2, 3–6, and 7–9 for poor, moderate, and good compliance with the diet. However, there are many other variants used to score adherence to a Mediterranean diet.

An example of the Mediterranean diet compared to the Western diet is the emphasis of fruits, vegetables, olive oil, nuts, and wine, being evident in one pattern with the ever-present "burger and fries" as one symbol of the Western diet. The concepts in the Mediterranean diet have also been presented by the Harvard School of Public Health in pyramid form which emphasizes the important foods by giving them larger areas at the bottom of the pyramid and putting at the top those foods that should be consumed less frequently. At the top are red meat and white rice and white bread, white pasta, soda, and desserts on the right. At the bottom are the preferred foods such as plant oils and whole grains along with exercise and weight control.

As noted at the beginning of this chapter, three diets are at the top of the US News and World Reports overall list for 2 years running.

Effects of the Mediterranean Diet on Health Outcomes

In the remainder of this chapter, we will argue the case for using the Mediterranean diet based on its beneficial effects on body weight, diabetes, cardiovascular disease, and the metabolic syndrome. Since many of the important conclusions about the value of this diet have come from a single large study called PREDIMED (PREvencio'n con DIeta MEDiterra'nea), the interventions using in this diet will be described [10, 11]. This was a study from Spain involving 7557 individuals including men age 55–80 and women age 60–80 who were assigned to one of the 3 groups including a control diet group (N = 2450), a Mediterranean diet group supplemented with extra virgin olive oil (EVOO) (N = 2453), or a Mediterranean diet group supplemented with mixed nuts (N = 2454). In this trial, the Mediterranean diet consisted of more than three servings/d of fresh fruits; more than two servings/d of vegetables; more than three servings/week of legumes; more than three servings/week of fatty fish, white meat rather than red meat, wine with meals; and more than seven glasses/week for the extra virgin olive oil; and more than 1 L/week of olive oil and for the group with supplemental nuts, 30 g nuts/d. Items such as soft drinks, commercial bakery goods, spread fats, and processed and red meats were discouraged. The control diet in this study consisted of more than three servings/d of fresh fruits, more than two servings/d of vegetables, more than three servings/d of low-fat dairy products, more than three servings/week of lean fish, and more than ≥3 servings/d of bread/rice/potato/pasta. The following items were discouraged in the group on the Western/control diet: vegetable oils, commercial baked goods, nuts and fried snacks, red and processed meats, fatty fish, spread fats, and visible meat fat.

Body Weight

At baseline, the use of a Mediterranean-type diet was scored in the participants in the PREDIMED trial. Using a 14-point scale to rate adherence to the diet, Martinez-Gonzalez et al. [12] found that those with lower scores of 8 had more central obesity, as expressed as weight/height, compared to the groups with scores above 10. A score of 9 had no change in central obesity.

In the PREDIMED trial, dietary food intake was evaluated every year using a food frequency questionnaire [13]. The 6942 individuals included in this study were followed for a median of 4.8 years. When 5% of energy from saturated fatty acids (SFA) in the diet was replaced by equivalent amounts of monounsaturated fatty acids (MUFA), there was a weight loss of −0.38 kg (95% CI: −0.69, −0.07 kg), and when replaced with polyunsaturated fatty acids (PUFA), there was a larger weight loss of −0.51 kg (95% CI: −0.81, −0.20). Similarly, replacing equivalent amounts of energy from dietary proteins with MUFA or with PUFA decreased the odds of becoming obese. When a serving of red meat was replaced by white meat, oily fish, or white fish, weight losses of 0.64, 0.75, and 0.87 kg were observed, respectively. These data clearly show that increasing the intake of unsaturated fatty acids at the expense of SFA, proteins, and carbohydrates had beneficial effects on body weight and obesity. The effects of several of the substitutions evaluated in this paper are shown in Table 15.1.

Diabetes

A number of studies have examined the relationship of the Mediterranean diet to the risk of developing diabetes or to the improvement in the control of this disease. Several of these trials are summarized in Table 15.2. It is clear that in most of these studies, the Mediterranean diet significantly reduced the risk of developing diabetes mellitus.

Table 15.1 Estimated mean changes in body weight (kg) and 95 confidence interval[a] after substitution of one daily portion of high-fat food items in the Mediterranean diet for healthier options*

Substitution	Mean body weight (kg) difference (95% CI)
White meat for red meat	−0.64 (−0.94, 0.35)*
Oily fish for red meat	−0.75 (−1.13, −0.38)*
White fish for red meat	−0.87 (−1.17, −0.56)*
Olive oil for butter	−0.25 (−0.56, 0.06)
Other vegetable oils for butter	−0.11 (−0.44, 0.22)
Olive oil for margarine	−0.04 (−0.18, 0.25)
Other vegetable oils for margarine	0.26 (0.02, 0.50)*
Walnuts for mixed nuts	−0.15 (−0.61, 0.32)

Adapted from Beulen et al. [13]

[a]Substitutions of a portion of 100, 10, and 30 g for meat/fish, butter/margarine/oils, and nuts, respectively. Adjusted for age, sex, baseline weight, recruitment center, intervention group, cumulative average of total energy intake, BMI, leisure-time physical activity (metabolic equivalent task in min/day), smoking status (never, former, current smoker), educational level (primary education, high school, university), working status (employed, unemployed, housewife, retired), and marital status (single, married). * $p < 0.05$

Table 15.2 Trials on the relationship of the Mediterranean diet and the risk of developing diabetes mellitus

Author/year	Comments
Mozaffarian 2007 [15]	Top quintile had 35% lower risk of diabetes
Martinez-Gonzalez 2008 [16]	2 unit increase in Mediterranean diet score reduced risk of T2D by 35%
De Koning 2011 [17]	Top quintile, 25% reduced risk of diabetes
Romaguera 2011 [18]	High Mediterranean diet score, 12% reduced risk of diabetes
Tobias 2012a [19]	Women top quartile, 24% reduced gestational diabetes mellitus (GDM)
Tobias 2012b [20]	Women with top quartile of Mediterranean diet score has 40% reduced of T2D
Abiemo 2013 [21]	Higher adherence to Mediterranean diet did not reduce risk of diabetes
Rossi 2013 [22]	Top quartile of Mediterranean diet score had 12% reduced risk of T2D

Adapted from Georgoulis et al. [14]

Using a nine-point scale to evaluate adherence to the Mediterranean diet, Martinez-Gonzalez et al. [16] showed that those with a score of 3–6 or 7–9 score which indicates moderate to good adherence to the diet, respectively, had a significantly lower risk of developing diabetes over 2 years than those with poor adherence and a score of <3. In a meta-analysis, Esposito et al. [23] demonstrated that hemoglobin A1c was significantly lower in those using the Mediterranean diet (mean difference − 0.47 (95% CI −0.56 to −0.38)) compared with either a control or low-fat diet. Body weight was also significantly reduced. In the PREDIMED study, there was an interesting relationship between levels of branched chain amino acids and the risk of developing diabetes. At baseline each quartile of increasing concentration of leucine, isoleucine, and valine was associated with a greater risk of diabetes after 1 year [24]. This effect was attenuated in the Mediterranean diet with the extra virgin olive oil (EVOO), but not in the Mediterranean diet supplemented with nuts.

Cardiovascular Effects

As with diabetes, the Mediterranean diet modulated the risk of cardiovascular disease. Most striking was the data from the PREDIMED trial where there was a 28–31% reduction in the composite end point of acute MI, stroke, and cardiovascular death [10]. However, total mortality was not reduced by this treatment. In addition to the effect on acute MI and stroke, there was a significant reduction in the incidence of atrial fibrillation over 4.7 years in the group receiving the Mediterranean diet + EVOO compared to the control group [25]. Supplementing the diet with nuts had no significant effect (Table 15.3).

Several meta-analyses have been done examining the relationship between the Mediterranean diet and cardiovascular disease [26, 31, 32]. In the first of these major adverse cardiovascular events (MACE), coronary events, heart failure, and stroke were all improved with the Mediterranean diet, but CVD mortality and all-cause mortality were not affected. In the second meta-analysis which included 38 cohort studies, CHD incidence, MI incidence, CHD incidence, and CVD mortality were significantly reduced along with stroke incidence and stroke mortality. In the third meta-analysis, all-cause mortality, CVD incidence, and mortality as well as cancer incidence and mortality were reduced, and there was less neurodegenerative disease [32]. Higher plasma concentrations of ceramides, a membrane lipid composed of sphingosine, and a long-chain fatty acid are associated in increased risk of cardiovascular disease. The effect of a Mediterranean diet on ceramides was undertaken in the PREDIMED study. The four principal fatty acids in the ceramides were hexadecanoate (C16:0), docosonoate (C22:0), tetracosanoate (24:0), and nervonate (C24:1). Higher levels of each of these ceramides were associated with a higher level of the composite end point in the PREDIMED study. The hazard ratio for highest vs. lowest quartile of MACE (nonfatal acute myocardial infarction, nonfatal stroke, or cardiovascular death) was HR = 2.39 (1.49–3.83, P trend <0.001) for hexadecanoate, HR = 1.91 (1.21–3.01, P trend = 0.003) for docosonoate, HR = 1.97 (1.21–3.20, P trend = 0.004) for tetracosanoate, and HR = 1.73 (1.09–2.74, P trend = 0.011) for nervonate [33]. For the individuals in the control/Western diet who had higher than the median ceramide levels at baseline, the Mediterranean diet + EVOO significantly reduced the effect of ceramides on major adverse cardiovascular events (MACE). It is interesting to note that for the effect on both atrial fibrillation and the adverse effects of ceramides, the extra virgin olive oil had more impact than the Mediterranean diet with nuts.

The Metabolic Syndrome

The metabolic syndrome is associated with abnormal values in a group of cardiovascular risk factors that includes central obesity, abnormal blood glucose, high triglycerides, low HDL cholesterol, and high blood pressure. The main definition for the cut points are provided by the American Heart Association guidelines and when international criteria are considered by the modifications proposed by Alberti et al. [34].

Table 15.3 Effect of the Mediterranean diet on cardiovascular risk in several studies

Author year	Title	MACE reduced	CVD mortality reduced	All-cause mortality reduced
de Lorgeril 1994 [27]	Lyon Ht study	Yes	Yes	Yes
Singh 2002 [28]	Indo-Mediterranean study	Yes	Yes	Yes
Burr 2003 [29]	The UK	–	No	No
Ng 2011 [30]	Hong Kong > 18 and HIV	–	–	Yes

Adapted from Liyanage et al. [26]

The Mediterranean diet has positive effects on the metabolic syndrome, just as it does on the risk for diabetes and obesity. In a study by Esposito et al. [35], 90 men and women with the metabolic syndrome were enrolled in an intervention group who were on average 44.3 years, and consumed a diet with a profile consistent with the Mediterranean diet. After 2 years, there were a number of statistically significant outcomes including decreased weight and waist circumference, increased HDL cholesterol, decreased triglycerides, decreased systolic and diastolic blood pressure, and improved glucose tolerance and insulin sensitivity, all of which are components of the metabolic syndrome. Pan et al. [36] similarly noted improvements in the components of the metabolic syndrome with the Mediterranean diet. HbA1c and fasting glucose were improved. There was weight loss and improvements in HDL-cholesterol, total cholesterol, and triglycerides.

Finally, using a Mediterranean diet as assessed by a modified Mediterranean diet score divided into quintiles, Steffen et al. [37] observed a graded decrease in the prevalence of the metabolic syndrome over a 25-year period. Thus not only are there acute effects on improving the short-term abnormalities in this syndrome, but there are long-term effects with predictive power out to 25 years.

In conclusion, it seems reasonable to give a high recommendation to the Mediterranean diet as a way to improve healthy living.

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Suggested Further Readings

Benson G, Hayes J. An update on the Mediterranean, vegetarian, and DASH eating patterns in people with type 2 diabetes. Diabetes Spectrum. 2020;33(2):125–32. This paper compares the Mediterranean Diet with two other major dietary patterns

Estruch R, Ros E, Salas-Salvadó J, Covas MI, Corella D, Arós F, Gómez-Gracia E, Ruiz-Gutiérrez V, et al. PREDIMED study investigators. Primary prevention of cardiovascular disease with a Mediterranean diet supplemented with extra-virgin olive oil or nuts. N Engl J Med. 2018;378(25):e34. This paper is the classic one on the reduction in cardiovascular disease and the Mediterranean Diet

Keys A. Mediterranean diet and public health: personal reflections. Am J Clin Nutr. 1995;1(Suppl):1321S–3S. This paper provides insight into the man who was instrumental in initiating interest in this dietary pattern

The DASH Dietary Pattern

16

Pao-Hwa Lin, Crystal Tyson, and Laura P. Svetkey

Keywords

DASH dietary pattern · Diet · Hypertension · Dietary intervention

Key Points

- Strong evidence supports the blood pressure lowering effect of the DASH dietary pattern and its long-term benefit on risk of hypertension, cardiovascular disease, and stroke.
- Observational evidence suggests that the DASH dietary pattern may be beneficial for kidney health and certain cancers.
- Implementation of the DASH dietary pattern is poor in the USA.
- Effective strategies in implementing the DASH dietary pattern are needed at the individual and population levels via avenues including health policy and food environment restructuring.

Introduction

The Dietary Approaches to Stop Hypertension (DASH) dietary pattern was first proven to reduce blood pressure (BP) in 1997 [1]. In the landmark randomized controlled feeding trial involving 412 participants, the DASH diet was shown to reduce both systolic and diastolic blood pressure (SBP/DBP) by 5.5/3.0 mmHg by 2 weeks, and the effect was sustained for the remainder of the 8 weeks of feeding [2]. The BP reduction was greater among participants who were hypertensive at baseline compared to those with pre-hypertension (−11.6/−5.3 mmHg vs. −3.5/−2.1 mmHg, respectively), similar to the magnitude of one BP-lowering medication. This dietary pattern was soon incorporated into the national guideline for BP control (JNC7) [3] and into the Dietary Guideline for Americans since 2005 [4]. The follow-up, large randomized controlled feeding trial (DASH-Sodium) further confirmed the BP effect of the DASH diet by showing that combining the DASH diet with sodium reduction led to BP reduction that was greater than each alone [5]. Many studies, observational and randomized controlled trials (RCT), have shown the benefit of the DASH diet not only on BP but also

P.-H. Lin (✉) · C. Tyson
Duke University Medical Center, Department of Medicine; Division of Nephrology, Durham, NC, USA
e-mail: pao.hwa.lin@dm.duke.edu; cs206@duke.edu

L. P. Svetkey
Duke University Medical School; Department of Medicine; Division of Nephrology, Durham, NC, USA
e-mail: laura.svetkey@duke.edu

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on cardiovascular disease (CVD) risk and risk for other chronic diseases. This chapter summarizes research findings since 2017 on the health benefits of and practical suggestions for implementing the DASH dietary pattern.

Design of the DASH Dietary Pattern

Based on epidemiologic associations between nutrient consumption and BP, the DASH dietary pattern was designed to be rich in fiber, potassium, magnesium, and calcium and compared to the typical American diet to be slightly higher in protein and lower in total fat, saturated fat, and cholesterol intake (Table 16.1) [6]. The resultant dietary pattern was high in fruits, vegetables, whole grains, moderately high in low-fat dairy, and seafood, includes nuts/seeds/legumes, and is reduced in meats, sweets, and sugar-sweetened beverages [7]. Even though the design of the DASH dietary pattern targeted the specific nutrients mentioned above, the totality of the food group pattern may have included other nutrients and/or food factors that also contributed to the BP effect. Previous research has shown that the DASH dietary pattern, being rich in fruits and vegetables, is also rich in antioxidants, and this has been verified with markers of antioxidant activity and oxidative stress [8]. Further, a secondary analysis of the DASH trial showed that there were 44 known serum metabolites that differed significantly between those who consumed the DASH diet as compared to those who consumed the control diet [9]. These metabolites included an amino acid, two pro-vitamin factors, and 44 lipids. These findings suggest that the impact of the DASH dietary pattern may extend beyond the targeted nutrients and beyond BP.

Table 16.1 Comparison of DASH dietary recommendation to the national average intake of American adults

Based on 2100 kcal/day	DASH diet	Average intake of American adults [10–13]
Macronutrients, % of kcal unless otherwise noted		
Carbohydrate	55	47
Total fat	27	36
Saturated fat	6	12
Monounsaturated fat	13	13
Polyunsaturated fat	8	8
Protein	18	16
Cholesterol (mg/day)	150	300
Fiber (g/day)	31	17.3
Micronutrients, mg/day		
Potassium	4700	2633
Magnesium	500	307
Calcium	1240	949
Sodium	3000	3536
Food group, # servings per day unless otherwise noted		
Fruit	4–5	1.8
Vegetable	4–5	3.2
Whole grains	3–4	1
Dairy	2–3	1.5
Meat/seafood	≤6	4.8
Nuts/seeds/legumes	4–5/week	0.81/day
Fats	2–3	12.6
Sweets (use added sugar as an example)	≤5/week	6/day

Effect of DASH on Blood Pressure and Hypertension

The BP lowering effect of the DASH diet has been repeatedly shown in different populations, cultures, and age groups. A significant and inverse association was found between DASH adherence and BP in large cross-sectional studies of Hispanic population [14], Filipino cohort [15], French cohort [16], and of children ages 4 to 18 [17–19]. Large prospective studies using data from the National Health and Nutrition Examination Survey (NHANES) [20] and Jackson Heart Study [21] showed that the higher the adherence to the DASH dietary pattern, the lower the BP, despite overall low adherence. When RCTs tested behavioral interventions designed to help participants follow the DASH dietary pattern, the BP results varied depending on the degree of adherence [22–24]. In the ENCORE trial, the DASH alone arm lowered SBP/DBP by 11.2/7.5 mmHg, while the control arm lowered by 3.4/3.8 mmHg ($p < 0.001$). When DASH intervention was combined with weight loss intervention, the BP reduction was greater (−16.1/9.9 mmHg). In addition, the more participants adhered to the DASH diet, the greater the reduction was in BP, independent of weight loss ($P \leq 0.01$) [25]. The PREMIER study also showed that a greater BP effect may be achieved the more participants adhered to the different components of the behavioral intervention including the DASH diet, weight loss, sodium reduction, alcohol moderation, and physical activity [23]. These findings suggest a potential dose-response relationship between adherence to DASH and the BP effect [26].

The potential dose-response relationship is important particularly in light of the low adherence achieved in many behavioral coaching studies and at the population level according to national surveys (Table 16.1). It is not surprising that when participants are coached to follow the DASH dietary pattern in a behavioral intervention trial, the adherence is not as high as in the original controlled feeding trials where all foods and beverages were provided for the entire study period. In many behavioral trials, participants were coached via group and/or individual sessions for an intensive contact schedule of weekly to monthly over 4–18 months. In the ENCORE trial, participants increased DASH adherence from a median score of 3.5 (full score of 10) at baseline to 6.5 following a 4-month behavioral intervention [25]. In the PREMIER trial, even though adherence to the DASH diet improved at 6 months, the overall adherence score was far from ideal and it relapsed at 18 months [27]. In the HIP behavioral trial which delivered interventions to both the participants and to their providers, the DASH adherence score increased from a mean of 3.41 (full score = 9) at baseline by 0.68 at 6 months and the increase relapsed slightly to 0.27 at 18 months [28]. These studies indicate the challenge in following the DASH dietary pattern fully and for a long term.

At the population level, despite various governmental efforts and efforts from major health organizations including the American Heart Association (AHA), American Dietetic Association (ADA), and the US Department of Agriculture (USDA), in promoting a healthy dietary intake such as DASH, the average dietary intake of American adults remains unsatisfactory and, specifically, adherence to DASH is poor (Table 16.1). Analyses using data from the 1988 to 2004 NHANES showed that less than 1% of the US population was fully adherent to DASH, and only 20% achieved half of the recommended DASH target nutrient levels [29]. In addition, the 2007–2012 NHANES data showed that the average DASH adherence score was 2.6, far from the potential full score of 9 [30]. Thus, it is obvious that effective strategies that help individuals follow the DASH dietary pattern are urgently needed [26].

Implementation of DASH

Many studies have been conducted to test various behavioral theories in helping participants make lifestyle changes for BP control including following the DASH dietary pattern. A 6-month RCT showed that tailoring intervention based on the transtheoretical model significantly increased compliance to the DASH diet among 533 adults with uncontrolled hypertension [31]. A comprehensive

reminder system based on the Health Belief Model also helped hypertensive ischemic stroke patients in improving health behaviors for BP control [32]. The importance of mindfulness and self-regulation in modifying behaviors was demonstrated in a small study that reduced SBP by 6.1 mmHg ($p = 0.008$) at 1 year [33].

Much research has shown the importance of self-monitoring in lifestyle modification; however, self-monitoring is often tedious and challenging to maintain. Technology may be useful in helping individuals overcome some of the challenges. For example, after 4 weeks of using a self-monitoring device for measuring urinary sodium, participants in a RCT were able to effectively reduce sodium/potassium ratio significantly [34]. The device seemed to have motivated the users to avoid high salt intake and is a creative approach in enhancing motivation for behavior change. Development of mobile apps for self-monitoring dietary intake has also been shown to be promising in helping individuals make lifestyle modification and follow the DASH pattern [26]. In a feasibility digital health intervention trial (DASH Cloud), an intervention that used a commercial tracking app with text messaging successfully increased diet quality of the participants. Currently, an ongoing 12-month RCT is testing a mobile app that features self-monitoring and reminders on adherence to the DASH diet and on BP among adults with high BP (NCT03875768).

Additional research is needed to identify the most effective strategy or technology for lifestyle modification and to identify characteristics of individuals who may benefit from particular strategies. Since socioeconomic status and cultural background influence both diet and incidence of hypertension, they should be taken into consideration in designing lifestyle modification strategies [35].

Peer support and technology-enhanced BP monitoring have also been shown to be effective for hypertension control [36, 37]. Including community health volunteers was highly cost-effective against usual care in reducing BP in a 12-month study in Nepal [38]. Even though physicians play a significant role in patients' compliance with lifestyle recommendation [39], clinical recommendations of non-pharmacological strategies for hypertension control were relatively low among 4000 hypertensive adult patients in a NHANES survey [40]. Lack of time and/or skill of the providers in addressing lifestyle modifications, or lack of resources in implementing effective strategies, may contribute to the challenges of implementing DASH.

Besides the need for developing effective strategies to help individuals make healthy dietary choices, the food environment also plays a critical role in shaping healthy eating for BP control. Restructuring food environment may involve reformulating food products provided by food manufacturers and restaurants, either voluntarily or involuntarily as required by policies. Specific strategies can vary, but the successful experience of sodium reduction in the UK may shed light on other areas of dietary modification [41]. From 2006 to 2014, the joint effort of the UK government in setting policy, clear targets for both the publics and the industry, and the compliance of the food manufacturers and retailers to the salt reduction targets led to a reduction of salt intake in the UK by about 11%. Innovative strategies are needed to restructure the food environment so that more adherence toward the DASH pattern may be achieved at the population level. Considerations of ways to improve dietary adherence are further discussed in Chap. 37 by Appleton.

Effect of DASH on the Risk of Other Chronic Diseases and Conditions

DASH and Cardiovascular Diseases

As can be expected from a healthy diet pattern like DASH, numerous observational studies have shown associations of following DASH and reduced risk in cardiovascular disease (CVD) and other chronic diseases and conditions including stroke, chronic kidney disease (CKD), metabolic syndrome, cancer, and mental health. A longitudinal study of 20,239 adults showed that a low adherence to DASH was associated with 11.2% excess risk of incident hypertension in black women [42]. A higher

adherence to DASH was associated with a lower risk for hypertension in both blacks and whites in the CARDIA study [43].

Further, high adherence to DASH was significantly associated with a lower risk of coronary artery disease (CAD) in prospective studies with large populations, including the Million Veteran Program [44], the Singapore Chinese Health Study [45], and the Caerphilly Prospective Study [46]. A meta-analysis showed that each 4-point increase in DASH adherence score (ranged from 8 to 40) was associated with a reduction in risk of CAD by 5% (RR 0.95; 95% CI 0.94–0.97) [47]. Analysis of the data from the ARIC trial also shows that a higher DASH adherence was associated with a lower risk of incident CVD, CVD mortality, and all-cause mortality among 12,413 US adults [48]. Additional strong evidence of the CVD benefit of DASH came from a meta-analysis of 15 unique prospective cohort studies, four systematic reviews, and meta-analyses of 31 unique controlled trials [49]. This analysis shows that greater DASH adherence was associated with lower incident CVD (RR, 0.80, 95% CI 0.76 to 0.85), CHD (0.79, 95% CI 071 to 0.88), stroke (RR 0.81; 95% CI 0.72–0.92), and diabetes (0.82; 95% CI 0.74 to 0.92) in prospective cohorts and lower SBP (−5.2 mmHg; 95% CI −7.0 to −3.4) and DBP (−2.6 mmHg; −3.5 to −1.7) in controlled trials.

Even though RCTs could provide more definitive evidence than observational research, there is very limited RCT data with CVD or other disease outcomes. As such, in the absence of outcome trials, the strong associations of following DASH and benefits in BP and other outcome markers from observational studies and limited RCTs provide strong rationale for recommending DASH to promote general CVD health. In the ENLIGHTEN RCT, the DASH diet intervention lowered CVD risk significantly after 1-year follow-up [50]. Overall, very few studies reported null association between DASH adherence and risk of CVD [51]. Thus, the AHA continues to recommend the DASH dietary pattern for CVD health [52].

DASH and Kidney Diseases

Even though the high potassium and increased protein content of the DASH diet had raised concern previously for its safety among individuals with kidney disease, research findings have suggested otherwise [53]. In a pilot controlled feeding RCT, consuming the DASH diet for 2 weeks did not lead to clinically significant hyperkalemia or progression of CKD among adults with moderate CKD (estimated glomerular filtration rate (eGFR) of 30–59 mL/min/1.73 m^2) and medication-treated hypertension. A meta-analysis of prospective and five cohort studies showed that adherence to the DASH pattern was associated with a lower risk of kidney disease [54]. In addition, three systematic reviews and meta-analyses have shown that adherence to DASH was actually associated with a significantly lower risk for developing CKD [55–57]. Adherence to DASH is associated with a lower risk of rapid decline in estimated eGFR ($p = 0.04$) [55]. Further, a greater risk of end-stage renal disease was found among individuals who had poor adherence to DASH as compared to those with high adherence [58]. Altogether, these findings suggest that DASH dietary pattern may be safe for CKD and may even be helpful in promoting kidney health.

DASH and Cancer

Although the DASH dietary pattern was not initially designed for the prevention or treatment of cancer, research has shown its potential benefit. The large prospective Sister Study of 50,884 US women showed that a high DASH adherence score was associated with a lower risk of breast cancer (HR 0.78; 95% CI 0.67–0.90, p-trend = 0.001) [59]. In an Iranian study with 50,045 adults followed for 10.64 years, a higher DASH score was associated with a lower risk of gastrointestinal cancer mortality in men (HR 0.55, 95% CI 0.30–0.99) and other cancer mortality in women (HR 0.50; 95% CI

0.24–0.99) [60]. Two meta-analyses also showed that high adherence to DASH was associated with decreased cancer mortality [61, 62]. In addition, a prospective study showed a strong dose-response association between increasing DASH adherence and decreasing risk of colorectal cancer (CRC) [63]. However, another analysis of two prospective studies found no association between adherence to the DASH pattern and risk of CRC [64]. Even though the exact mechanism underlying such a potential association is unclear, the high antioxidant content of DASH may play a role. This speculation is supported by previous studies. For example, a case control study showed that the dietary antioxidant capacity is significantly and inversely associated with risk of CRC [65]. Another population-based case control study also showed that low dietary antioxidant values were significantly associated with risk of CRC [66]. Further research is needed to clarify the role of DASH in cancer.

DASH, Cognitive Function, and Mental Health

A growing body of research shows that a healthy diet, such as DASH, may play a beneficial role in cognitive function and mental health. In two large prospective studies (N = 16,144 women ≥70 years old, N = 16,948 adults 45–74 years old), a greater adherence to the DASH diet was significantly associated with a better cognitive function [67] and a lower risk of cognitive impairment [68]. In addition, two large cross-sectional studies (N = 23,062 adults, N = 580 teenage girls) and one prospective study (N = 4,949 adults) showed that a greater adherence to DASH was significantly associated with a lower incidence or odds of depressive symptoms or recurrent depression [69–71]. Similarly, a cross-sectional study of 240 university students showed that a greater DASH adherence was associated with a better mental health, lower depression, anxiety, and stress [72]. Though not measuring DASH adherence specifically, a longitudinal study found that low fruit and vegetable intake (<1 portion/day) was a significant correlate of poor mental health across adolescence [73]. Taken altogether, this evidence suggests that a healthy eating pattern, like DASH, may benefit cognitive function and mental health; however, more definitive future research is needed.

Practical Tips

Clinicians play a critical role in the care of patients' health and in promoting healthy lifestyles including adopting healthy eating habits such as the DASH dietary pattern [22]. Even though time, training, and resources may be limited, simple and persistent effort can potentially produce meaningful impact. The evidence-based 5 A's approach (Ask, Advise, Assess, Assist, and Arrange) [74] can be useful to assist patients in following the DASH dietary pattern (Fig. 16.1).

Clinicians may use the tool in Table 16.2 and follow this approach to (1) ask the patient to recall his/her own eating pattern, (2) advise the patient what DASH is, then to (3) assess the patient's readiness to change his/her eating pattern, (4) assist the patient in identifying a goal toward better DASH adherence and setting an action plan, and lastly (5) arrange a follow-up visit to provide accountability. Repeating this process has the potential to shift patient's eating habits toward his/her goal.

The following lists a few additional tips:

- Utilize and share resources about the DASH diet with patients, e.g., pamphlets from the US government websites: https://www.nhlbi.nih.gov/files/docs/public/heart/dash_brief.pdf [75] https://www.nhlbi.nih.gov/health-topics/dash-eating-plan [76].
- Recommend salt substitute in exchange for regular salt. Various brands of salt substitutes are commercially available. Research has shown the effectiveness of using salt substitute in reducing salt intake and thus lowering BP at the population level [77].

Fig. 16.1 Using the five A's approach in assisting patients to follow the DASH dietary pattern

- Utilize more referral to dietitians for personalized behavioral intervention – Find local dietitians in the Academy of Nutrition and Dietetics website: https://www.eatright.org/find-an-expert [78].
- Utilize more referrals to affordable structured programs such as the diabetes prevention program offered in YMCA centers across the USA (https://www.ymca.net/diabetes-prevention) [79].
- Integrate digital tools into treatment recommendations, especially for self-monitoring of dietary intakes (e.g., MyFitnessPal) [80].
- Model healthy eating behavior – e.g., if your healthcare setting provides snacks, put healthy snacks out. Hang pictures of healthy foods and show healthy eating and lifestyle videos in waiting area.

Modeling healthy lifestyles within the healthcare setting is an important aspect of helping patients to adopt healthy lifestyles. How the clinicians convey the message of healthy eating with their patients can usually reveal to the patients how important the clinicians think of the message him/herself. Clinicians who make healthy eating a top priority topic at every visit and who persistently arrange for follow-up visits to keep patients accountable are likely to be successful at helping patients adopt the healthy behavior.

Conclusion

The DASH diet is a well-studied dietary pattern with a clear definition of its content and design. Numerous studies have demonstrated its benefit in not only BP and hypertension control, but also shown the associations with reduced risk for CVD, stroke, CKD, and cancer. This dietary pattern may also be beneficial for cognitive function and mental health; however, research in these areas is less well established. Even though major health agencies in the USA and other countries have endorsed this dietary pattern for over 20 years, implementation remains a huge challenge and needs to be addressed from various angles including government policies, reformulation of products by food manufacturers, and individual or group coaching. Research in confirming the dose-response association may be helpful in modifying implementation strategies so that more practical and achievable goals may be achieved. In addition, more effective strategies that incorporate tailored behavioral theories and technologies are urgently needed. Public policies that include and reenforce goals for the food

Table 16.2 Step-by-step guide in following the DASH dietary pattern

Food groups (serving sizes)	Vegetables (1/2 cup cooked, 1 cup raw leafy greens)	Fruit (1/2 cup, 1 medium-sized fruit)	Dairy (1 cup milk/ yogurt, 1 oz. cheese)	Whole grains (1/2 cup cooked, 1 slice bread)	Meat/ seafood (3 oz. cooked)	Nuts/seeds/ legumes (1/4 cup nuts/seeds, ½ cup legumes)	Sweets (1 serving of dessert, 8 oz. sweet drink)	Example fruit
1. How many servings of each of the food groups on the right do you usually eat in a day? Enter values, and then circle one(s) that are different from the values listed in the next row								0.5
2. Recommended servings according to the DASH dietary pattern for someone consuming about 2000 kcal/day	4–5 per day	4–5 per day	2–3 per day	3–4 per day	2 or fewer per day	4–5 per week	5 or fewer per week	4–5 per day
3. Among that one(s) your circled, which food group(s) would you likely work on in the next month? Check all that apply								✓ .
4. What specific goal would you set for the food groups you checked in #3								Increase 1 per day
5. Write down actions that will help you achieve your goal								Go shopping for fruit on Tuesday
My next visit date/time:								

industry to produce healthier products (e.g., with less salt in all processed foods and more vegetables in frozen meals) than the currently available products are critical to improve diet quality at the population level.

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The Vegetarian/Flexitarian Diets

17

Derek Miketinas and Catherine M. Champagne

Keywords

Vegetarian · Flexitarian · Vegan · Mediterranean diet · DASH diet · Health benefits · Nutrient deficiencies · Drug-nutrient interactions

Key Points

- Vegetarian diets are gaining popularity in the United States, although only a small fraction of the adult population follows some version of a vegetarian diet.
- Plant-based diets are heterogeneous in practice; it is important to assess each patient's diet to educate effectively.
- Well-planned vegetarian and flexitarian diets can be healthy and reduce risk for many chronic diseases.
- Unstructured vegetarian diets can be deficient in some nutrients like protein, omega-3 fatty acids, calcium, iron, zinc, vitamin B12, and vitamin D.

Introduction

Although vegetarian diets are among the most popular Internet searches globally, their practice within the United States remains low [1, 2]. People follow vegetarian diets for many reasons including ethical considerations, perceived health benefits, religious observance, and taste preferences. The Academy of Nutrition and Dietetics' position on vegetarian diets is that they are "healthful, nutritionally adequate, and may provide health benefits for the prevention and treatment of certain diseases" [3]. Nevertheless, these dietary patterns have implications for assessment, treatment, and counseling. This chapter will review vegetarian diets, their impact on human health, and clinical considerations.

D. Miketinas (✉)
Texas Woman's University, Department of Nutrition and Food Sciences, Houston, TX, USA
e-mail: dmiketinas@twu.edu

C. M. Champagne
Pennington Biomedical Research Center, Baton Rouge, LA, USA

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Classifications and Overview

Vegetarian diets can be classified into several distinct categories that vary in the degree to which animal protein is restricted: flexitarian, lacto-ovo vegetarian, pescatarian, and vegan. Each person might consider their vegetarian dietary pattern different from its classification within the literature. Therefore, it is important for the clinician to assess each patient's dietary patterns instead of relying solely on self-identified classifications. As with any diet, the goal is to emphasize consuming a wide variety of foods and food groups to ensure adequate nutrient intake.

Flexitarian Diet

Flexitarian diets generally allow only for intermittent consumption of red meat and poultry. The US News and World Reports listed the flexitarian diet as second best overall diet tied with the DASH Diet [4]. The flexitarian diet ranked third in healthy eating and fourth in weight-loss diets (tie). Flexitarian diets ranked sixth for best heart-healthy diets. The flexitarian diet is generally flexible and easy to follow and offers many individualized meal plans. There are various benefits associated with the vegetarian diet; by including some meat (though significantly less than other eating plans), it may be able to improve overall health and lower chronic disease risk.

Pescatarian Diet

Pescatarians exclude red meat and poultry but include seafood, fish, and other animal products like dairy and eggs. This dietary pattern is rich in animal sources of vitamin B12, calcium, vitamin D, and long-chain omega-3 fatty acids. Women who are pregnant or who may become pregnant should avoid larger fish with higher mercury levels like flounder, ahi tuna, swordfish, and sharks.

Lacto-Ovo Vegetarian Diet

The lacto-ovo vegetarian diet excludes red meat, seafood, and poultry but includes eggs, dairy, and other animal products. Those who follow this dietary pattern may overly rely on dairy consumption which could lead to excessive saturated fatty acid (SFA) intake and elevated calcium intake (which could affect iron absorption or interact with some medications) and may displace other important food groups.

Vegan Diet

Strict vegan diets abstain from all animal products including, but not limited to, red meat, poultry, seafood, dairy, eggs, gelatin, amino acids, and fatty acids derived from animals (e.g., omega-3 fatty acids from fish). Meeting nutritional needs can be difficult given the restrictive nature of this diet. Nutrients of concern include protein, iron, zinc, long-chain omega-3 fatty acids (DHA and EPA), calcium, vitamin B12, and vitamin D.

Other Vegetarian Diets

The previous edition of this book mentioned the following diets: raw food, fruitarian, and macrobiotic. We agree with the previous authors that these diets are extremely restrictive, potentially dangerous, and without scientific merit. Adherence to these diets should be discouraged.

Health Benefits of Vegetarian Diets

The Academy of Nutrition and Dietetics' Nutrition Care Manual considers vegetarian diets as preventative or therapeutic for the following diseases: cardiovascular disease (CVD), hyperlipidemia, ischemic heart disease (IHD), hypertension, overweight and obesity, cancer, and type 2 diabetes [5].

Cardiovascular Disease (CVD)

Epidemiological studies report lower CVD risk among vegetarians compared to non-vegetarians. Vegetarians tend to have lower relative risks for CVD-related death, IHD, and cerebrovascular disease compared to non-vegetarians [6]. These findings are likely due to observed improvements in lipid profiles, blood pressure, and weight.

The tendency for observational studies to group non-vegetarian dietary patterns into a single category can be misleading, especially since the DASH and Mediterranean diets are non-vegetarian dietary patterns that have clinical evidence to support their efficacy for reducing CVD risk factors. Results from the CARDIVEG study showed comparable improvements in BMI and fat mass between calorie-restricted vegetarian and Mediterranean diets [7]. Interestingly, the Mediterranean diet resulted in greater reductions in triacylglycerols (TAG), while the vegetarian diet resulted in greater decreases in LDL-c and serum B12; however, the vegetarian group's serum B12 was still within normal limits.

Obesity

Those who follow vegetarian, flexitarian, and vegan diets tend to have lower BMI, adiposity, and energy intake [8]. Vegetarian diets promote dietary habits conducive to weight loss like consumption of high-fiber vegetables and grains and restriction of potentially energy-dense animal products. Although weight loss may not be a goal for every patient, weight maintenance can reduce patients' risk for other chronic diseases.

Cancer

Processed meat consumption has been associated with small increases in the risk for colorectal, breast, and bladder cancers. However, the relative risk estimates are modest, inconsistent, and likely confounded by other lifestyle characteristics. Furthermore, meta-analyses have reported inconsistent associations between increased processed and red meat intake and colorectal cancer type (distal, proximal, and rectal). Those with greater red meat intake also reported greater BMI, alcohol consumption, saturated fat, and total fat intake while reporting lesser physical activity, fiber intake, and diet quality [9]. Improvements in lifestyle factors and diet quality may be driving the potential reduction in cancer risk observed in vegetarians; similar benefits have also been reported in those who adhere to the Mediterranean diet.

Randomized trials have not explored the use of therapeutic vegetarian diets to reduce mortality risk for cancer patients. Mixed results have been reported for the association between red meat consumption and cancer mortality. A recent meta-analysis of observational studies reported that total meat intake was associated with increased cancer mortality (RR = 1.12 per 100 g serving), but unprocessed red meat and processed meat consumption were not [10].

Type 2 Diabetes

Observational studies consistently report vegetarians have a lower risk for diabetes compared to non-vegetarians [11]; this is also observed to a lesser extent in flexitarians and lacto-ovo vegetarians. This risk reduction may be partly mediated by improvements in body weight.

The vegetarian diet is comparable to the Mediterranean and low-carbohydrate diets for reducing fasting glucose and HbA1c in patients with type 2 diabetes [12]. Following a vegetarian diet also

results in improvements in insulin sensitivity and body weight reduction [13]. Patients with diabetes who follow a vegetarian diet may improve their LDL-c status, thereby lowering their CVD risk.

Bone Health

Bone mineral density (BMD) of the lumbar spine and femoral neck tends to be lower in vegetarians compared to non-vegetarians; however, the differences appear to be clinically insignificant [14]. In studies that identified increased fracture risk among vegetarians and vegans, calcium intake better explained the association rather than the vegetarian diet status [15]. Risk for low BMD, osteoporosis, and fractures can be decreased with adequate intake of calcium, vitamin D, protein, and vitamin B12.

Health Benefits of Flexitarian Diets

In a recent review, Derbyshire [16] reported that there is a movement toward a semi-vegetarian diet that includes occasional meat consumption. That review included 25 studies with focuses on body weight, cancer, diabetes and metabolic health, diet quality, or other health outcomes. The potential health benefits associated with flexitarian/semi-vegetarian diets were weight loss, metabolic health, reduced risk for diabetes, lower blood pressure, and improved irritable bowel disease symptoms. Limiting or excluding meat tends to reduce calorie intake which may motivate those who seek weight loss or management.

Although there are many positive benefits of plant-based diets, the addition of animal products is a key component to acquiring high-quality protein, fatty acids, and other nutrients, such as bioavailable iron, zinc, and vitamin B12 in significant quantities relative to the proportion of energy. Draper et al. [17] studied the effects of vegan and animal meal composition on glucose and lipid responses and timing of meals. Glycemic and lipid parameters varied regardless of diet type, and both dietary patterns contained health-promoting and suboptimal nutrient combinations. The flexitarian diet is a healthy approach to meet nutritional needs while reducing overall meat consumption.

Nutrients in Vegetarian Diets

Protein

A common dietary concern for vegetarians is inadequate protein intake. On average, protein intake is typically lower among vegans (0.91 g/kg) and vegetarians (0.95 g/kg) compared to pescatarians (1.06 g/kg) and omnivores (1.14 g/kg). Although vegetarians' and vegans' average protein intakes are within the recommended range, the odds for inadequate protein intake for vegetarians are 4.2 and 5.3 times greater than meat eaters (males and females, respectively) [8]. For vegans, the odds are 7.7 and 7.3 times greater than meat eaters (males and females, respectively).

Plant-based protein sources contain indispensable amino acids necessary for human growth and function, albeit in lower amounts than animal protein sources. For example, legumes tend to have limited methionine content while having adequate lysine content; grains tend to have relatively low amounts of lysine (and threonine). These food groups are complementary proteins since, together, they provide a complete amino acid profile. Current recommendations state that complementary proteins do not need to be eaten together at a meal; however, emerging evidence indicates consuming complementary proteins together may increase methionine absorption and bioavailability [18].

The Institute of Medicine does not recommend separate protein requirements for vegetarians provided they consume a variety of plant proteins. Plant-based, protein-rich foods include legumes (e.g., soy, beans, lentils, peas), nuts (almond, cashew, peanuts), and seeds (sunflower, pumpkin, flax). Some plant-based food products may contain nutrients to reduce like sodium and saturated fatty acids; therefore, it is important to educate patients to choose healthier alternatives.

Carbohydrates and Fiber

The target range for total carbohydrate intake is 45–65% of energy from carbohydrates, although humans can eat considerably less without significant concerns. Exclusion of some carbohydrate-rich foods (such as whole grains, enriched cereals, and starchy vegetables or fruit) can lead to inadequate intakes of some vitamins, minerals, and fiber. Vegetarians and vegans tend to report a slightly greater carbohydrate intake compared to meat eaters; therefore, nutrient-dense carbohydrate sources, like those high in fiber, should be encouraged.

The current recommendation for dietary fiber is 14 g/1000 kcal per day; this is approximately 21–25 g/d for non-pregnant women and 30–38 g/d for men. This is based on the amount of dietary fiber intake associated with a reduced risk for CVD. Dietary fiber has a myriad of health benefits beyond a reduction in CVD risk and should be emphasized in any diet. Adequate dietary fiber intake promotes satiety and normal GI function [19]. Moreover, dietary fiber intake has been associated with dietary adherence, weight loss [20], reduced risk for some cancers [21], and reduced risk for hypertension [22].

Fat

Current recommendations for total fat consumption is 20–35% of energy from total fat, between 11 and 17 g/d of linoleic acid (omega-6), between 1.1 and 1.6 g/d of alpha-linolenic acid (omega-3), and less than 10% of energy from saturated fatty acids. Total dietary fat intake is comparable across meat eaters, fish eaters, vegetarians, and vegans; however, the fatty-acid profiles vary significantly for vegans [8]. Whereas vegetarians have similar saturated fatty acid and poly-unsaturated fatty acid intake to meat and fish eaters, vegans have lower intakes of these nutrients.

Saturated Fatty Acids

Saturated fatty acids contain no double bonds on their carbon chain. Current recommendations limit overall consumption of SFA as overconsumption is associated with an increased risk for chronic diseases. In contrast, emerging research suggests even-chain SFAs are positively associated with chronic disease risk, while serum levels of odd- and long-chain SFAs are inversely associated with chronic disease risk [23, 24].

Coconut and palm kernel oils contain almost entirely SFA, contributing approximately 82 g SFA per 100 g of oil. All of the SFA from these oils are even-chain SFA. Two tablespoons of either coconut or palm kernel oil exceeds the SFA recommendation for a person adhering to a 2000 kcal diet. Although these fats may have gained momentum as a "health food" in popular culture, their consumption should be limited to meet the recommendations.

Omega-3 Fatty Acids

Omega-3 fatty acids are polyunsaturated fatty acids; they include alpha-linolenic acid (ALA) and the elongated versions of ALA: docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). Humans

must consume ALA since it cannot be synthesized endogenously. Although humans contain the necessary enzymes to elongate ALA to DHA and EPA, this activity is limited and further suppressed by high linoleic intake (omega-6). While recommendations for DHA and EPA intake vary by professional organizations, the Dietary Guidelines for Americans recommend 250 mg/d, or 8 oz. per week of seafood. This is based on the observed decreased risk for cardiac deaths in those without preexisting CVD. Adequate omega-3 intake is also important for brain development in infants and children, organ function, cellular membrane integrity and function, and hormone production. Omega-3 intake can also improve serum lipid parameters, suppress inflammatory responses, and lower blood pressure.

Alpha-linolenic acid intake is similar among vegans, vegetarians, and non-vegetarians. Vegetarian intake of EPA and DHA varies according to the inclusion of supplements and seafood intake, whereas EPA and DHA intake is virtually non-existent in vegans unless they take supplements. Although vegans and some vegetarians may have low EPA and DHA intake, there appear to be no associated health consequences.

Calcium

Calcium intake for lacto-ovo vegetarians tends to meet or exceed recommendations, while those who follow vegan diets tend to have an increased risk for inadequate calcium intake [3, 8]. Compared to vegetarians, vegan men and women have 6.7 and 5.6 greater odds for inadequate calcium intake, respectively [8]. Oxalic and phytic acids bind to calcium and inhibit absorption; foods high in these calcium chelators include spinach, greens, beans, and sweet potatoes. Therefore, it is important for vegetarians to consume calcium-rich foods (Tables 17.1 and 17.2) and avoid co-consuming foods high in chelating agents. Vitamin D status can also influence calcium absorption.

Calcium malabsorption can be caused by prednisone (and other glucocorticoids), cyclosporine, antibiotics, and sulfonamides, to name a few [25]. Antiepileptics and lipase inhibitors (e.g., Orlistat) can impair vitamin D absorption, leading to secondary calcium deficiency. Calcium excretion can be upregulated by loop diuretics, corticosteroids, albuterol, antacids (containing aluminum), and others.

Vitamin D

Vitamin D is a fat-soluble vitamin that is important for calcium absorption in the small intestine, maintaining serum calcium and phosphorous concentrations, and for bone growth and remodeling. People can meet their vitamin D requirements with adequate sunlight exposure. Dietary sources of naturally occurring vitamin D are limited; rather, people must rely on fortified foods and dietary supplements if adequate sun exposure is unachievable. Factors that may impede adequate sunlight exposure include season, skin melanin content, sunscreen, length of day, and other environmental factors (e.g., urban environments, air pollution, and cloud cover). Latitude is an unreliable predictor of serum vitamin D levels.

Inadequate vitamin D intake does not appear to differ between vegetarians and non-vegetarians. However, the following groups appear to have increased risk for vitamin D deficiency: older adults, people who have certain medical conditions or are taking medications that inhibit fat absorption, people with obesity, and people who have had bariatric surgery. Although sun exposure is important for synthesis, sunlight exposure should be controlled to reduce risk for melanoma.

Table 17.1 Vegan sources of important nutrients

Nutrient	Vegan sources	Amounts per serving	Notes
Omega-3 fatty acids	Chia seeds	5.06 g (ALA)	Supplementation may be required. ALA is not efficiently converted to DHA and EPA in humans
	English walnuts	2.57 g (ALA)	
	Flaxseed	2.35 g (ALA)	
	Canola oil	1.28 g (ALA)	
	Soybean oil	0.92 (ALA)	
Calcium	Orange juice, calcium fortified	349 mg	Oxalate, phytate, low vitamin D intake, and drugs can reduce bioavailability and absorption
	Soy milk, fortified	299 mg	
	Tofu, made with calcium sulfate	253 mg	
	Breakfast cereals	130 mg	
	Greens, cooked (kale and turnip)	47–99 mg	
Iron	Breakfast cereals, fortified	18 mg	Non-heme iron absorption can be increased by vitamin c, retinol, carotenoids, and citric acid
	White beans	8 mg	
	Lentils	3 mg	
	Spinach	3 mg	
	Potato, baked	2 mg	
Zinc	Baked beans	2.9 mg	Phytic acid reduces zinc bioavailability. Zinc supplementation can impair tetracycline, penicillamine, and copper absorption
	Breakfast cereal, fortified	2.8 mg	
	Pumpkin seeds	2.2 mg	
	Cashews	1.6 mg	
	Chickpeas	1.3 mg	
Vitamin B12	Nutritional yeast, fortified	2.4 μg	Supplementation may be required. Aminoglycosides, antivirals, aspirin, ethanol, H2 blockers, metformin, oral contraceptives, and tetracyclines can increase risk of B12 deficiency
	Breakfast cereals, fortified	0.6 μg	
Vitamin D	Mushrooms, UV exposed	366 IU	Supplementation may be required. Risk for deficiency increases in older adults, bariatric surgery patients, people with obesity, and medications that inhibit fat absorption
	Soy milk, fortified	100–144 IU	
	Breakfast cereal, fortified	80 IU	
	Portobello mushroom	4 IU	

Omega-3 fatty acid recommendations include alpha-linolenic acid (ALA), docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA)

Iron

Iron deficiency can result from poor intake as well as poor absorption. Iron absorption is affected by amount consumed, the source of iron, and iron status. The two main forms of dietary iron include heme, which is easily absorbed and can be found in animal products, and non-heme, which is less bioavailable and can be found in plants and iron-fortified foods. The goal for vegetarian and vegan patients should be to promote consumption of iron-rich sources (Tables 17.1 and 17.2) while co-consuming foods or beverages that have nutrients that enhance iron absorption: vitamin c, retinol, carotenoids, fructose, stearic acid, and citric acid. Phytic acid is the major phosphorous storage form in plants, representing 50–85% of total phosphorus; 250 mg of phytic acid can impair iron absorption by 80% [26].

Table 17.2 Vegetarian sources of important nutrients

Nutrient	Vegetarian sources	Amounts per serving
n-3 fatty acids	Chia seeds	5.06 g (ALA)
	English walnuts	2.57 g (ALA)
	Flaxseed	2.35 g (ALA)
	Salmon	1.24 g (DHA); 0.35–0.59 g (EPA)
	Canola oil	1.28 g (ALA)
Calcium	Yogurt, plain	415 mg
	Orange juice, calcium fortified	349 mg
	Mozzarella	333 mg
	Sardines, with bones	325 mg
	Soy milk, fortified	299 mg
Iron	Breakfast cereals, fortified	18 mg
	Oysters	8 mg
	White beans	8 mg
	Lentils	3 mg
	Spinach	3 mg
	Tofu	3 mg
Zinc	Oysters	74 mg
	Crab, Alaska King	6.5 mg
	Baked beans	2.9 mg
	Breakfast cereal, fortified	2.8 mg
	Pumpkin seeds	2.2 mg
Vitamin B12	Clams	84.1 μg
	Fish (tuna, trout, salmon)	2.5–5.4
	Nutritional yeast, fortified	2.4 μg
	Milk	1.2 μg
	Yogurt	1.1 μg
	Breakfast cereals, fortified	0.6 μg
Vitamin D	Cod liver oil	1360 IU
	Fish (salmon and trout)	570–645 IU
	Mushrooms, UV exposed	366 IU
	Milk, fortified	120 IU
	Soy milk, fortified	100–144 IU

Omega-3 fatty acid recommendations include alpha-linolenic acid (ALA), docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA)

Iron supplementation may be necessary to achieve adequate intake; however, certain drugs and nutrients can inhibit iron absorption. Antacids (containing magnesium hydroxide), cholestyramine, H2 blockers, tetracycline, neomycin, penicillamine, haloperidol, calcium, and zinc can decrease iron absorption [25]. Aspirin, NSAIDs, haloperidol, deferoxamine, and stanozolol can increase the risk for iron store depletion. Normal serum iron ranges between 80 and 150 μg/dL (12–24 μmol/L) and should be monitored in patients at risk for deficiency.

Zinc

Animal products contain highly bioavailable zinc. Therefore, reliance on plant sources can lead to increased risk for inadequate intake. Moreover, plant sources of zinc also tend to be high in phytic and oxalic acids, which bind to zinc and inhibit its absorption. The requirements for vegetarians can exceed the RDA by as much as 50%. Compared to pescatarians, vegetarians have over 12 times greater odds for inadequate zinc intake [8]. Strategies to increase zinc bioavailability include

leavening bread and soaking/sprouting beans, grains, and seeds to reduce their phytic acid content at the time of ingestion.

Although bioavailability and intake may be low among vegetarians and vegans, serum zinc levels tend to stay within a normal range (60–130 μg/dL). Only in instances of malnutrition, infection, burns, and liver disease are serum zinc levels likely to fall below the target range. Drug interactions with zinc supplementation also need to be considered.

Zinc supplementation inhibits tetracycline and penicillamine absorption [25]. ACE inhibitors can decrease zinc absorption, while N-acetyl cysteine can increase zinc excretion in the urine. Copper absorption can be inhibited by zinc, leading to secondary copper deficiency; therefore, a zinc supplement should also include copper. Long-term zinc supplementation above the Tolerable Upper Limit (40 mg/d) could also lead to iron deficiency, impaired iron function, altered kidney function, and impaired immune function. High doses for medical treatment (short term) require monitoring; symptoms of toxicity include nausea/vomiting, diarrhea, dizziness, atherosclerosis, and renal failure.

Vitamin B12

Vitamin B12 (cobalamin) intake is especially important for neurological function, erythropoiesis, DNA synthesis, and prevention of neural tube defects. Meat and fish eaters are not at risk for inadequate B12 intake. Vegetarians have slightly greater odds for inadequate vitamin B12 intake compared to non-vegetarians; however, the odds for inadequate B12 intake among men and women who follow vegan diets are 27 and 38 times greater than a vegetarians' odds [8]. Although the frequency of inadequate intake is great for vegans, clinical manifestations of deficiency may not be present. Vegetarians and vegans should be encouraged to consume foods fortified with vitamin B12 like cereals, yeast, and soy milk or to receive supplemental vitamin B12 to mitigate the risk of inadequacy.

Drugs that increase the risk for B12 deficiency include (but are not limited to) aminoglycosides, antivirals, aspirin, ethanol, H2 blockers, metformin, some oral contraceptives, and tetracyclines [25]. Symptoms of B12 deficiency in adults include megaloblastic or macrocytic anemia, fatigue, poor cognition, tingling in the fingers, depression, macular degeneration, and hearing loss [3]. Tests for B12 status include serum B12, holotranscobalamin (HoloTC), homocysteine, methylmalonic acid, and 4cB12.

Summary

Vegetarian diets are increasingly popular in developed countries due, in part, to specific health claims. Although vegetarian diets have been associated with a reduced risk for chronic diseases, omitting meat is neither necessary nor sufficient for health promotion and disease prevention. The DASH diet and Mediterranean diet are as effective as vegetarian diets for overall health promotion and disease prevention. The flexitarian diet is gaining in popularity and offers benefits associated with limited meat or poultry consumption. Carefully planned vegetarian diets are safe and nutritionally adequate; however, proper implementation of any diet requires patient education, monitoring, and evaluation to meet nutritional goals.

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The Vegetarian Resource Group (VRG). For evidence-based information, polls, recipes, and handouts. www.vrg.org

Where Do Carbohydrate-Restricted (Ketogenic) Diets Fit In?

18

Blair J. O'Neill and Paolo Raggi

Keywords

Ketogenic diet · Carbohydrate restriction · Atkins diet · Obesity · Type 2 diabetes · Mediterranean diet · Cardiovascular risk factors

Key Points

- Most nutritional recommendations need more rigorous scientific evidence.
- The Mediterranean diet, although variably defined, is the only diet with proven effectiveness at reducing CHD events, but these results have mainly been reported in metabolically healthy people (see Chap. 15).
- Carbohydrate-restricted (Atkins/ketogenic) diets which liberalize fat intake have a limited amount of long-term CHD outcome data.
- Ketogenic diets consistently tend to have better weight loss than calorie-restricted low-fat diets.
- Weight loss and specifically ketogenic diets have been shown to improve control of type 2 diabetes.

Introduction

The European ancestral diet, probably followed until the late 1960s and early 1970s, consisted of about 40% fats, half of which were saturated animal fats, 35 to 40% carbohydrates, and the remainder proteins. Dr. Ancel Keys, the most influential nutrition scientist in modern history, was an effective proponent of the so-called diet heart hypothesis, the idea that fat in the diet leads to elevated cholesterol and a greater likelihood of coronary heart disease [1]. Yet, the diet heart hypothesis remains in search of evidence-based validation. There was no evidence from randomized control trials to support the concept that fat is harmful at the time of the introduction of food guidelines in the late 1970s and early 1980s, nor has any more evidence that saturated fats are harmful accumulated since [2, 3]. There is universal agreement that trans fats are detrimental to health, and these have been phased out of foods as a consequence [4]. Nevertheless, the hypothesis that fats, particularly saturated fats, favor the development of atherosclerosis is fixated in the psyche of most modern clinicians and most of our population.

B. J. O'Neill (✉) · P. Raggi
Mazankowski Alberta Heart Institute, Department of Medicine, Division of Cardiology, University of Alberta, Edmonton, AB, Canada
e-mail: oneill2@ualberta.ca

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Americans have been following the low-fat recommendations since the 1980s, and as a result they increased the consumption of carbohydrates and the population gained more weight than ever before [5]. Other studies show that as carbohydrate intake increases, obesity also increases. Conversely, increased fat intake is associated with decreased obesity [6].

In response to the epidemic of obesity and related metabolic diseases, Americans have turned to very low-carbohydrate (ketogenic) diets which anecdotally and by some confirmatory clinical trials [7] seem to lead to superior weight loss compared with low-fat diets. Nevertheless, the only diet that has proven outcome data is the so-called Mediterranean diet. Figure 18.1 is a comparative table of major modern diets and their macronutrient mix. There is considerable variation in the recommended macronutrients, and the foods contributing to them, among these popular diets. Not included, and beyond the scope of this chapter, are the plant-based, pescatarian, and omnivore-based variants of these diets. Obviously, the considerable differences in the recommended macronutrient components of these diets make comparisons more difficult. Given the conflicting evidence, what should clinicians advise their patients to do?

Food Groups	Atkins (induction)	Ketogenic	Low Fat Diet	Mediterranean
Red Meats	++	++	0 - +	+ - ++
Poultry	++	++	0 - +	++
Seafood	++	++	0 - +	++
Egg	++	++	0 - +	++
Starchy vegetables	0	0	++	++
Non-starchy vegetables	++	++	++	++
Legumes	0	0	++	++
Whole Grains	0	0	++	++
Refined Grains	0	0	0	0
Non-berry fruits	0	0	++	++
Nuts and Seeds	++	++	++	++
Low Fat Dairy	0	0	++	+
High Fat Dairy	0-1	++	0	0
Monounsaturated Oils	++	++	++	+++
Vegetable Oils	0-1	0	++	++
Saturated Oils (Chee, tallow,)	++	++	0	0-1
Sugar	0	0	0	0

Fig. 18.1 Simplified comparisons of food types included in various popular diets including low carbohydrate (Atkins/ketogenic), low fat, and Mediterranean. 0 = discouraged, 0–1 = limited amounts, + = permitted in moderate portions/frequency, ++ encouraged liberally or to satiety

Carbohydrate-Restricted/Ketogenic/Atkins Diets

Carbohydrate-restricted/ketogenic/Atkins diets have not been tested in outcome trials to prove that they reduce cardiovascular (CV) events or cancer. The best outcomes have been observed in patients with type 2 diabetes as reviewed below. A cardiologist, Dr. Robert Atkins, proposed the first popular low-carbohydrate diet and promoted it in the 1960s and 1970s. It has slightly greater protein content (> 20% of calories) but shares the severe carbohydrate restriction of ketogenic diets of ≤20 grams of carbohydrates daily. The Atkins diet calls for a strict carbohydrate limitation in the first 3–6 months and then liberalizes the intake to ≤50 grams/daily after 6 months [8]. Ketogenic diets have been used to treat epilepsy since the 1920s. Humans start life on a ketogenic diet (breast milk is 55% fat), and infants and children produce ketones much more readily than adults. This is thought to encourage early life brain development and provided resistance of young *Homo sapiens* against privation conditions in their evolution [9]. Strict ketogenic diets share the restriction of <20–30 grams per day. Figure 18.2 provides an outline of the Atkins and ketogenic diets [10, 11]. Routine ketone monitoring is not necessary but may be motivating to some patients. Blood (beta-hydroxybutyrate), breath (acetoacetate), or urine (acetone) measurement is available for home use. Blood ketones measured by finger prick remain the most accurate with levels of 0.5–3.0 mM representing nutritional ketosis. Urinary ketone measurement is easier, but its accuracy tends to fall with time as the body begins to use ketones as a body fuel and spill less of them into the urine [12].

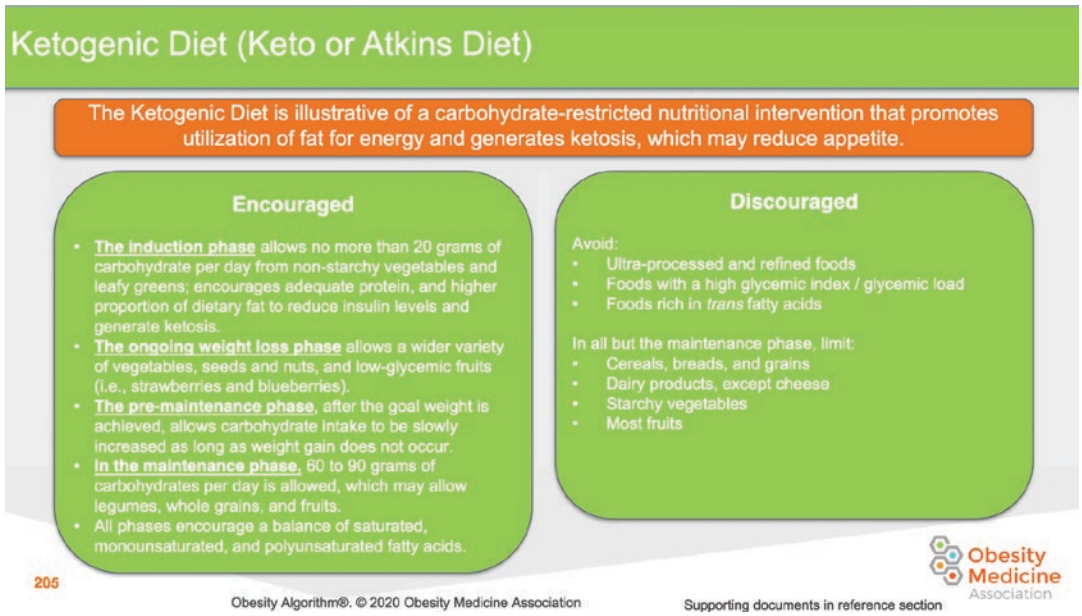

Fig. 18.2 Obesity Medicine Association examples of a carbohydrate-restricted/ketogenic diets [11]. (Reproduced with permission from the Obesity Medicine Association. Bays HE, McCarthy W, Christensen S, Tondt J, Karjoo S, Davisson L, Ng J, Golden A, Burridge K, Conroy R, Wells S, Umashanker D, Afreen S, DeJesus R, Salter D, Shah N, Richardson L. Obesity Algorithm Slides, presented by the Obesity Medicine Association. www.obesityalgorithm.org. 2020. https://obesitymedicine.org/obesity-algorithm-powerpoint/ (Accessed = March 25, 2020))

Low-Fat Diets

Low-fat diets have not improved outcomes as predicted despite lowering cholesterol [13]. A previous metanalysis of trials of low-fat versus low-carb diets showed greater weight loss with lower-carb diets (an additional 2 kg on average) and a greater reduction of the 10-year risk of cardiovascular events (ASCVD) compared to low-fat diets, despite the fact that the latter induced LDLc reduction [7]. A recent elegant systematic review and network metanalysis of randomized trials compared 14 popular diets including the ones reviewed in this chapter. This study suggested that differences between major macronutrient strategies low carb, low fat, and "moderate macronutrient" (e.g., Mediterranean diet) were minimal at 6 months and less at 12 months. The Atkins, DASH, and Zone diets produced more weight loss and blood pressure (BP) reduction at 6 months. However, at the end of 1 year, all cardiovascular benefits had disappeared with all diets, except the Mediterranean diet [14].

Mediterranean Diet

The Mediterranean diet (MedDiet) is the only diet that has been shown to improve cardiovascular disease (CVD) outcomes [15] and is discussed in greater detail in Chap. 15 by Bray and Champagne. There is debate, however, as to the exact definition of macronutrient mix. Some would advocate that the mix is the closest to the ancestral 40F/40C/20P mix of many European cultures. It certainly incorporates a high intake of olive oil, fruit, nuts, vegetables, and cereals; moderate intake of fish and poultry; low intake of dairy products, red meat, processed meats, and carbohydrates; and moderate wine consumption [11]. Versions of this diet have been addressed in both secondary and primary prevention trials.

The Lyon Heart Study (Southern France) was a secondary prevention study designed to compare the impact of the MedDiet vs a traditional Western prudent diet in 605 patients with prior myocardial infarction. Despite the originally planned 5-year duration, the study was reported after a mean follow-up of 27 months due to a highly statistically significant reduction in the rate of reinfarction and death in the patients following the MedDiet (risk ratio 0.27; 95% CI 0.12–0.59, p = 0.001) [16]. These results were confirmed in the extension study (adjusted risk ratios varying between 0.28 and 0.53) [17]. The intake of nutrients was substantially different between groups: patients following the MedDiet consumed significantly less lipids, saturated fat, cholesterol, and linoleic acid but more oleic and alpha-linolenic acids.

In the primary prevention PREDIMED (Spain) study, 7477 patients at high risk for CVD were randomized to a low-fat (AHA style) diet or a MedDiet supplemented with either extra-virgin olive oil (MEDIevoo) or nuts (MEDInuts) [18]. After a median follow-up of 4.8 years, there was a significant 31% reduction in the primary combined endpoint of myocardial infarction, stroke, CVD, or death in the MEDIevoo and a 28% reduction in the MEDInuts cohorts compared to the low-fat diet cohort. Of note, at baseline 50% of the patients enrolled had diabetes mellitus, the mean BMI was 30, and over 70% of the patients had dyslipidemias. Interestingly, a review of MedDiets showed that apart from the large increase in intake of EVOO and nuts, other dietary changes were small and unlikely to account for the dramatic reduction in risk of CVD. The authors suggested that the most plausible explanation was the EVOO or nuts [19]. However, adherence to the MedDiet, as assessed by a simple score based on the number of food items consumed per week, was strongly and inversely associated with risk of developing obesity [20].

Key components of the MedDiet are consumption of whole unprocessed food, and many would argue that the full benefits also incorporate regular physical activity along with a healthy and nutritious diet. However, although the results were consistent and reproducible, these diets have largely been studied in metabolically well patients, not those with severe obesity.

Unfortunately, the major problem Western societies have to face is the increasing number of metabolically unwell patients with severe obesity, the metabolic syndrome, and/or type 2 diabetes.

Ketogenic/Low-Carb Diet Reversal of Metabolic Syndrome and Type 2 Diabetes

Recent research is confirming that very low-carbohydrate diets can effectively reverse the metabolic abnormalities of patients with type 2 diabetes. Compared with low-fat diets, carbohydrate restriction produces significantly greater reduction in hemoglobin A1c and weight loss in patients with type 2 diabetes. A seminal trial in the treatment of type 2 diabetes involved 262 patients receiving a very low-carbohydrate diet and 87 controls receiving a diet based on standard guidelines [21]. The intervention group was treated with a ketogenic diet with blood measurements confirming nutritional ketosis, with beta-hydroxybutyrate levels between 0.4 and 0.6 mmol/L. Patients lost between 10 and 15% of their body weight. Inflammatory responses, as measured by hsCRP and white blood cell count, decreased significantly while they did not change or continued to increase in the usual care group. Virtually every important biomarker changed in a positive direction including triglycerides, HDL, and small dense LDL particle count, and, most importantly, the 10-year risk of atherosclerotic CVD decreased despite an increased LDL cholesterol level. Conversely, in the usual care group, virtually every biomarker continued to deteriorate over the 1-year follow-up including the 10-year risk of cardiovascular events [22]. The LDL cholesterol, however, decreased. Not surprisingly, in the ketogenic dietary intervention group, the average hemoglobin A1c decreased from 7.6% at baseline to 6.3% at 1 year. From a cost perspective, medication utilization was dramatically reduced, with half the patients completely discontinuing insulin and all discontinuing sulfonylureas as opposed to the usual care group where insulin doses and sulfonylurea use continued to increase. It is difficult to know which were the most important factors for success for these patients, but likely it was the combination of an effective diet and certified health coaches who used motivational techniques and accountability through objective changes in weight, body metrics, and metabolic markers.

Recommendations by Obesity Medicine and the American Diabetes Associations

In response to emerging evidence, both the Obesity Medicine Association (OMA) (Fig. 18.3) [10, 11] and the American Diabetes Association (ADA) have acknowledged multiple potential approaches to nutritional treatment of obesity, respecting patients' cultural norms and metabolic circumstances including options for either low-carbohydrate or calorie-restricted low-fat diets. However, the ADA now acknowledges that "reducing overall carbohydrate intake for individuals with diabetes has demonstrated the most evidence for improving glycemia and may be applied in a variety of eating patterns that meet individual needs and preference" [23].

Which Diet/Lifestyle Is the Best?

The OMA suggests that a diet restricted in either carbohydrates or calories is appropriate, and the choice depends on what the provider believes will be most effective, safest, and most likely to be adhered to as a lifestyle. The ketogenic diet (Fig. 18.2) has the most evidence at this time for diabetes reversal. Most diets will work for some time, the key factor being calorie restriction and temporary calorie deficit. Younger patients tend to have a higher basal metabolic rate and will respond to

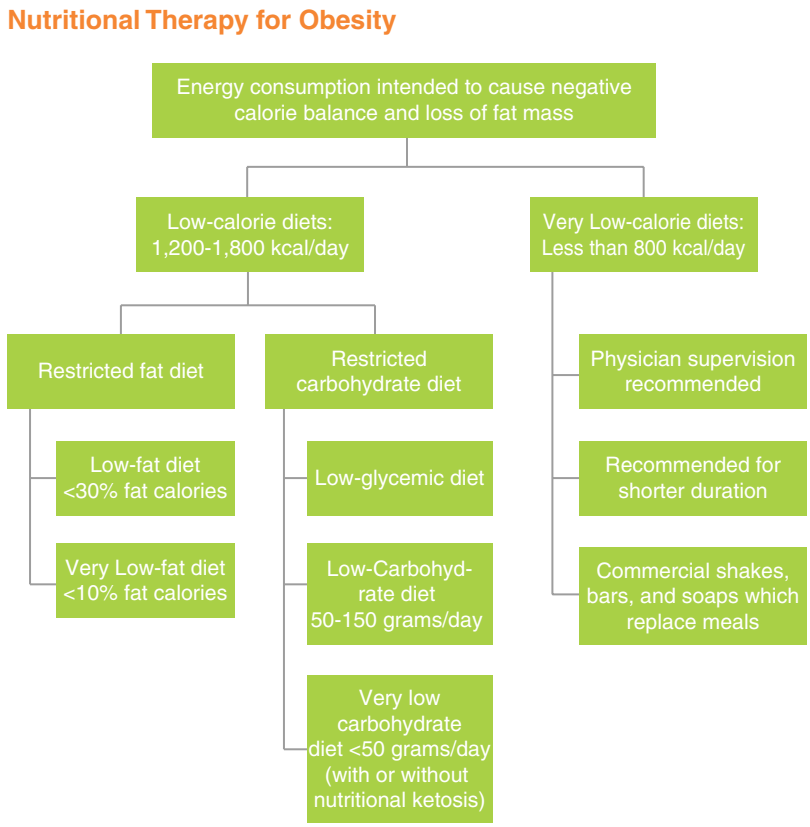

Fig. 18.3 Obesity Medicine Association nutritional options to treat obesity [11]. (Reproduced with permission from the Obesity Medicine Association. Bays HE, McCarthy W, Christensen S, Tondt J, Karjoo S, Davisson L, Ng J, Golden A, Burridge K, Conroy R, Wells S, Umashanker D, Afreen S, DeJesus R, Salter D, Shah N, Richardson L. Obesity Algorithm Slides, presented by the Obesity Medicine Association. www.obesityalgorithm.org. 2020. https://obesity-medicine.org/obesity-algorithm-powerpoint/ (Accessed = March 25, 2020))

virtually any calorie reduction. However, calorie counting is difficult to sustain, as anyone who has repetitively undertaken a restrictive diet can attest.

Ketogenic diets tend to be easier to follow as liberal ingestion of fat and protein (from unprocessed sources) leads to early satiety and, provided carbohydrates are avoided, to involuntary calorie deficits. Undoubtedly, there are early side effects such as "keto flu" related to re-engaging the body's metabolic flexibility through nutritional ketosis. Longer term, there is the difficulty in maintaining meal consistency and variety, especially given additional meal prep time because of the requirement for unprocessed foods without preservatives, and also avoiding our carbohydrate-laden world, in general. However, with appropriate support from health coaches and ever-increasing web resources, the keto diet is the best to reverse diabetes and achieve significant weight loss and can be very sustainable.

Once metabolic health goals are met, one can gradually add non-starchy carbohydrates to add variety but always remaining vigilant for weight gain. Although the MedDiet is the most evidence-based lifestyle for the general population. It is helpful for the prevention of obesity but has not been as extensively studied for obesity reduction or diabetes reversal. It would need to be accompanied by a calorie-restricted diet as part of a weight reduction strategy. The long-term safety of LDLc rise seen in a significant minority of patients following a keto diet remains to be determined in properly conducted studies.

Summary

One of the difficulties for busy clinicians in sorting out claims from the nutritional science literature lies in the systemic weakness of its largely epidemiologic nature, as well as intrinsic biases among various authors in the field. One of the unintended consequences of admonitions to cut fat was the increase in the consumption of carbohydrates, especially simple carbohydrates, which has increased overall caloric consumption and resulted in overnutrition of the population and the current obesity epidemic.

Traditional weight-loss advice was based on the simple formula of "calories in-calories out." Partnered with a "heart healthy" low-fat diet and caloric restriction, patients were encouraged to lose weight to maintain health and also to prevent and reverse diabetes. Unfortunately, the body's response to caloric restriction is simply to reduce the metabolic rate resulting in plateauing, frustration, and inevitable weight gain in most patients. The majority of clinical trials have not supported a low-fat diet as improving cardiovascular outcomes.

The only diet that has a strong supporting literature including randomized clinical trials is the so-called Mediterranean diet. Mediterranean diets are quite diverse and range from plant-based and red meat-restricted to fairly red meat-liberalized diets, but all do include healthy amounts of exercise, monounsaturated fatty acids (olive oil and nuts), and fish with the common theme being whole foods. They seem to be best at maintaining health and avoiding obesity. However, they have not been tested in severely obese and metabolically unwell people. If selected to attempt to lose weight, they would need to be coupled with a calorie counting strategy as all diets require a reduction in calorie intake to induce weight loss.

Carbohydrate-restricted diets, also known as ketogenic diets, do not have any outcome data in terms of improving cardiovascular mortality or cancer outcomes. They have compared favorably with low-fat calorie-restricted diets in terms of weight loss, improving glycemic control, diabetic dyslipidemia, and inflammatory markers along with the overall 10-year predicted atherosclerotic risk. They increase LDL cholesterol which can create clinical conundrums with respect to management. Clinicians are advised to follow published guidelines for primary and secondary prevention, but if patients are obtaining health benefits from a ketogenic diet in terms of general well-being, weight loss, improved hepatic steatosis, metabolic syndrome dyslipidemia (higher HDL and lower triglycerides) etc., they should be encouraged to continue.

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Part V

Nutritional Requirements Following Surgery and Acute Disease

Role of Nutrition in Understanding Common Gastrointestinal Disorders

19

Andy Liu, Ryan T. Hurt, and Michael Camilleri

Keywords

Gastroesophageal reflux disease (GERD) · Peptic ulcers · Food allergy · Constipation · Diverticulosis Inflammatory bowel disease · Colon cancer

Key Points

- Nutrition has a role in the etiology and management of gastrointestinal (GI) diseases.
- Overnutrition leading to overweight and obesity is a risk factor for gastroesophageal reflux disease.
- Nutritional requirements greatly increase with severe malabsorptive diseases such as celiac disease, pancreatic exocrine insufficiency, bariatric surgery, and Crohn's disease.
- To prevent weight loss associated with malabsorptive GI diseases, a variety of feeding methods, with emphasis on a high-calorie, high-protein diet that also includes micronutrient supplementation, should be the key.

Introduction

GI disorders occur when there is malfunction of one or more of the digestive organs, or when there is disruption of the mechanical or chemical processes of digestion. They are commonly encountered in primary care, and the prevalence of some diseases, including celiac disease, is increasing. According to a report from Blue Cross Blue Shield in the United States, the GI diseases, ulcerative colitis, and Crohn's disease are the tenth most impactful conditions affecting health and quality of life of people in the United States [1]. In addition, total expenditures for GI diseases in the United States are $135.9 billion annually, based on the 2015 Medical Expenditure Panel Survey. This chapter describes GI-related diseases in order of occurrence from esophagus to rectum and includes gastroesophageal reflux disease (GERD), peptic ulcer disease and *Helicobacter pylori* infection, celiac disease, constipation, diarrhea, diverticular disease, inflammatory bowel disease (IBD), and colorectal cancer.

A. Liu · M. Camilleri (✉)
Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN, USA
e-mail: camilleri.michael@mayo.edu

R. T. Hurt
Division of General Internal Medicine, Mayo Clinic, Rochester, MN, USA

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Because of the intricate relationship between nutrition and the GI tract, diet has an impact on the development and subsequent medical management of GI disorders, and the diseases discussed subsequently may benefit from dietary adjustments.

The GI conditions are best reviewed based on anatomical distribution of the disease or disorder.

Eosinophilic Esophagitis

This is a disease that often starts in childhood with eating difficulties and symptoms of GERD. However, it progresses with increasing inflammation, fibrosis, and strictures until the esophagus is anatomically narrowed, sometimes with the appearance of a ringed or "feline" appearance. Progressive remodeling of the esophagus appears to be gradual, although this is not universal, and the duration of untreated disease is the best predictor of stricture risk. The cellular, molecular, and genetic bases are increasingly understood with involvement of an exotoxin produced by infiltrating eosinophils and inflammatory interleukins (e.g., IL-5). Current incidence estimates range from five to ten cases per 100,000, and current prevalence estimates range from 0.5 to 1 case per 1000 [2].

Early recognition and treatment with an allergen-avoidance diet and topical steroids are key to treatment; an elemental diet is rarely required. A commonly prescribed diet to treat eosinophilic esophagitis is the six-food elimination diet, wherein the six most common dietary triggers are removed – these foods can be easily recalled with the mnemonic SWEDNS (soy, wheat, egg, dairy, nuts, and seafood).

Dietary intervention is efficacious in about two-thirds of patients [3]. Swallowed, viscous formulations of topical steroids, such as budesonide, are the main pharmacological therapies used, alone, or in combination with diet. A meta-regression study of the literature showed that histology, eosinophil count, and symptom response rates are similar with swallowed fluticasone, or budesonide, or a six-food (dairy, wheat, egg, soy, nuts, and seafood) elimination diet [4]. Effective treatment is essential to prevent long-term complications such as formation of strictures.

Gastroesophageal Reflux Disease

In accordance with the Montreal Definition, gastroesophageal reflux disease (GERD) develops when there is retrograde movement of gastric contents into the esophagus. About 6 to 30% of the US population experiences GERD each year, making it the most prevalent GI disorder associated with outpatient clinic visits [5]. The esophageal lining is susceptible to irritation by acid because it does not have the thick mucus protection of the stomach, attributable to the mucin-secreting gastric epithelial cells. Some people with GERD do not experience heartburn but may have difficulty swallowing, burning sensation in the mouth, a feeling that food is stuck at any level of the esophagus, or hoarseness in the morning [6].

There are a number of predisposing factors associated with GERD, including a hiatal hernia, cigarette smoking, alcohol use, being overweight or obese, and pregnancy. Foods such as citrus fruits, chocolate, caffeinated drinks, fried foods, garlic, onions, spicy foods, and tomato-based foods, such as chili, pizza, and spaghetti sauce, are associated with heartburn symptoms. Consumption of large high-fat meals requires prolonged gastric passage times and the increased stomach pressure may lead to movement of hydrochloric acid from the stomach into the esophagus. Additionally, lying prone after a meal promotes backflow of stomach contents and the development of symptoms [7].

GERD may result in persistent irritation of the esophageal lining; the resulting esophagitis may lead to malnutrition due to development of a stricture leading to dysphagia and a loss of appetite.

Bleeding related to chronic inflammation or surface epithelial erosive change causes loss of iron as well as other blood nutrients (minerals, vitamins, amino acids, glucose, fatty acids). Moreover, GERD is a major risk factor for the development of Barrett's esophagus, a pre-malignant lesion that gives rise to most, if not all, esophageal adenocarcinomas [8]. Patients with esophageal cancer are often malnourished, which is attributed to a combination of insufficient dietary intake from dysphagia (particularly when the esophageal lumen is narrowed to less than 13 mm), tumor-related loss of appetite, systemic inflammation, and effects of chemoradiotherapy used in the treatment of the cancer [9].

Effective treatments for GERD include identifying and avoiding foods that trigger increased acid production. People can reduce symptoms by eating smaller meals, waiting at least 3 h after a meal before lying down, and elevating the head of the bed by 4–6 inches to allow gravity to keep stomach contents down. In addition, weight loss is frequently recommended as an additional first-line therapy for GERD, with a longitudinal study of over 15,000 patients demonstrating an association between BMI reduction of greater than 2 kg/m^2 and GERD symptom improvement in patients with obesity [10]. Diet therapy may also require replacing lost nutrients with the use of vitamin and mineral supplements. Patient compliance may be low, but these lifestyle modifications are the first step in management, before prescription of a proton pump inhibitor.

Esophageal Cancer

From a global perspective, the most prevalent form of esophageal cancer is squamous cell carcinoma (ESCC), which accounts for about 90% of all cases. There is epidemiological evidence of association of this form of cancer with the ingestion of preserved foods. For example, a strong association exists between the consumption of salted meat products and ESCC in an exposure-response relationship, with people consuming more than 150 grams per week at highest risk [11]. As well, a meta-analysis demonstrated a twofold increased risk of ESCC in people who consumed large amounts of preserved vegetables, which may contain carcinogenic mycotoxins and N-nitroso compounds formed as part of the pickling process [12]. These findings are consistent with a large Chinese case-control study demonstrating that diets high in processed foods (e.g., salted meats and eggs and preserved vegetables) were significantly associated with ESCC development [13].

Conversely, a diet high in fresh fruits and vegetables may be protective against ESCC. For every additional 100 grams of vegetable consumed daily, there is an associated decreased risk by 9%, whereas the same increment of fruit intake is associated with a 16% decrease [14]. Although the World Cancer Research Fund/American Institute for Cancer Research Continuous Update Project (2016) mentions that there is "limited/suggestive" evidence for fruits and vegetables at decreasing the risk of ESCC, a high-fiber diet may also be protective.

Regarding habits, the chewing and consumption of betel quid, which consists of areca nuts wrapped in a betel leaf, is a practice common in South and Southeast Asia and one that increases the relative risk of ESCC by 2.2 to 5.6 times [14]. Cigarette smoking, a well-known risk factor itself for both ESCC and esophageal adenocarcinoma, plays a synergistic role. In addition, a large Swedish case-control study demonstrated that people who consume large amounts of alcohol have a significantly higher risk of ESCC compared to those with a healthy diet high in vegetables, tomatoes, fruits, fish, and poultry [15]. Finally, multiple studies have also demonstrated the association between large consumption of very high temperature beverages, especially the herbal tea known as yerba maté, and ESCC development [16]. A recently published study [17] from Golestan in Iran based on a 10-year follow-up of 50,045 individuals, 40 to 75 years old, showed that 76% of esophageal cancer cases were attributable to combined exposures to opium smoking, drinking hot tea, low intake of fruits and vegetables, excessive tooth loss, and drinking unpiped water.

Peptic Ulceration

Peptic ulcers are erosions or sores of the mucosal lining of the stomach and duodenum. The majority of ulcers occur in the duodenum which lacks the thick, protective mucosal lining of the stomach and is, therefore, more susceptible to damage by the acidic chyme before it is neutralized by bicarbonate secreted from the pancreas. One in ten Americans develops a peptic ulcer at some time in his or her life [6].

The primary cause of peptic and duodenal ulcers is now widely accepted to be an infection with *Helicobacter pylori* (*H. pylori*); prolonged use of nonsteroidal anti-inflammatory drugs (NSAIDs) remains an additional cause. For many years, the cause of ulcers was thought to be stress, alcohol, and spicy foods, but this focus on lifestyle and diet has changed since the discovery of *H. pylori* as the chief causative agent. However, stress is still thought to play a role because of its effects on behavioral changes such as increased use of alcohol which is a potential risk factor [6].

Upper abdominal pain occurring 1–3 h after eating remains a primary symptom. Duodenal ulcer discomfort may be relieved by eating, while the discomfort due to gastric ulcers may also be paradoxically aggravated by food and cause loss of appetite and subsequent weight loss. Peptic ulcers can also be accompanied by hemorrhaging, resulting in iron deficiency anemia, and vomiting, leading to electrolyte losses.

The goals for peptic ulcer treatment include relief of symptoms, promotion of mucosal repair, and prevention of recurrence. This is achieved with a combination of medications including antibiotics to eradicate *H. pylori*, mucosal protectants, antacids, proton pump inhibitors, and stopping NSAID use. Dietary recommendations are adapted to individual food tolerances. Foods that trigger acid secretion, such as alcohol, caffeine and caffeine-containing beverages, and spicy foods, should be avoided. Patient compliance is generally poor, and this is less important with the highly effective treatments with antibiotics and proton pump inhibitors. Dietary modification has not been shown to increase the rate of healing [18].

Gastroparesis

Gastroparesis results in symptoms and objective findings of delayed emptying from the stomach in the absence of mechanical obstruction. Typical causes are diabetic, post-vagotomy, or idiopathic. The disorder typically represents abnormal extrinsic or intrinsic neural supply to the gastric smooth muscle. Gastroparesis may present with significant nutritional deficiencies, and attention to hydration and nutrition is essential for proper management of patients. A "gastroparesis diet" consisting of foods low in fat and fiber is frequently recommended as a first-line treatment, as these substances are well known to delay gastric emptying, while bland substances, such as saltine crackers, Jell-O, and graham crackers, may actually improve symptoms [19]. Patients with gastroparesis should also consume smaller, more frequent snacks instead of larger meals. Finally, a randomized, controlled trial demonstrated symptomatic benefit of a small size particle diet, which included foods such as paté, puréed fruit, spreadable cheese, and others that are "easy to mash with a fork, e.g., mealy potatoes" [20]. Unfortunately, in an NIH gastroparesis registry, only 2% of patients were adherent to a diet suggested for their gastroparesis, and other management strategies including pharmacotherapy are frequently required and are detailed elsewhere.

Bariatric Surgery

Bariatric surgeries, such as Roux-en-Y gastric bypass (RYGB), sleeve gastrectomy, and the less frequently performed biliopancreatic diversion with duodenal switch, are effective at inducing significant weight loss; dietetic counseling is mandatory during the first year to enhance the efficacy of the weight loss intervention. However, these operations can be associated with nutritional deficiencies and malnutrition. The nutritional considerations of bariatric surgery are discussed in greater detail in Chap. 24 by Christopher Larson. Preoperative nutritional assessment and correction of vitamin and micronutrient deficiencies, as well as long-term postoperative nutritional follow-up, are required. Operations, such as RYGB (especially with a long Roux limb) and biliopancreatic diversion, may result in significant steatorrhea which leads to enteric hyperoxaluria (as in Crohn's disease) because unabsorbed fatty acids saponify intraluminal calcium ions, preventing the formation of calcium oxalate that is normally lost in the stool; this may be prevented by reduction of dietary oxalate (e.g., tea, spinach) and calcium supplementation. Patients must also be aware of the need for high water consumption and avoidance of high osmotic loads (which may aggravate diarrhea) post RYGB, targeting enough intake to maintain at least 2.5 L of urine output daily in order to minimize the risk of renal calculi development [21].

Food Allergy

A food allergy is characterized by an abnormal immune reaction to a particular component in food, usually a protein. Food allergies are far less common than most other GI disorders, but their prevalence appears to have increased markedly over the last 50 years. Approximately 30,000 Americans require emergency room treatment and 150 people die each year because of allergic reactions to food. However, these are predominantly the result of generalized anaphylactic reactions, as may occur with peanut allergy, rather than allergies associated with GI symptoms. Food allergy usually manifests in early childhood as part of the so-called atopic march and most commonly involves one or more of the following foods: cow's milk, hen's egg, soy, peanuts and tree nuts, wheat, sesame seed, kiwi fruit, and seafood [22].

The diagnostic approach to adverse reactions to food is based on accurate clinical history and objective examination and further execution of specific tests when allergy or intolerance is suspected. Such testing may include skin prick tests, specific IgE measurements, and oral food challenges against the suspected allergens [23]. Symptoms may be localized or systemic and rarely lead to anaphylactic shock, though they may occur with certain seafoods such as shellfish. The treatment for food allergies is the elimination of the food to which hypersensitivity has been found; this strategy can lead, especially in pediatric age, to tolerance. If elimination diets cannot be instituted or if it is not possible to identify the food to eliminate, some drugs (e.g., antihistaminics, steroids) can be administered, although in the setting of anaphylaxis, there is no substitution for emergency intramuscular epinephrine autoinjection. Specific allergen immunotherapy has been introduced, and it is fundamental to prevent food allergy, especially in high-risk subjects [24].

Celiac Disease

Celiac disease, or sprue, is a genetic disorder characterized by intolerance to gluten, the primary protein found in wheat, rye, and barley. Approximately one in 133 people in the United States is affected by this disease, although the prevalence differs by ethnic group [25]. More than 95% of celiac patients share the major histocompatibility complex II class human leukocyte antigen (HLA) DQ2 or DQ8

haplotype; patients negative for both haplotypes are unlikely to suffer from the disease [26]. Some cases of sprue develop in infancy or childhood, and others occur later in life.

In susceptible individuals, the cells of the small intestine mount an immune response against gluten, with subsequent damage and erosion of the intestinal villi. The damage to the brush border, which normally absorbs nutrients, can lead to malabsorption and, over time, malnutrition can occur. Deficiencies of fat-soluble vitamins (A, D, E, and K), iron, folate, and calcium are common in people afflicted with celiac disease. There is an increased risk of osteoporosis from poor calcium absorption, diminished growth because of overall nutrient malabsorption, and seizures as a result of inadequate folate absorption. The only effective treatment for celiac disease is a gluten-free diet, which is cumbersome and difficult to strictly adhere to, given the many sources of hidden gluten, such as in contaminated oats, sauces, and drug fillers [27]; referral to registered dieticians trained in celiac disease counseling is therefore recommended [28]. However, successful elimination of dietary gluten can improve symptoms, repair intestinal damage, improve bone mineral density, resolve infertility, and prevent enteropathy-associated T-cell lymphoma and ulcerative jejunitis [28]. There are many gluten-free foods such as meats, milk, eggs, fruits, and vegetables. Rice, potatoes, corn, and beans are also gluten-free. Specialty food stores and many supermarkets now provide specially formulated gluten-free breads, pasta, and cereal products.

Constipation

Constipation is a common problem of the lower GI tract and is associated with stools that are infrequent (less than three times per week), hard, and lumpy (Bristol Stool Form Scale 1 or 2), associated with significant straining, associated with a sensation of incomplete evacuation, or associated with digitation. The prevalence of constipation (~15–20%) is higher in women than men and appears to increase with age over 65 years. A low-fiber diet (<12 g/day), which is typical of a North American "meat and potatoes" diet, often contributes to constipation. The lack of bulk that comes with low-fiber diets causes slow colonic transit, resulting in excessive absorption of water from the colon. This leaves dry hard stools that are hard to pass. As a result, fiber supplementation is often required, with the recommended total fiber intake being 14 grams per 1000 kcal consumed or about 20–30 grams daily [29]. Other nutrition-related causes of constipation include use of aluminum-containing antacids and iron and calcium supplements [30]. Paradoxically, these substances are often used to treat other GI disorders or are a part of standard vitamin/mineral supplementation regimens, and so co-consumption with laxatives, such as magnesium citrate, should be considered (e.g., take both aluminum and magnesium products concurrently). Although it is commonly recommended that a high water intake is necessary for normal bowel function, this is insufficient to change stool consistency unless there are osmotically active foods or medications in the lumen (osmotic laxatives) to retain water within the intestinal tract.

Diarrhea

Diarrhea is characterized by frequent (more than three) watery to loose stools in a 24-hour period. Diarrhea can be classified as acute or chronic.

Acute diarrhea is usually caused by an infection from a bacteria, virus, or parasite, which may be present in animal and human fecal matter or in contaminated food, milk, or water. Symptoms may persist for 1–2 days with or without serious consequences; however, persistent diarrhea lasting more than 3 days may lead to dehydration and electrolyte imbalance and can be fatal, particularly in children and the elderly. Other symptoms of diarrhea may include cramping, abdominal pain, bloating, nausea, fever, and bloody stools.

Prolonged diarrhea that lasts for a month or longer is chronic; it may be caused by a large number of diseases, some of which are related to nutrients, such as allergies to cow's milk, lactose intolerance, celiac disease, or pancreatic insufficiency. Consumption of large quantities of caffeine and highly osmotically active substances, such as artificial sweeteners found in chewing gums and carbonated beverages or artificially sweetened beverages used by patients with diabetes, can also cause chronic diarrhea, and so a thorough dietary history should be elicited from all patients.

Nutritional therapy for diarrhea is aimed at replacing fluids and electrolytes through consumption of beverages, such as water, juices, or sports drinks, and eliminating the cause of diarrhea (contaminated foods). Juices and carbonated beverages should be diluted since they are often hyperosmolar and would otherwise aggravate the diarrhea. The optimal fluid replacement therapy has an osmolality at or below that of plasma (~280 mOsm/kg). If solid foods are tolerated, restricting insoluble fiber can assist in slowing gut transit time; yogurt with probiotics may be helpful in replacing commensal gut flora.

Irritable Bowel Syndrome and Dietary Therapy Based on Low FODMAP Ingestion

Irritable bowel syndrome (IBS) is a functional disorder in which chronic abdominal pain is associated with bowel movements. A positive diagnosis of IBS can be made if a patient fulfills the Rome IV criteria. These symptoms may be reduced by dietary supplementation with single probiotics like *Bifidobacterium infantis* or combination probiotics, such as VSL#3. Probiotics are discussed below under inflammatory bowel diseases.

A diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) is frequently recommended as an early approach to the treatment of IBS. The rationale behind this stems from the belief that FODMAPs, a collection of short-chain carbohydrates that are poorly absorbed by the small intestine, produce gas in the lower GI tract when they become fermented by colonic bacteria. FODMAPs are also thought to be osmotically active, drawing water into the intestinal lumen. The combination of increased colonic gas and water leads to symptoms typical of IBS in susceptible individuals [31].

Proper implementation of the low-FODMAP diet consists of three distinct phases occurring over at least two clinical appointments by a trained dietician. The first phase involves dramatic FODMAP restriction over a 4- to 8-week period to induce rapid symptom relief. If there is adequate response, patients proceed to the second phase, which involves reintroduction of FODMAP-containing challenges in 3 consecutive day increments with close monitoring for an additional 6 to 10 weeks. The third phase involves FODMAP personalization, where successfully challenged foods are safely consumed long term, with ongoing avoidance of failed challenges to prevent symptom recurrence [32]. Numerous societies have endorsed the low-FODMAP diet for the treatment of IBS [33, 34].

However, the available evidence demonstrating the efficacy of the low-FODMAP diet is conflicting. For instance, in a randomized, controlled, crossover study comparing the low-FODMAP diet to a typical Australian diet in 30 IBS patients and eight controls, the low-FODMAP diet was found to significantly reduce overall GI symptoms in the IBS patients [35].

An alternative strategy to loosen the strict restrictions imposed by the low-FODMAP diet is to selectively restrict the FODMAP subgroups most likely to cause symptoms only, especially in patients already at risk for malnutrition. The most likely culprit is lactose, a disaccharide found in milk and natural yogurts, as 65 to 90% of adults have some degree of lactase deficiency, with the highest prevalence seen among East Asians. Following this, additional FODMAPs can be restricted based on patient-reported triggers. Should this initial tailored restriction provide adequate symptom relief, no further restrictions are required; whereas, additional FODMAP subgroup elimination can then be considered if symptoms are persistent [36].

There is evidence that probiotics may have some beneficial effect in IBS. There have been a number of randomized, controlled trials to evaluate probiotics for IBS, and, like other disease states, there are a number of factors that likely determine benefit. These factors include number of colonies, type of strains, and combining multiple strains. A recent systematic review of 35 randomized, controlled trials found that probiotics exerted beneficial effects on global symptoms, bloating and flatulence score, and abdominal pain score [37] with use of strains from the genera *Bifidobacterium* and *Lactobacillus* and combination strains such as VSL#3. The side effects attributed to probiotics have been minimal and typically associated with the delivery media such as yogurt.

Diverticulosis and Diverticulitis

Diverticulosis refers to a disorder in which pouches develop in weakened areas of the intestinal wall, typically at the site where arteries normally penetrate from the outside of the wall toward the internal lining or mucosa. Most people with diverticulosis are asymptomatic. However, some people may develop inflammation (diverticulitis), typically when the pouch is blocked; this can manifest as persistent abdominal pain and alternating constipation and diarrhea, with possible loss of fluids and electrolytes. Patients have tenderness on examination over the inflamed area of the colon.

About 10% of Americans older than age 40 and about 50% of people over 60 years have colonic diverticulosis [38]. A major risk factor for developing this includes a low-fiber diet. Such a diet facilitates development of increased intraluminal pressure that induces tubular sacs or pouches to form and protrude on the serosal side, away from the intestinal lumen of the colon.

Nutrition may play a role in treatment of diverticulosis and diverticulitis. When diverticulitis occurs, a low-fiber diet is recommended to facilitate smooth passage of stools through the inflamed area. Once healing is restored, the approach is to encourage an increase in fluids and the insoluble fiber content of the diet to prevent future diverticuli. Previous recommendations for patients with diverticular disease to avoid nuts and seeds are no longer indicated since there is no firm evidence that these foods trigger inflammation. There are preliminary data suggesting use of certain probiotic strains in all stages of diverticular disease [39], although more robust trials and data are required before making this recommendation.

Inflammatory Bowel Diseases

Inflammatory bowel diseases (IBDs) are characterized by chronic inflammation and diarrhea of the lower GI tract and include Crohn's disease and ulcerative colitis. Crohn's disease usually affects the small and large intestines, and less frequently the mouth, esophagus, and stomach, and causes damage that may extend through all layers of the gut wall. In contrast, ulcerative colitis involves the colon and the very end of the small intestine with tissue damage limited to the surface layers. IBDs usually present between 15 and 30 years of age and are now generally classified as autoimmune diseases with a genetic basis.

Malnutrition in Crohn's disease is common and has a multifactorial pathogenesis. Many patients have reduced caloric intake due to abdominal pain and increased metabolic demands due to chronic inflammation. In addition, pharmacotherapy for Crohn's disease may impair the absorption of certain nutrients, while patients who have had previous bowel resections have decreased absorptive capacity for nutrients; the classical example is B12 deficiency and fat and fat-soluble vitamin malabsorption in patients with ileal resection or disease.

The rectum is generally involved in ulcerative colitis and lesions may extend into the colon. In mild cases, patients experience diarrhea and there may be weight loss, fever, and weakness, but in more

severe forms, the disease is characterized by anemia, dehydration, electrolyte imbalance, and protein losses.

Approaches to nutritional therapy are variable and are based on individual symptoms, complications, and documented nutritional deficiencies. A high-calorie, high-protein diet is generally indicated, and adults with advanced disease may require 40 kcal/kg/day, or approximately 2.2 times the basal metabolic energy needs due to catabolic state and poor nutrient absorption [40]. Nutritional supplements may be recommended, especially for children whose growth has been retarded. Special high-calorie liquid formulas are sometimes used for this purpose. Because of fat malabsorption, limiting fat intake may help, and medium-chain triglycerides may be better tolerated as they can be absorbed without the participation of bile salts. In some patients, a low-fiber diet may be indicated if there is a partial narrowing of the small intestine, while in others lactose restriction is to be recommended if the patient has proven lactose intolerance.

Dietary therapy for inflammatory bowel disease can not only correct underlying nutritional deficiencies, but by itself it can also alter the course of inflammation, particularly in the pediatric population. For instance, the use of exclusive enteral nutrition in children with Crohn's disease has been shown to be as effective as systemic corticosteroid therapy for inducing clinical remission and to be superior for mucosal healing. Although incompletely understood, it is believed that exclusive enteral nutrition works by altering the microbiome composition, reversing impaired intestinal permeability, and decreasing proinflammatory cytokines [41]. A small number of patients may require short periods of parenteral nutrition to provide extra nutrition, to allow the intestines to rest and hopefully heal, or to bypass the intestines for individuals who cannot absorb enough nutrition from oral or enteral nutrition. Long-term parenteral nutrition use in IBD should be limited to those patients with medically refractory disease with malnutrition and those with complications such as enterocutaneous fistulas that cannot be fed enterally.

Prebiotics are nondigestible dietary oligosaccharides that affect the host by selectively stimulating growth, activity, or both of selective intestinal commensal bacteria. These commensal bacteria may provide protection, stimulate local immune responses to combat infectious organisms, or suppress inflammation caused by antigens [42]. Although more clinical studies need to be done, preliminary results from animal models and humans indicate that prebiotics and probiotics may provide effective treatments for people with IBD [43]. The best evidence for the use of probiotics in IBD is in the treatment of ulcerative colitis. Like IBS, combination probiotics (specifically, VSL#3) have been shown to be beneficial in the treatment of pouchitis, a common problem among those who have had ileal pouch-anal anastomosis surgery for ulcerative colitis, and in ulcerative colitis, but not in Crohn's disease [44].

There has been an explosion of prebiotic and probiotic products in the market in recent years. They are added to dairy products , such as yogurt drinks, and are also sold in the form of capsules. Like other supplements many commercial prebiotic and probiotic products are incorrectly labeled, have contaminants, or do not list the strains on the label.

Colorectal Cancer

People with either ulcerative colitis or Crohn's disease are at an increased risk of colon cancer. Excluding skin cancers, colorectal cancer is the third most common cancer diagnosed in both men and women in the United States, and the lifetime risk of developing colorectal cancer is about one in 22 (4.49%) for men and one in 24 (4.15%) for women [45].

Although a high-fat diet was thought to contribute to an increased risk of colon cancer, recent studies reveal factors found in red meat, other than fat, that are correlated with a higher risk [46]. Some epidemiological data indicate that a high-fiber diet is protective against colorectal cancer; however, short-term human clinical trials have not produced supportive findings. Other population studies show that people who consume higher amounts of raw and cooked garlic lower their risk for colorectal

cancer [47]. A study on the adherence to the USDA Food Guide, Dietary Approaches to Stop Hypertension (DASH) Eating Plan, and the Mediterranean Dietary Pattern concluded that people who follow these dietary recommendations have a reduced risk of colorectal cancer, and the risk reduction is higher for men. It is possible that these diets are protective against colorectal cancer because they emphasize consumption of generous amounts of fruits and vegetables – foods rich in antioxidants and fiber – though their causative links remain unconfirmed.

Further investigation of vitamin D's effects is needed, and further long-term studies are needed to clarify the role of nutrients including folic acid, fat, probiotics, and fiber.

Conclusion

The digestive system serves as the gateway into the body for nutrients that are derived from mechanical and chemical digestion of food. Foods and nutrients, such as caffeine and caffeine-containing beverages, alcohol, spicy foods, onions, garlic, and fried foods, affect the secretory function of the stomach, possibly aggravating GERD and peptic ulcers. Inadequate fiber and fluids in the diet can cause hypomotility of the intestinal wall, leading to constipation.

The absorptive function of the gut is impaired by diseases of the small and large intestines, including celiac disease, IBDs, diverticulitis, and colorectal cancer. In severe cases, these malabsorptive diseases can result in serious energy and nutritional deficiencies. Nutritional care is important in the prevention and management of GI diseases and should adapt food intake to the symptoms and complications of the disease and at the same time consider individual food tolerances. Current dietary recommendations, such as the USDA's Food Guide and the DASH diet, provide useful dietary practices for reducing risk of some diseases, such as colorectal cancer. Additionally, prebiotics and probiotics have potential as treatments for Crohn's disease, ulcerative colitis, and irritable bowel syndrome and warrant further investigation.

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Suggested Further Readings

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Food Allergy and Intolerance: Diagnosis and Nutritional Management

20

Janetta Harbron

Keywords

Food allergy · Food intolerance · Non-allergic hypersensitivity · IgE tests · Oral food challenge Elimination diet

Key Points

- Food hypersensitivity is categorized as reactions that are either immune-mediated (food allergy) or nonimmune-mediated (food intolerances).
- Diagnosis of food allergy consists of clinical history combined with diagnostic testing (through skin prick testing or serum-specific immunoglobulin E [IgE] testing) or oral food challenges (OFC).
- Nutritional management of food allergy involves avoidance of exposure to the allergen and establishing through OFC whether baked forms of the allergen are tolerated.
- Food intolerance is diagnosed with an elimination diet and OFC.
- Treatment of food intolerance does not usually require complete avoidance, but determining lower amounts that can be tolerated.

Introduction

Adverse reactions to food may develop at any age and to any food [1]. This chapter focuses on nontoxic food hypersensitivity (FHS), which include FHS causing an immune response (food allergy; FA) and FHS where the immune system is not involved (food intolerance or non-allergic food hypersensitivity) (Fig. 20.1) [1–5]. FA and food intolerances are important public health concerns worldwide. In the United States, nearly 8% of children and 11% of adults have a FA [6]. The prevalence of food intolerance ranges between 15% and 20% [7]. The management of FA involves strict avoidance of the food allergen, while exclusion or decreased intake of trigger food(s) is necessary in those with food intolerances. Misinformation regarding the diagnoses and management of these conditions may lead to decreased quality of life, unnecessary food avoidance, and nutritional inadequacies. It is important that the physician identifies these conditions in primary care, follows correct diagnostic procedures, and refers the patient to a dietitian and allergy specialist when necessary.

J. Harbron (✉)
Health through Physical Activity, Lifestyle and Sport Research Centre (HPALS), Division of Physiological Sciences, Department of Human Biology, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa
e-mail: janetta.harbron@uct.ac.za

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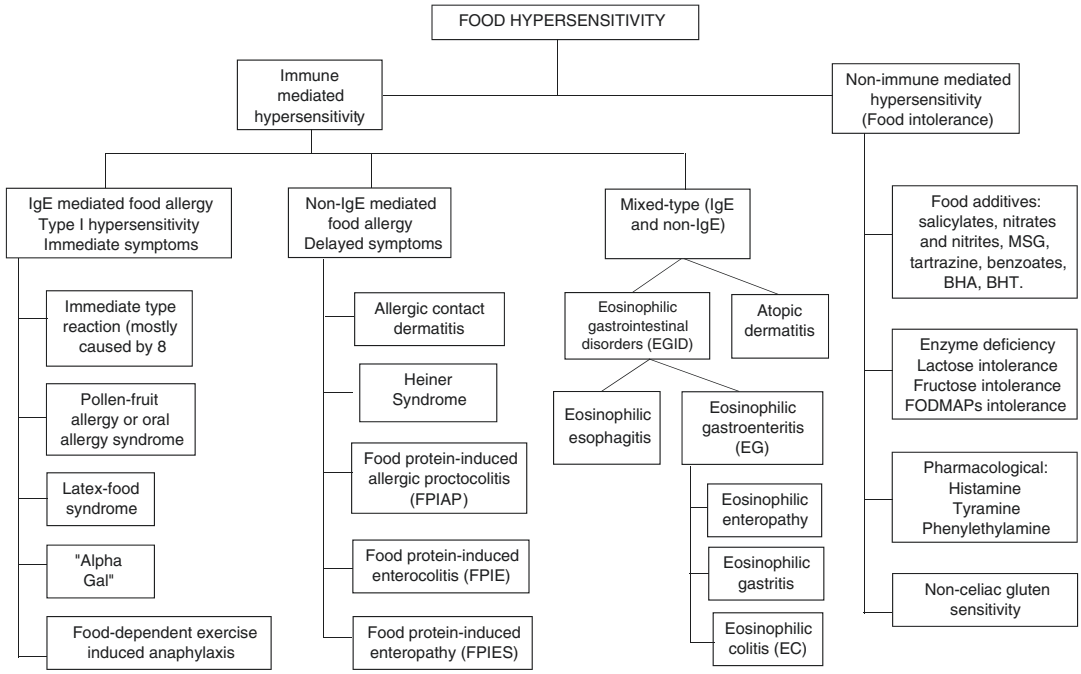

Fig. 20.1 Classification of food allergy and intolerances

Food Allergy

Food allergy (FA) is defined as an adverse immune response toward food proteins or allergens and classified based on the underlying immunology as immunoglobulin E (IgE)-mediated, non-IgE-mediated, or mixed type (overlap between IgE and non-IgE mechanisms) [1, 2, 5]. The symptoms may vary from mild to severe and involve one or several organ systems (Table 20.1).

Types of Food Allergies

IgE-Mediated FA

About 90% of all FA are caused by eight "major" food allergens including cow's milk (CM), egg, peanuts, tree nuts, soy, wheat, fish, and shellfish [1, 2, 8]. In infants, the most common allergies are to CM and egg. Allergies to peanuts, CM, shellfish, tree nuts, eggs, and fin fish are usually observed in older children, while adults are more prone to shellfish, peanuts, tree nuts, fin fish, wheat, sesame, and pollen allergies causing cross-reactive FA [6]. The "major" food allergens mostly cause type I hypersensitivity reactions, which occur when the immune system that naturally reacts to parasites/pathogens targets food allergens. The food-specific IgE antibodies that are produced bind to mast cells or basophils, which are now sensitized to the allergen (IgE sensitization). During subsequent exposure, the food allergen binds to the food-specific IgE antibodies resulting in degranulation of the mast cells or basophils to release mediators, such as histamine, leukotrienes, and prostaglandins, which induce immediate hypersensitivity reactions [2, 9].

Oral allergy syndrome (OAS) is an allergic reaction to certain foods that develops due to cross-reactivity with aeroallergens such as pollens and house dust mite. Almost all patients with OAS first develop IgE sensitization to the aeroallergen. Upon subsequent ingestion of the trigger food, the aeroallergen-specific IgE antibodies recognize and bind to food proteins with homologue epitopes to

Table 20.1 Symptoms and diagnosis of food allergies and intolerance

IgE	Non-IgE and mixed-type	Food intolerance
Symptom onset		
Rapid within minutes to 2 h of ingestion Acute reactions Can result in multisystem manifestations Symptoms recur every time when exposed to food Severity of symptoms may change over time	Immediate to delayed onset (see Tables 20.2 and 20.3)	Delayed onset Prolonged symptomatic phase Symptoms often dependent on dose of causative food, with small doses being tolerated
Symptoms		
Dermatological symptoms Urticaria/hives, flushing, angioedema, pruritus, atopic dermatitis, exacerbation of existing eczema *Oral and orbital* Itching of mouth, tongue, lips Swelling of lips/tongue Eye itching, redness, and watering Periorbital edema *Gastrointestinal symptoms* Throat discomfort, reflux, nausea, vomiting, abdominal cramps, diarrhea *Respiratory symptoms* Nasal itching, rhinorrhea and nasal obstruction, sneezing, laryngospasm, cough, chest tightness, dyspnea, wheezing, asthma *Systemic* Hypotension, arrhythmia, vascular collapse *Oral allergy syndrome* Mild symptoms affecting the lip, mouth, and throat. Immediate urticaria, itching, tingling of lips, tongue, and throat. Angioedema/blistering occasionally. Symptoms are worse during high pollen season. Anaphylaxis can occur, but rare	*Dermatological* Contact dermatitis, atopic dermatitis/eczema *Gastrointestinal* Abdominal pain, nausea, vomiting Diarrhea Malabsorption Constipation Rectal bleed with mucus in a healthy neonate, bloody stools Ascites Chronic diarrhea/steatorrhea Dysphagia Food impaction Heartburn *Other* Mostly absence of systemic symptoms Failure to thrive Feeding difficulties Irritability Weight loss Anemia Growth failure	*Dermatological symptoms* Urticaria/hives, flushing, angioedema, pruritus, eczema *Gastrointestinal upset* Bloating Flatulence Vomiting Abdominal cramps Diarrhea *Respiratory symptoms* Nasal obstruction, runny nose, asthma, shortness of breath *Other symptoms* (Some fall within spectrum of common medically unexplained symptoms) Headaches and migraine Fatigue Musculoskeletal problems Behavioral changes Dizziness Balance problems Visual disturbances
Diagnosis		
1. Clinical history and physical examination 2. IgE testing: SPT or sIgE 3. Oral food challenges (OFC) 4. Elimination diets	1. Clinical history and physical examination 2. Elimination diets and OFC 3. SPT or IgE testing mostly not helpful 4. Endoscopic evaluation and GI biopsies	1. Clinical history and physical examination 2. Fructose and lactose breath testing 3. Elimination diets 4. OFC

Sources: Refs [1, 2, 4, 5, 10, 13]

the aeroallergen resulting in an immune reaction and allergy symptoms. Examples of common overlapping antigens in OAS include [1, 4, 10, 11]:

- Birch pollen with apple, peach, cherry, apricot, carrot, celery, parsley, almond, or hazelnut.
- Ragweed pollen with melon, watermelon, cantaloupe, cucumber, zucchini, banana, or kiwi.
- Mugwort pollen with celery, carrot, parsley, peppers, mustard, cauliflower, broccoli, garlic, or onion.
- Orchard grass with melon, peanut, potato, or tomato.
- Timothy grass with Swiss chard or orange.
- Chironomidae (house dust mite) with shellfish.

Latex-food syndrome refers to an allergic reaction to certain fruit and vegetables (e.g., avocado, kiwi fruit, papaya, banana, mango, passion fruit, and tomato) in individuals with latex allergies due to cross-reactivity [1, 10, 11].

Food-dependent exercise-induced anaphylaxis (FDEIA) refers to the presence of FA symptoms during or soon after exercise and within 2–4 h after ingestion of a trigger food. Common trigger foods include shellfish, cheese, celery, and tomatoes. Although the synthesis of food-specific IgE antibodies occurs, these foods are well tolerated when the patient is not exercising [3, 11].

Non-IgE-Mediated and Mixed-Type FA

The underlying mechanisms involved in non-IgE-mediated FA are not well understood. They occur mostly in children and are usually outgrown [12]. The classification of these FA is illustrated in Fig. 20.1, and the main symptoms, diagnostic procedures, and treatment recommendations for some of these are briefly summarized in Tables 20.2 and 20.3.

Diagnosis

The diagnosis of most FA is made using a detailed clinical history combined with diagnostic testing of the suspected food(s) identified through the clinical history, to confirm IgE sensitization. In addition, elimination diets and oral food challenges (OFC) can be used to establish clinical relevance of SPT or sIgE results, if necessary to confirm the diagnosis or to establish tolerability levels [2, 3, 5]. A physical examination may reveal chronic signs of asthma, allergic rhinitis, and atopic dermatitis, but is not diagnostic of FA [3].

Detailed Clinical History

The clinical history aims to identify the possible presence of FA, symptoms, trigger food, other known risk factors, and the underlying immunological mechanism (e.g., IgE, non-IgE, or mixed). Examples of structured questions that should be used to obtain the information are summarized elsewhere [2, 3, 5].

Diagnostic Tests

Both SPT and sIgE tests (Table 20.4) detect IgE-mediated sensitization to food allergens. A positive SPT or sIgE result in the absence of clinical history suggesting FA is not diagnostic. Testing for large panels of food allergens should be discouraged as false-positive SPT or sIgE results may lead to unnecessary dietary elimination. A negative SPT or sIgE result combined with a strong clinical history suggesting FA should be interpreted with caution and warrant further investigation [2, 5]. SPT is more commonly used than sIgE testing due to their lower costs and near instant results [3].

Table 20.2 Features of non-IgE-mediated food allergy (FA)

	Food protein-induced enterocolitis syndrome (FPIES)	Food protein-induced allergic proctocolitis (FPIAP)	Food protein-induced enteropathy (FPIE)
Age of onset	Infants <9 months, usually within first few weeks of life	Newborn or first few weeks of life	Infants or toddlers 0–24 months of age
	Delayed in breastfed infants to >5 months		
Primary FA	Infants: cow's milk (CM), soy	Infants: CM	Primarily: CM
	Older children/ adults (>1 solid food): Rice, oats, barley, meat, chicken, eggs, orange vegetables, fruit, fish, shellfish	Breastfed infants: CM, soy, or egg in mother's diet	Other: Soy, egg, rice, poultry, fish, shellfish
Symptom onset	Infants: Around 2 h after ingestion, resolve within 6–12 h	Delayed, 48–72 h after ingestion	Gradual onset within few weeks after intro of causal food
	Older children/adults: Delayed onset of reaction		
Symptoms	Infants: Severe form with protracted vomiting 1–3 h after feeding (bloody), diarrhea, hypotension, severe dehydration	Stools with fresh blood and mucus; infant is otherwise healthy	Chronic diarrhea, steatorrhea, failure to thrive
	Other: Irritability, anemia, abdominal distention, failure to thrive	Stools may be more frequent but diarrhea is absent	Also anemia, hypoalbuminemia
	Older children/adults: Mild chronic form with nausea, abdominal cramps, lethargy vomiting, hypoproteinemia		
Diagnosis	Presence of symptoms with improvement after elimination	Disappearance of bloody stools with causal food exclusion and reappearance after OFC	Clinical history
	Supervised OFC to confirm diagnosis if needed	SPT/sIgE not recommended	Often confirmed with endoscopy and biopsy
	SPT or sIgE usually negative and not recommended (however, 25% have raised sIgE to causative food)	Colonoscopy and biopsies usually not necessary and only used if symptoms persist after trial elimination diets	SPT and sIgE not recommended
Treatment	Completely eliminate causal food	With breastfeeding mothers, test the exclusion of CM first, then soy, and then egg	Completely eliminate causal food
	Avoid potentially cross-reactive food if not yet been introduced	With other infants, change to elemental formula	
	Avoid breastfeeding if it causes symptoms in child		
Symptom resolution	Symptoms improve within 24 h	Symptoms resolve within 48–72 h	Symptoms resolve within 1–3 weeks
Natural course	90% develop tolerance by age 3 years	Tolerance in most at age 1 year	Tolerance in most by age 2–3 years
	FPIES to solid food tend to resolve at older age		

Sources: Refs. [1, 4, 12, 13]

Table 20.3 Features of mixed-type IgE and non-IgE food allergy (FA)

	Eosinophilic esophagitis (EoE)	Eosinophilic gastroenteritis (EG)	Atopic dermatitis (AD)
Age of onset	Any age	Any age	Early infancy, can also present in children/adults
Primary causal food	Cow's milk (CM), soy, egg, wheat	CM, egg	Associated with FA in 35% of children with moderate to severe AD. Major food allergens: CM, egg, peanut
Symptoms onset	Gastrointestinal (GI) tract symptoms occur after eating but are chronic	Can be after intake but mostly delayed and chronic	Symptoms can be a combination of immediate within 2 h or delayed, 6–48 h after OFC
Symptoms	Symptoms after eating: Reflux, vomiting, dysphagia, abdominal pain, food impaction, cough, chest pain Young children: Reflux, feeding difficulties, failure to thrive, irritability Adolescents and adults: Dysphagia, food impaction, heartburn 50% have other atopic diseases (asthma, allergic rhinitis, eczema)	Can affect any part of GI tract from esophagus to colon, e.g., • eosinophilic gastritis • eosinophilic enteropathy • eosinophilic colitis Symptoms (depend on site affected): Ascites, nausea, vomiting, diarrhea, malabsorption, edema, obstruction, anemia, abdominal pain, weight loss Infants: Projectile vomiting Eosinophilic colitis: Abdominal pain, bloody stools, diarrhea 50% have other atopic diseases	In general, extreme pruritic, erythematous, morbilliform rash Immediate symptoms: Urticaria, angioedema, flush, and pruritus Delayed symptoms: Eczema flares with typical distribution at specific sites
Diagnosis	Diagnosis is challenging. SPT/sIgE indicate sensitization to multiple food and aeroallergens, can sometimes be helpful to indicate role of FA Diagnosis is confirmed with elimination diet (choose between a targeted one-food or six-food, four-food, and total elimination diet) for 2–6 weeks, followed by symptom improvement and OFC of one food at a time Endoscopy with multiple biopsies often performed and repeated after OFC to confirm histologic remission		Clinical history Children <5 years with moderate to severe AD should be evaluated for major allergens with SPT/sIgE testing Elimination diet, symptom improvement, and, if necessary, an OFC to confirm diagnosis
Dietary treatment	Completely eliminate causal food	Completely eliminate causal food	Eliminate causal food. Whether strict avoidance is always necessary is still being debated
Symptom resolution	2–6 weeks	2–6 weeks	2–6 weeks
Natural course	Likely persistent	Some resolve before age 5 years	AD usually resolves during childhood; however, if peanut or tree nut FA is the cause, it is more likely to be persistent
	Often poor response to anti-reflux drugs	In many patients, EG is persistent at 5 years of follow-up	

Source: Refs [1, 4, 12, 13]

Table 20.4 Characteristics of skin prick tests and serum-specific IgE tests for diagnosis of food allergy

	Skin prick testing (SPT)	sIgE
Advantages	Near instant results (within 15 min)	No risk of anaphylaxis
	High sensitivity (>90%)	Order from physician's office without specialist referral
	High negative predictive value accuracy, e.g., a negative SPT correctly indicates absence of IgE-mediated allergy in 90–95% of cases Can be performed on all age groups (even infants) Causes minimal discomfort Suspected food samples can be tested even if no commercial tests or food extracts are available	Can be used when SPT is contraindicated or ineffective: • pregnant women • significant anaphylaxis risk • severe skin disease (dermographism, extended or severe atopic dermatitis) • unable to stop using B-blockers or antihistamine for testing purposes
Disadvantages	Moderately specific (≈50%) Moderate positive predictive value (50%), e.g., a positive results indicate sensitization but not allergy Cannot be used as a screening tool Cannot predict prognosis Cannot predict severity of future reactions Requires referral to specialist/allergy clinic	High chance of false-positive results (e.g., the individual is not allergic) Lower sensitivity (e.g., it may miss 10–25% of true allergies) Cannot predict prognosis Cannot predict severity of future reactions
Procedure (short summary)	Apply small drop of commercially prepared food extract on the skin of the forearm or upper back 3 cm between drops One drop with positive control (histamine) and one with negative control (physiological glycerine) Prick (1 mm) each drop with a new sterile lancet Hold for 3 s to avoid bleeding Remove allergen with blotting paper If the individual is sensitive to the food IgE antibodies, a wheal will develop on the skin Measure wheal diameter after 15 min *Prick-to-prick method:* • to establish sensitization to: – Fresh food such as fruit and vegetables – Food for which commercial extracts are not available • method: Prick the fresh fruit or vegetable and then the patient's skin with the same lancet, followed by usual SPT protocol	Phlebotomy required Analyses of the blood sample for food sIgE antibodies using standardized assays in certified laboratories. • fluorescence enzyme immunoassay (FEIA) tests such a ImmunoCap® • Radioallergosorbent test (RAST®) Results available depending on laboratory schedule, usually the next day
Diagnosis of sensitization to a food	In general, a positive SPT result is defined by a wheal diameter ≥ 3 mm measured after 15 min Different wheal diameter cutoffs have been defined for egg, milk, and peanut FA in children	Food-specific diagnostic cutoffs for sIgE results where clinical symptoms are associated with a PPV >95% have been identified for several of the major food allergens A high total IgE level is often associated with multiple false-positive food sIgE levels and this is particularly important to consider in patients with severe eczema

Source: Refs [1, 2, 5, 13]

Other Diagnostic Tests

Component-resolved diagnostics (CRD) makes it possible to detect the exact proteins or epitopes in allergenic food against which the sIgE antibodies are being produced. CRD may help to discern true food allergens from cross-reactive allergen molecules and allow for predicting the severity of allergic reactions. Promising tests that are currently under investigation to effectively discriminate between IgE sensitization and clinical allergy include the basophil activation test (BAT) and mast cell activation test [3, 5].

Elimination Diets

Elimination diets are particularly useful in the diagnosis of non-IgE-mediated and mixed-type FA. The clinical history and SPT or sIgE testing should guide which food should be eliminated [3]. There are several different types of elimination diets that can be used including the allergy-directed diet (elimination of specific food(s)), the oligo-antigenic diet, the extensively hydrolyzed elemental diet, and the six-food or four-food group elimination diet. In order to achieve symptom relief, the elimination diet should be followed for a period of 2–4 weeks if suspecting IgE-mediated FA or for up to 6 weeks for non-IgE-mediated FA. The elimination phase is then followed by a well-planned reintroduction phase of eliminated allergens according to specified guidelines [13].

Oral Food Challenges (OFC)

The double-blind placebo-controlled oral food challenge is the gold standard procedure for objective diagnosis of FA [2, 3, 5]. As this test is expensive, labor intensive, and time-consuming [13], open or single-blinded OFC are often used in clinical practice [5]. OFC should be performed in a specialist practice where emergency treatment is available to treat symptoms of anaphylaxis [2, 5, 13]. Protocols for performing OFC exist and involve reintroduction to one food allergen at a time, in specific dosages that increase in a stepwise manner over several hours while monitoring symptoms [2, 13].

Alternative Tests

The use of alternative tests for the diagnosis of FA or intolerances should be discouraged as evidence in support of their use is lacking. Examples include electrodermal tests, hair analyses, applied kinesiology, IgG and food-specific IgG4 levels, iridology, lymphocyte stimulation, gastric juice analyses, endoscopic allergen provocation, cytotoxicity assays, and facial thermography [1, 5, 8].

Monitoring for Tolerance

Most children outgrow FA to egg, CM, wheat, and soy by adolescence. Fish, shellfish, peanut, and tree-nut allergies most often continue into adulthood [3]. Children who outgrow peanut allergy can at a later stage reacquire the allergy, especially if peanuts have been avoided [4]. Favorable factors associated with outgrowing FA include younger age, type of allergy, lower sIgE levels, mild symptoms, and absence of other FA. A decline in IgE sensitization indicates that the patient is likely outgrowing the FA and may help in deciding when an oral food challenge (OFC) is warranted [14]. It is recommended that diagnostic tests (SPT or sIgE) be repeated every 12–18 months in children <5 years old and every 2–4 years in those >5 years old to establish change in sensitization [14]. An OFC is the gold standard procedure to confirm that FA is no longer present [5, 14].

Nutritional Management

General Dietary Recommendations for FA

Dietary elimination of the food allergen(s) is essential in the management of FA [13]. Oral intake may result in mild to severe reactions even when ingesting a trace amount of the allergen [14]. The severity

of symptoms may change over time, e.g., a child may initially only present with hives to peanut exposure, but in subsequent accidental exposures may develop anaphylaxis [14].

Self-elimination of foods can cause nutritional deficiencies, significant stress, and poor quality of life. Referral to a dietitian is important to ensure effective dietary management of FA. During dietetic consultations, tools, education, and practical advice on any of the following can be provided [1, 2, 10, 13–15]:

- Diet sheet indicating food allowed and eliminated as well as alternatives for these.
- Well-planned nutritionally balanced avoidance diet.
- Evaluation of nutritional status, including growth monitoring in children.
- Analyzing detailed food diaries to identify possible causative food, hidden ingredients, or pattern of reactions.
- Supplementation if necessary.
- Reading labels and examples of terms used in the ingredient list that refer to the causative allergen.
- Commercial food products and available brands that can be used instead of the usual product that contains the allergen (e.g., imitation cheese instead of regular cheeses).
- Recipe adaptations. Provide example recipes and alternatives that can be used instead of CM, egg, flour, etc.
- High-risk situations where cross-contamination is likely and how to deal with this, e.g., ice cream parlors, seafood and Asian restaurants, bakeries (peanut, egg, CM, and tree nuts), and buffets (all food).
- Guidelines for eating in restaurants: order plain food, be careful of fried food, sauces, condiments, pastries, bakery items, and desserts.
- Tips for travelling abroad as this can be particularly challenging. Translated information may be necessary on food products and emergency treatment.
- Special occasions such as children's birthday parties. There may be a need to inform the host of the FA and take own food.
- School food environment: ideas for lunch boxes and arrangements with school canteen.
- Cross-reactive food. Cross-reactivity often occurs between the following food and exclusion of the other food in the same group may be necessary:
  - Peanuts with other tree nuts and sesame.
  - CM with goat, sheep, and other mammalian milk.
  - Fin fish with all fish species.
  - Chicken eggs with eggs of other species such as turkey, duck, and goose.
- Contamination of food during preparation, serving, and storage. Provide designated areas in fridge and storage area. Label dishes, cutlery, crockery, and cutting boards that are used solely for allergen-free food preparation. The use of household disinfectant cleaning sprays or sanitizing wipes to eliminate the allergen from surfaces.
- Breastfeeding. Although food allergens are detected in breastmilk, breastfeeding remains the first choice milk for infants with FA.
- Milk choice for infants with cow's milk protein allergy (CMPA) that are formula fed:
  - Partially hydrolyzed formula milk is inappropriate for CMPA.
  - Extensively hydrolyzed milk is the first choice for mild to moderate CMPA.
  - Amino acid-based formula is indicated for a subgroup of infants, usually those with severe CMPA.
  - Plant-based milks (rice and oat milk) are not suitable as a sole infant formula, but might be used in older children, adolescents, and adults.
  - Food reintroduction and "milk ladder."

Managing Oral Allergy Syndrome

Patients with OAS must avoid the raw trigger fruit and vegetables. However, they may eat the trigger fruit and vegetable when cooked or processed as structural changes in the proteins occur which reduce

the binding capacity to IgE antibodies. In some instances, peeling the trigger fruit or vegetable may also be effective as the epitopes are often in the skin [1].

Ingestion of Baked Cow's Milk or Egg

About 63–84% of children with CM or egg allergy can tolerate baked CM or egg as the extensive heating modifies the proteins to be less allergenic and interactions with a food matrix, such as wheat, during baking decrease IgE recognition. Adding baked CM and egg to the diet of a child with CM or egg allergy generally improves variety of food choices and increases their likelihood to outgrow the CM and egg allergies. Tolerance to baked egg and CM should be established using physician-led OFCs according to standardized protocols [16].

Prevention

The avoidance of major allergenic food during pregnancy, breastfeeding, and infancy is not recommended for allergy prevention. Most feeding guidelines worldwide recommend exclusive breastfeeding for the first 4–6 months of life and early introduction of allergenic foods [3, 9, 15].

The introduction of age-appropriate amounts of peanut products at age 4–6 months in infants with severe eczema, egg allergy, or both is now recommended to reduce the risk of peanut allergy [17]. Research on whether early introduction of the other major allergenic food also prevents FA is ongoing [8, 9, 17].

Emerging Therapeutic Options

Oral immunotherapy (OIT) entails ingestion of increasing doses of the allergen over months until a top maintenance dose is achieved with the goal to increase the threshold that triggers an allergic reaction or achieve desensitization [2, 9, 18]. The first treatment for peanut allergy, an OIT named Palforzia, has been approved in January 2020 by the US Food and Drug Administration for patients aged 4–17 [6].

Epicutaneous immunotherapy (EPIT) and sublingual immunotherapy (SLIT) are immunotherapies currently under investigation. EPIT involves a patch with the allergen that is placed on the skin, while with SLIT the food protein extract is placed under the tongue [2, 5, 9, 18].

Food Intolerance

Food intolerance is a non-allergic reaction to food with the immune system not being involved (Fig. 20.1) [1, 7]. The differences and similarities in symptoms between FA and food intolerance are summarized in Table 20.1.

Types of Food Intolerance

Enzymatic Deficiencies or Transport Defects

The majority of reported food intolerance is caused by either enzymatic deficiencies or transport defects in the gastrointestinal (GI) tract, which leads to incomplete digestion or absorption of food that contains substances collectively termed FODMAPs (fermentable oligo-, di-, monosaccharides, and polyols). These substances are short-chain carbohydrates that consequently enter the colon where bacteria will ferment them and produce gas. This gives rise to symptoms of food intolerance in some

individuals such as abdominal distention, cramping, bloating, and flatulence. Nausea, vomiting, and osmotic diarrhea may also occur as increased water in the lumen is needed to dilute the osmotic load. FODMAPs include lactose (disaccharide), fructose (monosaccharide), fructans and galactans (oligosaccharides), and polyols such as sorbitol, mannitol, and xylitol. Individuals may have a food intolerance to one of these FODMAPs (e.g., most notably lactose or fructose intolerance) or a combination of different ones [7, 19].

Reactions to Pharmacological Agents in Food

Some individuals are sensitive to certain pharmacological agents in food such as vasoactive or biogenic amines (e.g., histamine, tyramine, and phenylethylamine). Histamine intolerance occurs mostly due to enzyme deficiencies, while a drug-food interaction between tyramine in food and monoamine oxidase inhibitors leads to majority of cases of tyramine intolerance. Symptoms range from migraine headaches and dizziness to urticaria, eczema, nausea, and vomiting [7, 20].

Reactions to Food Additives

Intolerance to specific food additives such as salicylates, nitrates and nitrites, glutamates (e.g., monosodium glutamate), artificial colorants (e.g., tartrazine), benzoates, butylated hydroxyanisole (BHA), and butylated hydroxytoluene (BHT) can also cause adverse reactions manifesting in a variety of symptoms such as hives, asthma, angioedema, migraine, and GI tract symptoms. Underlying mechanisms have been proposed, but the pathophysiology is, in general, poorly understood [7, 20].

Nonceliac Gluten/Wheat Sensitivity

Individuals with nonceliac gluten/wheat sensitivity (NCG/WS) develop GI symptoms to gluten/wheat exposure, but do not have celiac disease or wheat allergy. These individuals report that dietary gluten elimination results in improvement of a wide array of symptoms; however, clinical studies show conflicting results [7].

Diagnosis

The most reliable method for diagnosing food intolerance is avoidance of possible trigger food followed by symptom improvement, as well as gradual reintroduction of the food followed by symptom induction. A low-FODMAP diet should also be followed for 4–6 weeks, thereafter re-challenges of each FODMAP group should be done over 6–8 weeks, and lastly reintroduction of FODMAPs should occur [7, 19].

Histamine intolerance is diagnosed if two or more of the typical symptoms are present and improvement of symptoms is achieved through a histamine-free diet or antihistaminergic medication [7]. Hydrogen and/or methane breath testing can be used to identify lactose or fructose malabsorption in those experiencing symptoms [21]. Breath tests for sorbitol, mannitol, fructans, and galactans are not useful for identifying malabsorption and are therefore not recommended.

Nutritional Management

Food sources of lactose include milk produced by cows, sheep, and goats and products from these such as yoghurt, ice cream, custard, buttermilk, and soft cheeses. It is unnecessary to completely eliminate lactose from the diet as the majority of lactose-intolerant individuals can consume about 5 g lactose (100 mL milk) or 12–15 g lactose (250–320 mL milk) daily, or even higher amounts, without any symptoms [1, 21]. The tolerance threshold is dependent on several factors and should be individually determined. Fermented products such as yoghurt and buttermilk are better tolerated. Including a

tolerable amount of lactose in the diet is important as dairy provides several essential nutrients, such as calcium and vitamin B_{12}. Although lactase supplements can be prescribed, this is expensive and unnecessary for the majority of patients [21].

Fructose is naturally found in fruit, sugarcane, and honey. It is also added as a sweetener to sugar-sweetened beverages (SSBs) and other food, often as high-fructose corn syrup (HFCS). Dietary recommendations include limiting the total fructose content of a meal/snack. Foods that usually contain high fructose content per standard serving include dried fruit, fruit bars, two or more fresh fruits, fruit juice, fruit concentrate, fortified wines, food sweetened with HFCS, SSBs, and indulgent quantities of confectionaries. The intake of "free fructose" food should be limited [19]. Examples of foods high in fructans, galactans, and polyols can be found in FODMAP diet guidelines. It is advised to restrict FODMAPs globally using a low-FODMAP diet protocol rather than restricting individual FODMAPs [19].

Food additives and pharmacological agents are widely spread in food and elimination may lead to nutritional inadequacies; careful planning of such elimination diets is necessary [9, 20].

Conclusion

Food allergies and intolerances are concerning public health problems worldwide. The underlying mechanisms involved in food allergies (FA) and food intolerances are different; an immune response is only triggered in FA. However, a variety of symptoms caused by food intolerances are similar to those caused by FA. The adverse reactions of food intolerance are less severe and small tolerable amounts of the offending food/substance might still be allowed. FA, by contrast, may cause life-threatening anaphylaxes; complete dietary elimination of the allergen is necessary to prevent symptoms. It is therefore important to rule out FA through clinical history, diagnostic testing, and oral food challenges. Referral to a dietitian is necessary to help educate patients and plan nutritionally balanced and individualized diets.

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Suggested Further Readings

American Academy of Allergy, Asthma, and Immunology. www.aaaai.org
Asthma and Allergy Foundation of American. www.aafa.org and www.kidswithfoodallergies.org
European Academy of Allergy and Clinical Immunology. http://www.eaaci.org/resources/position-papers.html
Food Allergy Research and Education (FARE). https://www.foodallergy.org/resources

Nutrition in Patients with Diseases of the Liver and Pancreas

21

Roman Perri and Erin A. Bouquet

Keywords

Cirrhosis · Liver disease · High-protein diet · Acute pancreatitis · Chronic pancreatitis · Obesity-related liver disease

Key Points

- Patients with liver disease are at high risk for malnutrition and should be screened at regular intervals as malnutrition is associated with higher mortality.
- A high-protein diet of 1.2–1.5 g/kg/day is recommended for all patients with cirrhosis. Sodium restriction is reserved for those with ascites or other clinical signs of volume overload.
- Patients with cirrhosis should be screened for vitamin and mineral deficiencies and offered supplementation if necessary. The most common deficiencies are in fat-soluble vitamins.
- Patients with acute pancreatitis should be offered nutrition as soon as tolerable. Those with severe acute pancreatitis are at higher risk for malnutrition and should be offered early enteral feeding if needed.
- Chronic pancreatitis can result in exocrine insufficiency which may be ameliorated with pancreatic enzyme replacement therapy.

Introduction

Diseases of the liver and the pancreas are vast in number and varied in physiology. However, cirrhosis and pancreatitis (both acute and chronic) are two of the most common diseases encountered in general practice. These diseases are highly morbid and often lead to frequent contact with the healthcare system and poor quality of life. One aspect of these diseases that is often overlooked is that of nutrition. Specific evidence-based strategies exist that, when utilized, can meaningfully impact not only the disease morbidity but also patient quality of life.

R. Perri (✉) · E. A. Bouquet
Division of Gastroenterology, Hepatology and Nutrition, Vanderbilt University Medical Center, Nashville, TN, USA

Department of Internal Medicine, Vanderbilt University Medical Center, Nashville, TN, USA
e-mail: roman.perri@vumc.org; erin.a.bouquet@vumc.org

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Patients with Liver Disease

Cirrhosis is a severe disease with a high mortality rate with as many as two million global deaths each year. Complications of cirrhosis include ascites, gastrointestinal hemorrhage, hepatic encephalopathy, and infection, all of which also confer a high degree of morbidity [1]. While advances in the treatment of hepatitis C virus have reduced mortality due to viral liver disease, the mortality rates associated with alcoholic liver disease and non-alcoholic fatty liver disease (NAFLD) continue to increase [2]. The management of cirrhosis is challenging and requires optimization of many factors, including nutritional status.

Patients with cirrhosis are at high risk for protein-calorie malnutrition (PCM) and its associated complications. Up to 90% of patients with cirrhosis have findings of PCM, and the prevalence of PCM increases with disease severity [3]. Patients with alcoholic liver disease have the highest rates of PCM when compared to patients with cirrhosis due to other etiologies, and PCM is an independent predictor of morbidity and mortality [4]. For this reason, those caring for cirrhotic patients should understand the underlying mechanism of and treatment strategies for PCM in liver disease.

Malnutrition in liver disease arises for several reasons. Patients with ascites and gastrointestinal edema experience nausea and early satiety which leads to poor intake. Those with hepatic encephalopathy may struggle with the mechanics of eating and have little desire to eat. Impairment in bile acid metabolism may result in small bowel maldigestion. Additionally, the liver is a major site of protein catabolism and glycogen storage; disruption of those processes results in malnutrition [3, 5]. Ultimately, malnutrition in patients with cirrhosis results in sarcopenia, an independent predictor of increased mortality.

Patients with liver disease should be screened for PCM through history, physical examination, and objective data. Physical examination identifies temporal and proximal muscle wasting and decreased muscle strength, which indicate severe malnutrition and are less sensitive for those in early stages of malnutrition. As obesity rates increase, it has become increasingly difficult to identify those with significant sarcopenia as BMI does not distinguish between adipose and non-adipose mass, an important distinction when assessing nutritional status [6].

Laboratory measurements including serum albumin, transthyretin (prealbumin), and international normalized ratio (INR) have traditionally been used to estimate body protein stores, and therefore PCM, but they are imperfect measures and susceptible to confounding by concomitant hepatic dysfunction and inflammation. Assessment of skeletal muscle mass on imaging (based on abdominal muscle mass or psoas muscle diameter) is a useful metric, but specialized software is required and is not widely available [5, 7]. These limitations in identification of PCM require clinicians to pay close attention to subtle signs of malnutrition in this patient population.

Dietary modifications are of paramount importance in the management of patients with advanced liver disease. A high-protein diet is an important recommendation that is made to all patients with cirrhosis, regardless of nutritional status. A goal of 1.2–1.5 g/kg/day is recommended to counteract the muscle breakdown that occurs in advanced liver disease. The presence of hepatic encephalopathy does not warrant protein restriction. Very-low protein intake (<0.8 g/kg/day) has been shown to independently affect mortality [8]. For those patients with decompensated cirrhosis or malnutrition, the total calorie goal should be set at 30–35 kcal/day, often divided over 4–6 small meals to combat symptoms of early satiety and anorexia. A protein-enriched bedtime snack can help patients increase their daily protein intake and is associated with improved clinical outcomes.

Sodium restriction is recommended in the presence of ascites or other signs of volume overload. Ascites is the most common complication of cirrhosis and occurs in 50–60% of patients within 10 years of diagnosis. Ascites develops due to portal hypertension, splanchnic vasodilation, and impaired renal sodium excretion. A diet that restricts sodium intake to 2000 mg/day is recommended for patients with ascites. Daily fluid restriction may be warranted in patients with significant dilutional hyponatremia [9].

Appropriate vitamin supplementation is an important consideration in patients with cirrhosis. These patients are often deficient in fat-soluble vitamins due to poor intake and malabsorption. Vitamin D deficiency results in osteopenia and osteoporosis. Repletion is inexpensive and well tolerated. Vitamin A deficiency can result in visual changes, and levels should be monitored periodically, with replacement provided if necessary. Over-repletion of vitamins A and D may cause adverse outcomes, so levels should be monitored during repletion. Patients may also have deficiencies in B vitamins and folate as well as in minerals such as copper and zinc [3]. B1 (thiamine) deficiency is common in those with alcoholic liver disease and may result in neurological dysfunction. Zinc deficiency can cause dysgeusia, and replacement may result in better dietary intake and improved nutritional status [10].

Deficiencies in the three essential branched-chain amino acids (BCAAs) valine, leucine, and isoleucine are common in patients with chronic liver disease. Supplementation with BCAAs may improve hepatic encephalopathy, reduce muscle catabolism, and improve quality of life. BCAAs may be most beneficial in patients with sarcopenia, and supplementation with BCAA is a reasonable choice especially in those patients requiring a supplemental protein source. These supplements are well tolerated but may be difficult to obtain due to poor insurance reimbursement [11].

The prevalence of obesity-related liver disease and cirrhosis is rising. This creates a unique situation in which the need for adequate nutrition is balanced with the need for weight loss. Patients with obesity-related liver disease should be encouraged to lose 7–10% of their body weight. Weight loss to this degree results in reduced hepatic steatosis and decreases the rate of liver disease progression. Strategies for weight loss should include caloric limitation. Recent literature points to the benefit of a Mediterranean-type diet in patients with cirrhosis. This diet, which is discussed more thoroughly in Chap. 15, encourages consumption of fruit, vegetables, and whole grains, while limiting processed sugars and unrefined carbohydrates has been shown to reduce hepatic steatosis and improve insulin resistance [12]. Finally, a high-protein diet, as detailed previously, should be recommended to this patient population, regardless of BMI.

Often, despite diligent effort, patients with chronic liver disease are unable to maintain oral intake due to factors such as hepatic encephalopathy, early satiety, and frailty. In these patients, alternative methods of nutrition are considered. Enteral feeding remains the preferred method for nutrition whenever possible including via feeding tube [13]. Enteral nutritional supplementation should not be initiated without first discussing goals of care and anticipated disease course. Enteral nutritional supplementation may be a necessary choice for those awaiting liver transplantation to decrease the severity of malnutrition and improve surgical outcomes. Total parenteral nutrition is a well-tolerated means of nutritional support but can lead to parenteral nutrition-associated liver disease and bloodstream infections [14, 15].

Patients with Pancreatic Disease

Acute pancreatitis is an inflammatory disease of the pancreas that results in nausea, vomiting, and abdominal pain that may be worsened by oral food intake. The diagnosis of acute pancreatitis is based on the presence of typical epigastric abdominal pain, elevations in serum amylase and lipase, and often cross-sectional imaging showing inflammation of the pancreas. Treatment strategies for acute pancreatitis include early and aggressive intravenous fluid resuscitation coupled with analgesics. Previously, bowel rest was included in this strategy; however, starvation has been associated with increased intestinal inflammation and atrophy. Oral intake should be resumed as soon as clinically tolerated and often can be reinitiated within a few days of presentation [16]. A solid diet is preferred as studies have shown no increased length of hospitalization with initiation of a low-fat solid diet when compared to a clear liquid diet [17].

Severe acute pancreatitis is characterized by a systemic inflammatory response syndrome and can be accompanied by multiorgan failure associated with high morbidity and mortality. Patients are often

unable to tolerate oral intake for an extended period of time and risk malnutrition due to the catabolic nature of the disease process. They should be evaluated for enteral nutrition once the severity of their disease is appreciated. Studies show benefit in starting enteral nutrition within 24–72 h of admission via either nasogastric or nasojejunal tube with no clear preference for formulation of feeds. If patients have difficulty tolerating enteral feeds, strategies such as decreasing the rate of infusion or changing to a different formulation may improve tolerability. Because parenteral nutrition has been associated with higher risk of infection and other complications, its use should be avoided unless absolutely necessary [18, 19].

Chronic pancreatitis is a disease caused by progressive inflammation of the pancreas that leads to fibrosis and eventual loss of both exocrine and endocrine function. The most common etiology of chronic pancreatitis is alcohol use disorder, but it may also result from genetic and autoimmune disorders. Symptoms may be similar to those of acute pancreatitis and include abdominal pain, nausea, and anorexia, all leading to malnutrition. The pancreas acts as an exocrine gland by producing enzymes such as lipase and trypsin that aid in fat digestion. In chronic pancreatitis, acinar cell destruction leads to impaired enzyme production, and overt steatorrhea occurs once enzymatic function falls to <10%. A diagnosis of pancreatic exocrine insufficiency can be confirmed by measuring fecal elastase-1, with low levels confirming the diagnosis [20].

Pancreatic enzyme replacement therapy (PERT) should be initiated in patients with pancreatic exocrine insufficiency but should not be routinely offered in those without exocrine dysfunction. PERT may be started at 20,000–50,000 IU (lipase) with every meal (half dose with snacks) and uptitrated based on response. Some patients may require up to 90,000 IU. Patients should ingest PERT along with meals and snacks and not before or after. Proton pump inhibitors may improve the effectiveness of pancreatic enzyme replacement. PERT is typically effective in relieving steatorrhea and allows patients to eat a normal fat diet. Low-fat diets are only recommended in patients who have steatorrhea refractory to PERT supplementation that can lead to malabsorption of fat-soluble vitamins. Patients with chronic pancreatitis should be screened for deficiencies in these vitamins at least annually [18, 21]. Patients should also be screened for type 3c diabetes mellitus (T3cDM) (pancreatogenic diabetes mellitus). T3cDM may be difficult to manage with oral diabetes agents and often requires insulin therapy. These patients should be counseled on the nutritional goals of a diabetic diet [22].

Even in patients without overt exocrine insufficiency, malnutrition is common. This is due in part to the symptoms of chronic pancreatitis which can be difficult to control. Pain in particular leads to frequent hospitalizations and poor quality of life. Analgesia with non-opiate medications is preferred but is often ineffective. Endoscopic and surgical options to relieve pain are available but must be carefully considered on a case-by-case basis. Patients who are malnourished secondary to pain should be advised to eat small, frequent meals to improve tolerance. Enteral nutrition is sometimes necessary in severe cases, but parenteral nutrition is rarely indicated due to high risk for complications [20].

Conclusion

The management of cirrhosis and pancreatitis is complex and treatment requires manipulation of many variables. Optimal treatment of these diseases should involve early and careful assessment of nutritional status to improve disease outcomes. By working to educate and empower patients to improve nutritional status, quality of life and overall outcomes can be improved. With the information presented, clinicians should be able to identify and treat these patients who are at high risk for malnourishment. Additionally, a multidisciplinary approach involving colleagues who specialize in nutrition should also be considered for all patients.

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Nutrition Care for Kidney Disease and Related Disorders

22

Desiree de Waal

Keywords

Chronic kidney disease (CKD) · Acute kidney injury (AKI) · End-stage kidney disease (ESRD) Acidosis · Hemodialysis · Peritoneal dialysis · Kidney stones · COVID-19

Key Points

- Lifetime risk of chronic kidney disease (CKD) is increasing.
- Diabetes and hypertension are the leading causes of CKD.
- CKD is graded using estimated glomerular filtration rate (eGFR) and urine albumin-to-creatinine ratio (UACR).
- Kidney disease increases the risk for cardiovascular disease. Fluid retention may lead to severe hypertension, pulmonary edema, pericarditis, and heart failure.
- Appropriate nutrition choices can reduce incidence of acidosis, prevent hyperkalemia, improve nutrition biomarkers, and slow the progression of CKD.
- CKD is a risk factor for poor outcomes of COVID-19.
- A referral to a dietitian with expertise in kidney disease should be recommended upon diagnosis of CKD.

Introduction

Chronic kidney disease (CKD) has a major effect on global health and is an important risk factor in cardiovascular disease. It was ranked as the 12th leading cause of death worldwide in 2017 [1, 2]. The Centers for Disease Control and Prevention (CDC) estimates that kidney diseases are the eighth leading cause of death in the United States in 2019 with an estimated 15% of the adult population being affected with most adults not knowing they have it [3]. Diabetes and hypertension are the leading causes of kidney disease. CKD is detected and monitored by estimated glomerular filtration rate (eGFR) and urine albumin-to-creatinine ratio (UACR). CKD is a progressive disease and is defined as a reduction of kidney function (eGFR <60 mL/min/1.73 m^3 for >3 months) and/or evidence of kidney

D. de Waal (✉)
University of Vermont Medical Center, Department of Nephrology, South Burlington, VT, USA
e-mail: desiree.dewaal@uvmhealth.org

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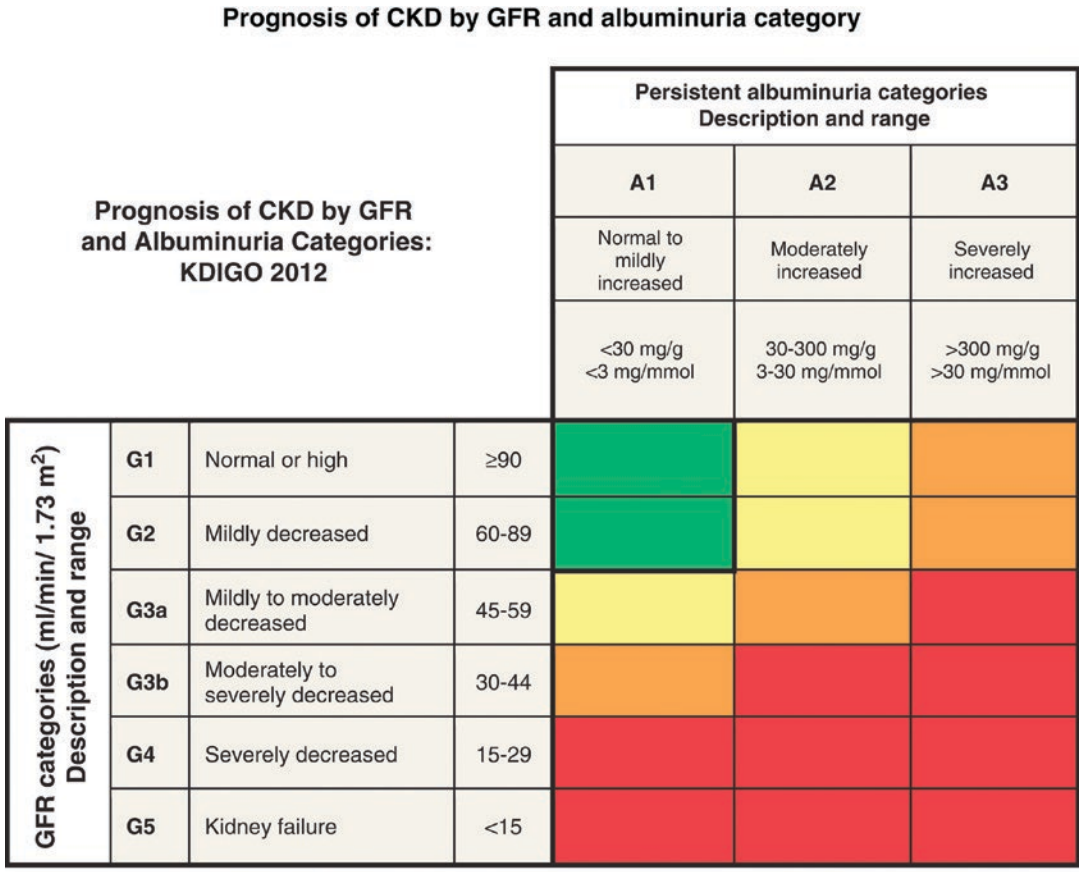

Fig. 22.1 Prognosis of CKD by GFR and albuminuria category [5]. (Reproduced with permission from Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group [5])

damage, including persistent albuminuria (≥30 mg of urine albumin per gram of urine creatinine for >3 months). The classification and relative risk ranked by GFR and albuminuria is reviewed in Fig. 22.1 with colors showing which groups of patients are at higher risk for major health outcomes [4, 5]. One of the major goals for CKD is a reduction in new cases of kidney disease and its complications, disability, death, and economic cost [6].

The basic function of the kidney includes the removal of waste products from the blood while regulating body water and electrolytes. As kidney disease progresses, altered nutrition biomarkers are observed which may be related to poor dietary habits [7]. The typical American is high in protein and processed foods which can affect the balance of the body's minerals, including electrolytes, and contributes to the uremic environment of the digestive system. Evolving evidence of a link between the gut and kidney health [8] suggests a need for emphasis on nutrition for the care of a patient with compromised kidney function.

Patients do not notice any symptoms in the early stages of CKD. But the presence of kidney disease increases the risk for cardiovascular disease, including heart attacks and strokes. Fluid retention may lead to edema, severe hypertension, and heart failure. Other common health-related consequences in CKD include anemia, metabolic acidosis, hyperkalemia, and bone and mineral disorders [5].

Kidney failure or end-stage renal disease (ESRD) refers to the condition where the kidneys are no longer able to remove waste products. It is typically defined as an eGFR <15 mL/min/1.73 m^2 [3, 5]. Early treatment of CKD with drugs and lifestyle changes can decrease the rate at which CKD worsens and can prevent additional health problems. This helps improve patient outcomes [6]. However, the numerous and sometimes conflicting guidelines for CKD can make providing appropriate care challenging.

Common Disorders in CKD and Their Relationship to Nutrition

Metabolic Acidosis

Accumulating evidence suggests that acidosis is not only a consequence of but a contributor to CKD progression [9]. The kidney maintains the balance of bicarbonate levels so when kidney function is compromised, the ability to neutralize acid is compromised. Acidosis is defined as a serum bicarbonate level < 22 mEq/L. Metabolic acidosis can contribute to bone disease, hyperkalemia, and protein catabolism with decreased protein synthesis. The diet consumed by most Americans results in a high dietary acid load because of its high content of animal protein and low content of fruits and vegetables [10]. The findings from studies that investigated dietary acid load and the incidence of CKD suggest a potential avenue for reducing CKD risk through diet [11]. Increasing the intake of fruits and vegetables improves serum bicarbonate levels, much like the use of sodium bicarbonate, and does not induce hyperkalemia. The addition of fruits and vegetables to the diet has also demonstrated some preservation of kidney function [12, 13].

Hyperkalemia

Hyperkalemia is often seen in patients in the later stages of kidney disease. Reduced potassium excretion and metabolic acidosis induce high serum potassium levels. Clinical risk factors for hyperkalemia include poorly controlled diabetes, cardiovascular disease, heart failure, urinary obstruction, severe constipation, plus some medications (such as certain blood pressure medications, NSAIDS) [14, 15]. A high dietary acid load (animal protein and dairy products) is not only high in potassium but also contributes to the metabolic acidosis found in CKD. Other contributors to the dietary potassium load include the use of low-sodium products (such as salt substitutes or low-sodium canned soups which have added potassium chloride in place of sodium chloride), many beverages (energy, electrolyte, coffee, smoothies, and juices), and a high chocolate intake. Patient education intended to reduce potassium levels is often focused on fruits and vegetables that are high in potassium rather than other causes of their hyperkalemia. Recent literature indicates that fruits and vegetables are not necessarily the cause of hyperkalemia; in fact, they can help manage acidosis [12, 13].

The management of hyperkalemia requires a review of clinical risk factors and medications for any that may cause high potassium levels. It is important to manage diabetes to prevent hyperglycemia. Incidents of hypoglycemia would be better treated with glucose tablets, cranberry juice cocktail, or apple juice which is lower in potassium rather than orange juice. Beverages containing phosphorus additives such as colas or fruit punch are contraindicated to treat hypoglycemia in kidney disease. It is preferable to manage acidosis with diet, though sodium bicarbonate is effective. A high-fiber diet, which includes fruits and vegetables, will also help manage constipation, a risk factor for hyperkalemia.

Bone and Mineral Disorders

Chronic kidney disease-mineral bone disorder (CKD-MBD) is a systemic disorder of mineral and bone metabolism manifested by either one or a combination of the following three components: abnormalities of calcium, phosphorus, parathyroid hormone (PTH), fibroblast growth factor 23 (FGF23), and vitamin D metabolism; abnormalities in bone turnover and mineralization; and extra skeletal calcification. In the early stages of CKD, there are physiologic adaptations that prevent phosphorus retention so hyperphosphatemia is generally only seen in the later stages of CKD. Calcium balance in CKD is poorly understood, but the recommendation is to provide adequate calcium in diet and avoid excessive amounts in the form of calcium supplements and calcium-based phosphate binders. As CKD progresses, vitamin D levels decline and parathyroid hormone levels rise. Long-term high phosphorus blood levels contribute to disequilibrium in bone minerals causing secondary hyperparathyroidism (increased levels of PTH), which contributes to adverse CKD outcomes [16–19].

One of the most challenging areas for patients is the control of their phosphorus levels through their choices of food and beverages. Evidence shows that a diet high in phosphorus contributes to adverse kidney disease outcomes including vascular calcification, an additional cardiovascular risk in CKD. The source of phosphorus is important to consider when educating patients. Phosphorus occurs naturally in foods which contain protein, but processed foods often have phosphorus added. Patients who frequently eat processed food and fast foods therefore have a high dietary phosphate load. A diet high in animal protein also contributes to the phosphorus load. On the other hand, vegetable proteins are not as bioavailable and have been shown to decrease FGF23 levels, a marker of CKD bone and mineral disorder [20, 21]. If vitamin D levels are low, supplementation of nutritional vitamin D is recommended [18]. The RD/RDN with expertise in kidney disease is able to recommend the best nutrition therapy to help manage CKD-MBD.

Kidney-Gut Connection

Many patients with CKD complain of digestive disorders. Recent literature on how the gut microbiome is influenced by diet has brought about a shift in the focus on dietary management in CKD [22]. Uremia can impair the intestinal barrier structure of the gut due to the accumulation of gut-derived uremic toxins. Changes in the gut microbiome may have a role in systemic inflammation and CVD [23]. Research in the area of microbial modulating therapies, in the form of probiotics, is promising but is often hampered by the unfavorable milieu in the gut of the CKD patient. For probiotic therapy to have a favorable outcome requires an improvement in the gut's biochemical microbiome with the addition of prebiotic nutrients to help the bacteria in the digestive tract to thrive and grow. Prebiotic foods contain certain types of non-digestible carbohydrates (soluble fiber) found in fruits, vegetables, and whole grains which promote the health of the gut. Evidence for gut microbial modulating therapy is preliminary and hopefully in coming years will lead to positive advances in the treatment of CKD.

Medical Nutrition Therapy in Kidney Disease

Sound nutrition is crucial in healthcare models of wellness, health promotion, disease prevention, and disease management. One key aspect of this is medical nutrition therapy (MNT) and it should play an important role in the treatment of CKD. The key practitioners of MNT are registered dietitians (RDs) and registered dietitian nutritionists (RDNs). They use an evidenced-based application of the nutrition-care process including food and/or nutrient delivery, nutrition education, nutrition counseling, and coordination of nutrition care [24].

Eating patterns are often entrenched as part of a person's lifestyle, and there is no immediate negative response to poor dietary choices. As a result, dietary changes are one of the most challenging obstacles patients face. An RD/RDN with experience in kidney disease is uniquely qualified to coach patients with positive dietary choices that can help preserve their kidney function. Because the nutrition involved with CKD is highly specialized, a RD/RDN who specializes in kidney disease has more training in how foods affect kidney function, bones, and the heart. Unfortunately, MNT provided by a RD/RDN for kidney disease is presently underutilized. With costs of kidney disease rising, it seems prudent to recommend a therapy that has been shown to delay the progression of kidney disease and improve biomarkers [25]. Quality of life is dependent on the ability to make choices, and offering broader dietary choice provides patient empowerment which contributes to greater enjoyment of life with a better nutrition status. MNT has the potential to improve quality of life of patients with kidney disease by improving their nutritional biomarkers, slow the decline in kidney function, and keep them off dialysis longer. MNT by a RD/RDN specializing in kidney disease should be recommended as one of the first therapies as soon as a medical diagnosis of kidney failure or even proteinuria has been made.

Food guides, such as the USDA MyPlate, help guide patients into learning which foods are best and in what amounts. Chapter 40 provides detailed information on food guides as well as for dietary choices in general. Mediterranean eating patterns which include the DASH diet (Dietary Approaches to Stop Hypertension) are high in fruits, vegetables, and whole grains with adequate amounts of calcium and protein. Diets that are either vegetarian or consist mainly of plant-based foods have been found to help slow the decline in kidney function, probably due to their lower content of available phosphorus and generous content of phytochemicals that are anti-inflammatory. MNT with a RN/RDN who has renal experience can help guide CKD patients into making better food choices so as to reduce the incidence of acidosis and manage hyperkalemia and the balance of bone minerals [24, 25].

End-Stage Renal Disease

End-stage renal disease (ESRD) refers to the condition where the kidneys are functioning minimally or not at all. Dialysis helps keep the body in balance by removing waste products and excess water, maintaining the proper levels of certain chemicals (potassium, sodium, and bicarbonate), and helping to control the blood pressure. Dialysis prolongs life but some patients may choose not to have dialysis and instead follow conservative care. MNT in ESRD focuses on protein, phosphorus, potassium, sodium, and fluid. The diet is individualized based on laboratory levels, the patient's nutrition status and lifestyle, and the modality of dialysis. With patients who choose conservative care rather than dialysis, the focus is on managing the symptoms of uremia. A kidney transplant center will assess if a patient is a suitable candidate for a kidney transplant [5].

In hemodialysis, the choice is in-center (HD), home hemodialysis (HHD), or nocturnal home dialysis (NHD). The diet for HD and HHD is very similar, whereas patients on NHD require fewer restrictions. The time needed for dialysis depends on residual kidney function, how much fluid weight has been gained, and body mass index (BMI). The greatest challenge for nutrition therapy is related to fluid, potassium, and phosphorus. The diet is individualized based on serum levels of potassium and phosphorus and also weight gain between dialysis sessions. The albumin level, a marker of inflammation, and protein catabolic rate (PCR) are also monitored to ensure that patients have adequate protein intake and status. The focus of MNT in hemodialysis is to ensure the patient is receiving adequate nutrition while maintaining the balance of the body's minerals (potassium, phosphorus, and calcium) and fluid levels. When patients are unable to meet their protein needs, the RD/RDN will recommend nutrition supplements or intra-dialytic amino acid solutions to improve the nutrition status [24].

There are two choices with peritoneal dialysis (PD), namely, continuous ambulatory peritoneal dialysis (CAPD) or continuous cyclic peritoneal dialysis (CCPD) also known as automated peritoneal

dialysis (APD). The basic treatment is the same for each with exchanges of dialysate (usually a dextrose or icodextrin solution). CAPD is "continuous," machine-free and done several times during the day with exchanges done using gravity to drain and then fill the peritoneum in a sanitary environment. With CCPD/APD a machine (cycler) delivers and then drains the dialysate. The treatment is usually done at night while the patient is sleeping. Patients on peritoneal dialysis require more protein and potassium in their diets. The dextrose used in the dialysate has calories which may contribute to weight gain and thereby aggravate existing diabetes and lipid disorders. If a patient is not able to meet their protein needs, nutrition supplements or dialysate with amino acids may be recommended [24, 26].

For all types of treatment for ESRD (HD, PD, transplant, or conservative care), the RD/RDN experienced in kidney disease recommends changes to medications so as to manage disorders in serum levels of minerals (such as potassium, phosphorus, and calcium) or PTH and vitamin D levels. The assessment of nutritional risk factors will allow RD/RDNs to provide customized MNT. The RD/RDN will help patients with nutrition choices to optimize their nutrition status and fluid balance and assist the patient with their nutritional goals [24].

Other Kidney Disorders

Kidney Stones

There is much confusion about nutrition and kidney stones. There is no "one size fits all" dietary recommendation for all stone formers; a diet low in oxalate is a thing of the past [27]. People form different types of stones and for different reasons. The key to nutrition therapy is to treat the individual problem or problems based on the type of stone, but occasionally there is no nutritional cause (e.g., cysteine stones). The major promoters of kidney stones include a low intake of fluid or of fruit and vegetables, a high intake of sodium or acid-promoting foods (animal flesh proteins), and an intake of calcium that is low, suboptimal, or excessive. Other potential factors include alcohol, high-sugar intake, certain over-the-counter (OTC) supplements (such as high intake of vitamin C), and excessive energy intake. The first strategy for all stones is to optimize fluid intake and encourage awareness of their hydration status. Urine studies over 24 h are preferred over corrected spot urines because of the individual's variability of excretion rates throughout the day. These 24-h urine samples are helpful in determining individual factors such as urine pH and volume, calcium, sodium, phosphorus, citrate, and uric acid. MNT by a RD/RDN with experience in kidney stones can identify areas in the diet (promoters) and educate the patient on how to minimize these risk factors. This can also serve as an opportunity to increase fruit and vegetable intake [28].

Gout

Gout is caused by the abnormal metabolism of purines and hyperuricemia (increased levels of uric acid in the blood). This results in deposition of urate crystals which then causes a form of acute arthritis with inflamed joints (usually the knees and feet). Uric acid kidney stones often precede gouty attacks. The disease tends to affect men, especially older men, and is sometimes hereditary. The management of gout can be challenging given the disease frequently presents in association with comorbid conditions such as obesity, diabetes, renal insufficiency, or hypertension. Drug therapy (anti-inflammatory drugs or antihyperuricemic drugs) is the primary method of treatment for lowering plasma uric acid levels; however, some patients do not respond to medications [29]. Patients should be educated on diet and lifestyle triggers for gout. Food triggers include large servings of animal protein, high-fat foods, alcohol, and foods high in processed sugars. Drastic weight loss measures such as fasting, low-calorie diet, or high-protein diets can also trigger an attack. A healthy eating pattern which includes adequate fluid intake, fruits, vegetables, and whole grains is encouraged.

Table 22.1 Staging of AKI [31]

Stage	Serum creatinine	Urine output
1	1.5–1.9 times baseline Or ≥0.3 mg/dl (≥26.5 mmol/l) increase	<0.5 ml/kg/h for 6–12 h
2	2.0–2.9 times baseline	<0.5 ml/kg/h for ≥12 h
3	3.0 times baseline Or Increase in serum creatinine to ≥4.0 mg/dl (≥354 mmol/l) Or Initiation of renal replacement therapy, or, In patients <18 years, decrease in eGFR to <35 ml/min per 1.73 m^2	<0.3 ml/kg/h for ≥24 h Or Anuria for ≥12 h

Reproduced with permission from Kidney Disease: Improving Global Outcomes (KDIGO) [31]

Acute Kidney Injury

Acute kidney injury (AKI) is a sudden and usually reversible decline in eGFR. Table 22.1 shows staging for acute kidney injury [5, 30, 31]. There is an elevation of blood urea nitrogen (BUN), creatinine, and other metabolic waste products that are normally excreted by the kidney. The general recommendation for AKI is to determine the cause(s) and treat those that are reversible. Patients should be evaluated within 3 months after acute kidney injury for resolution, new onset, or worsening of pre-existing CKD. About 5–10% of patients in intensive care with AKI are treated with continuous renal replacement therapy (CRRT); this is a slow continuous dialysis therapy which is necessary as these patients have hemodynamic instability. These patients are very ill with catabolism and poor nutrition can affect outcomes. The goal of medical nutrition therapy (MNT) in CRRT is to maintain or improve nutrition status, enhance wound healing, and support host defense and recovery without exacerbating metabolic derangements. Survivors of acute kidney injury (AKI), if there is residual renal impairment, should be managed according to CKD guidelines.

Glomerulonephritis

Glomerulonephritis is a group of diseases (including nephritis, nephritic syndrome) that injures glomeruli and is manifested by hematuria, proteinuria, hypertension, edema, nocturia, foamy urine, and hyperlipidemia. When the kidney is injured, it cannot get rid of wastes and extra fluid in the body. If the illness continues, the kidneys may stop working completely, resulting in kidney failure [32, 33]. MNT goals for nephrotic syndrome are similar to CKD with a focus on a healthy eating pattern.

Implications of COVID-19 for Kidney Health and Nutrition

Kidney disease has emerged as a risk factor for poor outcomes of COVID-19 [34–36]. Acute kidney injury incidence in hospitalized patients with COVID-19 has also been observed in patients with high-risk conditions (elderly, hypertension, diabetes, obesity, heart disease, immunocompromised including transplant recipients), with many of them developing kidney failure and require dialysis while in the ICU [37]. Patients with existing CKD and those on dialysis were more likely to be hospitalized than without kidney disease [38].

Poor nutrition status can cause patients to be immunocompromised putting them at higher risk for poor outcomes if they get an infection that includes COVID-19 [39]. Impaired immune function or inadequate dietary intake paired with increased requirements during periods of infection or stress decreases the nutrition stores within the body. Immune systems require multiple micronutrients including vitamins A, D, C, E, B6, B12, folate, zinc, iron, copper, and selenium that have synergistic

roles at various stages of immune response [40–42]. As previously mentioned, vitamin D levels are often low in CKD. Vitamin D deficiency or insufficiency frequently was seen in some people with greater severity of COVID-19. In-center hemodialysis patients are also at risk due to "No Eating During Dialysis" policies due to masking during dialysis and transportation. Nutrition strategies in CKD to improve nutrition status are critical in helping prevent poor outcomes with COVID-19. It is important to encourage good balanced eating habits to provide the essential nutrients to support a healthy immune system [40].

Summary

MNT facilitated by a RD/RDN who has experience with renal disease should be encouraged when a patient is diagnosed with kidney disease. Improved nutrition awareness can contribute to a slowing in the progression of kidney disease and improving nutritional biomarkers in patients with CKD.

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Suggested Further Readings

GFR Calculator: https://www.kidney.org/professionals/KDOQI/gfr_calculator
Kidney Disease: Improving Global Outcomes (KDIGO). https://kdigo.org/
The Kidney Foundation of Canada: http://www.kidney.ca
Kidney Health Australia: http://www.kidney.org.au
National Institute of Diabetes and Digestive and Kidney Diseases: http://www.niddk.nih.gov
National Kidney Foundation: www.kidney.org
National Kidney Federation, UK: http://www.kidney.org.uk/

Eating Disorders: Disorders of Under- and Overnutrition

23

Maija Broox Bruzas and Kelly C. Allison

Keywords

Eating disorders · Anorexia nervosa · Bulimia nervosa · Binge eating disorder · Avoidant/restrictive food intake disorder · Night eating syndrome · Purging disorder

Key Points

- For anorexia nervosa (AN), inpatient treatment featuring a multidisciplinary team and family-based therapy (e.g., Maudsley family therapy) or outpatient family-based therapy are the first-line treatments. No pharmacological agents are indicated to assist in the treatment of the core symptoms of AN.
- For bulimia nervosa, cognitive behavior therapy (CBT) and CBT with adjunct pharmacotherapy are the best supported treatment approaches. Selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, the MAOI phenelzine, and the anticonvulsant topiramate are supported psychopharmacological treatments. The SSRI fluoxetine is the only FDA-approved medication for bulimia nervosa.
- For binge eating disorder, CBT is indicated to address eating disorder cognitions and behaviors, while behavioral weight loss (BWL) is indicated to produce weight loss in the patients with overweight or obesity. A combination approach can be used as well. The stimulant lisdexamfetamine, SSRI antidepressants, and the anticonvulsants topiramate and zonisamide are supported psychopharmacological agents for this disorder. The stimulant lisdexamfetamine is the only FDA-approved medication for binge eating disorder.
- CBT for avoidant/restrictive food intake disorder is currently being investigated and preliminary results are promising. There is some evidence that the tetracyclic antidepressant mirtazapine may help with weight gain.
- Night eating syndrome can be effectively treated with CBT, psychoeducation, progressive muscle relaxation, and the SSRIs sertraline and escitalopram.

M. B. Bruzas
Center for Weight and Eating Disorders, Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

Health Psychology Associates, P.C, Greeley, CO, USA

K. C. Allison (✉)
Center for Weight and Eating Disorders, Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA
e-mail: kca@pennmedicine.upenn.edu

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Introduction

Eating disorders represent extremes in nutrition. These extremes of under- and overnutrition can exist within the same person, as in anorexia nervosa-binge eating/purging type. Alternatively, the extremes can be found in anorexia nervosa-restricting type and binge eating disorder. Current diagnostic criteria for eating disorders are outlined in the Diagnostic and Statistical Manual of Mental Disorders-fifth Edition [1] from the American Psychiatric Association and include anorexia nervosa (AN), bulimia nervosa (BN), binge eating disorder (BED), avoidant/restrictive food intake disorder (ARFID), and otherwise specified feeding or eating disorder (OSFED). Night eating syndrome (NES) and purging disorder (PD) are two forms of disordered eating that are growing in recognition and are included in the OSFED category. This chapter includes diagnostic criteria for these eating disorders, their prevalence, behavioral and psychopharmacological treatments, and prevention efforts.

Eating Disorder Diagnostic Criteria

Anorexia Nervosa

Anorexia nervosa (AN) frequently begins in adolescence or young adulthood [1]. AN features a significant restriction of energy intake relative to physical requirements, leading to a significantly low body weight for one's age, height, sex, developmental trajectory, and physical health status. For adults, a body mass index (BMI) of <17.0 kg/m^2 is considered by the World Health Organization to indicate "significantly low body weight." For children and adolescents, a BMI percentile below the fifth percentile on the Centers for Disease Control and Prevention's BMI-for-age-and-sex percentile charts is typically used to classify "significantly low body weight."

Another key feature of AN is an intense fear of gaining weight or of having overweight and persistent engagement in behaviors that cause weight loss or interfere with weight gain [1]. This intense fear is rarely alleviated with weight loss. Another core feature of AN is excessive influence of weight or shape on self-evaluation. There is a disturbance in how one experiences one's weight or shape, and typically there is a persistent lack of recognition of the negative consequences of one's low body weight. Many individuals with AN may not recognize or admit their fears of weight gain and are not likely to present for treatment for AN, but may be brought to treatment by loved ones or present with complaints of somatic and psychological symptoms related to their malnutrition or comorbid mental health conditions.

There are two subtypes of AN [1]. The restricting subtype of AN involves sole use of caloric restriction and excessive exercise as a means of weight control. The binge eating/purging subtype of AN includes binge eating and/or inappropriate compensatory measures, such as vomiting or misuse of laxatives, diuretics, or enemas. Those with AN binge eating/purging subtype have extremely low body weight, which differentiates them from those with BN. Others may notice that individuals with AN appear low weight, seem fatigued, have trouble tolerating the cold, have lanugo on their upper body, have spells of dizziness or fainting, report gastrointestinal complaints, and have irregular or absent menstrual periods [2].

All physical systems are negatively impacted by the malnutrition and weight loss in AN [3, 4]. Physical effects of restrictive eating include cardiovascular abnormalities (e.g., bradycardia, hypotension), hypoglycemia, osteoporosis, slowed gastric motility, hypothermia, dental problems, amenorrhea, infertility, and an increased risk of miscarriage and having a child with low birth weight [1, 3, 4]. In the binge eating/purging subtype, purging causes additional physical damage (see the section on BN).

Mortality rates are higher for AN than many other psychiatric disorders (4). Twenty to 30% of deaths in those with AN are due to suicide and approximately half of deaths are due to medical complications [3, 4].

Bulimia Nervosa

Bulimia nervosa frequently begins in adolescence or young adulthood [1]. The core features of BN are binge eating and subsequent use of inappropriate compensatory behaviors to prevent weight gain or to lose weight. A binge episode is defined as an episode in which a person eats an unambiguously large amount of food within a 2-hour period and experiences loss of control when eating. What is considered as unambiguously large is based upon what most people would eat in a 2-hour period under similar circumstances. Inappropriate compensatory behaviors include vomiting, restrictive eating, excessive exercise, or misuse of laxatives, diuretics, or enemas. Vomiting is the most common method of purging in those with BN. For those with BN, caloric intake prior to purging is an average of 2722 calories [5]. As with AN, there is an over-valuation of weight and shape in self-evaluation [1]. The binge episodes and inappropriate compensatory behaviors must occur at least once per week for at least 3 months. Screening for BN is difficult because individuals typically have normal weight or overweight status.

Common signs of regular vomiting include "Russell's sign" (thickening of the skin on the knuckles due to self-induced vomiting), swollen cheeks, and dental erosion [3]. Vomiting can cause electrolyte imbalance, cardiac arrhythmias, gastroesophageal reflux disease, tears and ruptures of the esophagus, gastric ruptures, and metabolic alkalosis [1, 3].

Overuse of laxatives can cause severe electrolyte disturbances, especially low levels of potassium in the blood, which can contribute to muscle weakness or paralysis, notable renal impairment, and cardiac arrhythmias [6]. It can also cause inflammation, ulceration, and neuropathy of the colon and steatorrhea. Other consequences include dehydration, hypotension, tachycardia, dizziness, and metabolic alkalosis [1, 6].

Binge Eating Disorder

Binge eating disorder frequently begins in adolescence or young adulthood, but sometimes begins in adulthood [1]. The hallmark of BED is recurrent binge episodes (see definition above). Additionally, at least three of the five following signs must be present during binge episodes: (a) eating more rapidly than normal, (b) eating until feeling uncomfortably full, (c) eating when not physically hungry, (d) eating alone due to embarrassment, and (e) feeling disgusted, depressed, or markedly guilty afterward. Diagnosis requires that the episodes occur, on average, at least once per week for 3 months. BED is positively associated with overweight and obesity and prospectively increases risk of developing obesity [7].

Avoidant/Restrictive Food Intake Disorder

Avoidant/restrictive food intake disorder (ARFID) frequently begins in infancy or early childhood [1]. ARFID is characterized by lack of interest in eating or food, aversion to the sensory characteristics of certain foods, and/or avoidance of eating broadly or eating certain foods due to fears of aversive consequences (e.g., choking, vomiting). ARFID leads to weight loss or difficulty with weight gain, nutritional deficiencies, dependence on enteral feeding or oral nutritional supplements, and/or considerable interference with psychosocial functioning. Most individuals with ARFID are not preoccupied with being thin, as is the case with AN. The medical consequences of ARFID include the side effects of malnutrition, which are also seen in AN, such as fatigue, dizziness, amenorrhea, bradycardia, orthostatic hypotension and tachycardia, cold intolerance and hypothermia, pallor, and lanugo [8]. These consequences are often noticeable and concerning to caregivers.

Other Specified Feeding or Eating Disorders

There are types of disordered eating that cause psychological and physical distress that do not fit the diagnostic criteria for the aforementioned disorders. These are captured in the OSFED category [1].

Night Eating Syndrome

Night eating syndrome (NES) typically appears in young adulthood or adulthood [9]. NES involves consuming at least 25% of one's daily calories after the evening meal and/or experiencing at least two nocturnal eating episodes (rising from sleep to eat) per week, for at least 3 months [10]. For a diagnosis of NES, three of the five following features must be present: (a) a lack of desire to eat in the morning and/or breakfast is omitted on four or more mornings per week; (b) a strong urge to eat between dinner and bedtime and/or during the night; (c) sleep onset and/or sleep maintenance insomnia occur four or more nights per week; (d) the belief that one must eat in order to get to sleep; and (e) mood is frequently depressed and/or mood worsens in the evening. Individuals with NES must have awareness and recall of the evening and nocturnal eating episodes; if they do not then clinicians should assess for sleep-related eating disorder, which is a parasomnia marked by impaired consciousness and often includes the consumption of unusual food or nonedible objects in addition to normal food. The nocturnal ingestions in NES are typically the size of a snack or small meal and do not need to be objectively large, as is the case of objective binge eating episodes in BED and BN. People who live with an individual with NES may notice the individual waking up at night and may observe signs that the individual ate food between bedtime and the morning.

There are mixed findings regarding the association between NES and BMI, with approximately half of studies showing a positive correlation and the other half showing a nonsignificant association [11]. Whether NES produces weight gain may be dependent on the frequency of evening eating and nocturnal ingestions and the quantity and type of foods and beverages ingested during these episodes. Individuals with NES demonstrate worse control of diabetes and higher diabetes complication rates than individuals without NES [9]. Nocturnal ingestions also predict worse oral health.

Purging Disorder

The onset of purging disorder (PD) is typically in young adulthood [12]. PD features weekly purging behaviors (e.g., vomiting, laxative use, or diuretic misuse) for a course of 3 months with the intention to influence one's weight and shape [1, 12]. Individuals with PD do not engage in binge eating and do not have significantly low body weight [1]. Some individuals with purging disorder experience subjective binge episodes, in which they eat a portion of food that is not unambiguously large and feel a sense of loss of control. Over-valuation of shape and weight is frequently experienced by individuals with PD, and they often have high levels of dietary restraint and endorse specific dietary rules, such as "I cannot eat fried foods, because they will cause weight gain. If I do eat any fried food, then I have to purge."

Caloric intake before purging in those with PD is 535 calories on average, which is significantly lower than the average 2722 calories consumed before purging in those with BN [5]. The signs and consequences of purging in PD are described in the section on BN.

Atypical Anorexia Nervosa

In atypical AN, an individual has lost a significant amount of weight and all of the criteria for AN are met, except the person has not reached a significantly low body weight [1]. This disorder can occur in individuals with overweight or obesity who have lost a significant amount of weight rapidly with behavioral weight loss efforts, bariatric surgery, and/or weight loss medication and have developed extremely restrictive eating practices and/or excessive exercise routines.

Bulimia Nervosa (of Low Frequency or Limited Duration)

In subclinical BN all diagnostic criteria for BN are met except that the frequency of the binge episodes and compensatory behaviors is, on average, less than once per week and/or for less than 3 months [1]. An example would be an individual who purges three or fewer times per month and has three or fewer objective binge episodes per month. This person might have more frequent subjective binge eating episodes, which involve a sense of loss of control when eating a quantity of food that is not unambiguously large (e.g., five small cookies).

Binge Eating Disorder (of Low Frequency or Limited Duration)

In subclinical BED all diagnostic criteria for BED are met except that the binge episodes occur, on average, less than once per week and/or for less than 3 months [1]. An example would be an individual who has a combination of subjective and objective binge eating episodes or only occasional objective binge eating episodes, with three or fewer objective binge eating episodes per month.

Unspecified Feeding or Eating Disorder

This diagnosis may be used when any individual has subthreshold symptoms for an eating disorder and shows significant distress or psychosocial impairment and not enough information has been collected to make a full diagnosis (e.g., in an emergency situation) or further diagnostic clarification is needed [1].

Prevalence of Eating Disorders

The cross-gender lifetime prevalence of the DSM-5 eating disorders reported in US adults is 0.80% for AN, 0.28% for BN, and 0.85% for BED [13]. Gender-specific lifetime prevalence value for AN is 1.42% of women and 0.12% of men, for BN is 0.46% of women and 0.08% of men, and for BED is 1.25% of women and 0.42% of men [13]. In North America, 5–12% of patients presenting for eating disorder treatment at outpatient clinics meet criteria for ARFID [8]. The prevalence of NES ranges from 1 to 2% in community samples and increases in samples seeking treatment for obesity [9]. Lifetime prevalence of PD across age groups is 6.2% [14].

Behavioral Treatment for Eating Disorders

Table 23.1 provides an overview of effective behavioral and pharmacological treatments. Health insurance coverage for behavioral treatments is variable across all of the eating disorder diagnoses, and many providers may be out of network for coverage, so individuals must check with their insurance providers to determine coverage.

Psychotherapy for Anorexia Nervosa

Anorexia Nervosa Inpatient Treatment

Indicators for inpatient treatment for AN include a precipitous drop in body weight, a BMI <15 kg/m^2, significant nutritional deficiencies and medical consequences of the disorder (e.g., bradycardia, biochemical disturbances), a longer duration of illness, a history of multiple relapses, failure to respond to outpatient treatment, and/or having severe comorbid mental health conditions or suicidality [4].

Table 23.1 Effective behavioral and pharmacological treatments for eating disorders

Disorder	CBT	SSRIs	Other
Anorexia nervosa	Moderate support for CBT-enhanced	No	Adolescents: Family-based treatment, Maudsley family therapy, inpatient multidisciplinary treatment, adolescent focused therapy, family system therapy Adults: The Maudsley model of anorexia nervosa treatment for adults, specialist supportive clinical management, focal psychodynamic psychotherapy No medications proven effective for core symptoms
Bulimia nervosa	Strong support	Yes	Other psychotherapy approaches have some support, but CBT produces the best outcomes Tricyclic antidepressants: Desipramine, amitriptyline, imipramine Others: Anticonvulsant-topiramate, MAOI-phenelzine *Contraindicated:* Unicyclic antidepressant bupropion-immediate-release
Binge eating disorder	Strong support	Yes	BWL for patients with overweight or obesity and a desire to lose weight without severe eating disorder behaviors and cognitions Stimulant: Lisdexamfetamine dimesylate Anticonvulsants: Topiramate, zonisamide Others: Unicyclic antidepressant-bupropion, mood stabilizer-lamotrigine
Night eating syndrome	Moderate support	Yes	Progressive muscle relaxation Psychoeducation on night eating syndrome, healthy eating, and sleep
Avoidant/ restrictive food intake disorder	Preliminary support	Unknown	The tetracyclic antidepressant mirtazapine may help with weight gain

CBT cognitive behavioral therapy; *SSRI* selective serotonin reuptake inhibitor; *MAOI* monoamine oxidase inhibitor; *BWL* behavioral weight loss

Increased mortality is seen in patients with BMIs <17.5 kg/m^2, so inpatient treatment should be considered in individuals with a BMI below this level who also have other indicators suggesting inpatient treatment.

Inpatient treatment involves nutritional restoration (refeeding) including therapeutic meals, typically involving health professionals and/or family members, where patients are challenged to eat nutritionally balanced meals and snacks at regular intervals each day [2]. Initial caloric intake depends on age. For adults, an initial intake of 1600 kcal/d is recommended. This is increased by 300 kcal per day every 2–3 days, reaching up to 3500–4000 kcal per day for optimal refeeding. The goal is for patients to gain approximately 1–2 lb. per week. Care must be taken to avoid refeeding syndrome, which can occur when a malnourished individual eats too many calories early in refeeding and develops hypophosphatemia and other laboratory abnormalities. This can lead to delirium, cardiac and respiratory failure, profound muscle weakness, and in the worst cases, death.

Psychological treatment during inpatient treatment typically involves group and individual psychotherapy, with treatment involving family members for adolescents. Once a patient is well nourished, has made progress toward or reached the target weight, and is medically stable, the patient can be transitioned to partial hospitalization or day treatment programs. Then, they can transition to outpatient treatment.

Anorexia Nervosa Outpatient Treatment in Adolescents

For adolescents, family-based therapy (e.g., Maudsley model) is the favored treatment approach, with the best outcomes [15]. In family-based therapy, caregivers are initially tasked with taking control of

their child's eating behavior and weight restoration. Later in treatment, parents transition the majority of control of eating behavior and weight back to the child. These therapies also focus on fostering positive relationships within the family. There is moderate evidence to support the use of family system therapy, adolescent focused therapy, and cognitive behavioral therapy-enhanced (CBT-E) for adolescents.

Anorexia Nervosa Outpatient Treatment in Adults

Treatment options for adults with AN that have moderate support include CBT-E, the Maudsley model of AN treatment for adults (MANTRA), specialist supportive clinical management (SSCM), and focal psychodynamic psychotherapy [15]. CBT-E involves determining what stimuli, behaviors, and thoughts are maintaining the eating problem and making goals to manage them. MANTRA is a cognitive-interpersonal treatment that involves helping the patient build an identity separate from the disorder. SSCM is a supportive therapy involving psychoeducation, setting weight, eating behavior, and nutrition goals and monitoring progress. Focal psychodynamic psychotherapy focuses on creating a positive therapeutic alliance, exploring ego-syntonic beliefs that lead into the disorder and pro-anorexic behaviors, and examining the interaction between interpersonal relationships and the eating disorder behaviors. None of these psychotherapies is superior to the others for treatment of AN in adults.

Bulimia Nervosa

Individual cognitive behavioral therapy (CBT) is the first-line treatment for BN, producing the best results in terms of achieving full remission, reducing binge eating and compensatory behavior, and reducing eating disorder cognitions [16]. Other forms of psychotherapy (e.g., interpersonal psychotherapy, behavioral therapy) and combined treatment (multiple forms of psychotherapy or psychotherapy coupled with pharmacotherapy) are second-line treatment approaches, followed by self-help as a third-line treatment. Pharmacotherapy alone is not adequate as a treatment approach.

Binge Eating Disorder

Cognitive behavioral therapy (CBT), behavioral weight loss (BWL), and a combination of the two are the first-line treatments for BED [17, 18]. Pharmacotherapy is an efficacious adjunct treatment, which can help improve eating behaviors and weight, but cannot produce significant changes in eating disordered cognitions. In terms of reduction and elimination of binge eating and eating disorder cognitions, CBT typically outperforms BWLT. However, in terms of weight loss, BWL outperforms CBT. CBT produces larger reductions in binge episodes as compared to other psychotherapies (interpersonal, humanistic, and psychodynamic therapies) and self-help treatment [17].

Treatment choice is largely dependent on the patient's goals for treatment, weight status, level of eating disorder psychopathology, and psychiatric comorbidities. When a patient with BED presents with a desire to lose weight, has overweight or obesity, and has mild eating disordered behaviors and cognitions, behavioral weight loss (BWL) would likely be the treatment of choice. In this case, a clinician should also tell the patient that he/she can discuss pharmacotherapy options with his/her doctor if this is of interest. When a patient with BED presents with severe disordered eating behaviors and cognitions, regardless of their weight status or desire to lose weight, CBT would be the treatment of choice and transition to BWL could occur once eating disorder psychopathology significantly improved. Combined treatment might be optimal if a patient has overweight or obesity, desires to lose weight, and has moderate eating disordered behaviors and cognitions.

Avoidant/Restrictive Food Intake Disorder

Cognitive behavioral therapy (CBT) for ARFID, typically 20–30 sessions, is the primary treatment in children 10 years of age and older [8]. Preliminary data show improvements in weight, nutritional deficiencies, and dietary variety. For patients with ARFID who are underweight, increasing dietary volume and correcting nutritional deficiencies are the first goals, followed by increasing dietary variety. For individuals with normal weight, maintaining or increasing dietary volume and increasing dietary variety can be targeted simultaneously. A primary aspect of treatment is behavioral exposure to avoided foods, both inside and outside of psychotherapy sessions.

Purging Disorder

No randomized controlled trials have examined treatment for PD [5]. However, a case series reported that in 57 women who received 16 sessions of CBT, 17.5% achieved full remission and 24.6% achieved partial remission [19].

Night Eating Syndrome

One uncontrolled clinical trial indicated that a ten-session course of cognitive behavioral therapy (CBT) for NES was able to significantly reduce evening hyperphagia and frequency of nocturnal ingestions [10]. One randomized-controlled trial comparing three groups across a 21-day intervention demonstrated that engagement in psychoeducation groups and a psychoeducation plus progressive muscle relaxation group (PMR) resulted in significant reductions in evening hyperphagia and nocturnal ingestions, and the group that practiced PMR showed a significantly greater reduction in evening hyperphagia as compared to those who only received psychoeducation [20].

Pharmacological Treatment for Eating Disorders

Psychotropic medications serve various purposes in the treatment of eating disorders, and Table 23.1 provides an overview of effective behavioral and pharmacological treatments. They can be used to augment treatment in patients that have not responded strongly to psychotherapy, for patients who do not have access to psychotherapy for eating disorders, for patients who have comorbid mental health disorders, and/or for patients who have a preference for medication treatment rather than psychotherapy, with the exception of patients with AN [21].

There are no FDA-approved medications for the treatment of AN [22]. There is no evidence that psychotropic medications can effectively treat the core symptoms of AN, although psychotropic medications can be added to treat comorbid mental health conditions [4, 15]. Sometimes a second-generation antipsychotic, such as olanzapine, is used in addition to psychotherapy to induce weight gain in patients with AN, but many patients with AN are not willing to take a medication known to cause weight gain [21]. No clinical trials have investigated the use of psychotropic medications to treat ARFID or purging disorder [5, 8]. However, a small uncontrolled study has indicated that the tetracyclic antidepressant mirtazapine may be helpful in promoting weight gain in patients with ARFID [21].

Selective serotonin reuptake inhibitors (SSRIs) are helpful in the treatment of bulimia nervosa (BN), binge eating disorder (BED), and night eating syndrome (NES). Fluoxetine, sertraline, citalopram, and escitalopram are effective in reducing symptoms of BN and BED [21, 23]. The SSRI fluoxetine is the only FDA-approved medication for bulimia nervosa. Sertraline and escitalopram can

effectively reduce night eating symptoms, with sertraline helping with weight loss among those with overweight or obesity [10]. The serotonin-norepinephrine reuptake inhibitor duloxetine improves symptoms of BED [21]. The unicyclic antidepressant bupropion improves symptoms of BED, but immediate-release bupropion is contraindicated in patients with BN due to medical consequences of purging and the lowered seizure threshold that this medication produces. Various tricyclic antidepressants (desipramine, amitriptyline, imipramine) and the monoamine oxidase inhibitor phenelzine are other effective treatments for BN.

The stimulant lisdexamfetamine dimesylate is the only FDA-approved medication for BED and has been approved for use for moderate to severe BED in adults since 2015 and is able to significantly reduce binge eating episodes and body weight [17, 22, 23].

The mood stabilizer lamotrigine successfully reduces symptoms of BED [21]. The anticonvulsant topiramate has shown promise for reducing binge eating and weight in those with BED and binge eating and purging in those with BN [23]. Zonisamide is another anticonvulsant that is helpful with binge eating and weight in patients with BED. However, the use of anticonvulsants is limited by their undesirable side effect profile.

Prevention

Universal prevention efforts for eating disorders target a broad sample with varied level of risk for eating disorders, typically adolescents [24–26]. Media literacy interventions, e.g., Media Smart, show the most efficacy for universal prevention [24, 25]. They provide psychoeducation on how the media affects body image, distortions, and misleading messages in advertising that relate to body and appearance, skills to become critical media viewers, and ways to engage in consumer activism [26].

Selective prevention efforts for eating disorders target individuals at increased risk for eating disorders, usually late adolescents and young adults [24, 25]. Cognitive dissonance interventions, e.g., the Body Project, show the most efficacy for selective prevention [24, 25]. These interventions have participants speak, write, or behave in a manner that conveys opposition to societal norms including the thin ideal and other appearance-related ideals. Cognitive dissonance intervention groups as compared to control groups showed significantly larger reductions in dieting, thin ideal internalization, and body dissatisfaction. Two other beneficial selective prevention interventions, which produce smaller beneficial effects, are cognitive behavioral therapy (CBT) and Healthy Weight prevention programs. CBT intervention groups, e.g., Student Bodies, as compared to control groups showed significantly larger reductions in dieting, body dissatisfaction, and bulimic symptoms. Healthy weight intervention groups, e.g., the Healthy Weight prevention program (this program targets small improvements to diet and exercise), as compared to control groups, showed significantly larger reductions in body mass index and significantly, although smaller, reductions in thin-ideal internalization and body dissatisfaction.

Conclusion

Eating disorders range from severe caloric restriction to severe overeating. Extreme dissatisfaction with weight and shape is present across most of the diagnoses. For anorexia nervosa (AN), weight restoration is the first goal, followed by psychological improvements. In adolescents, the most effective approaches are inpatient treatment involving the family and a multidisciplinary team or family-based outpatient treatment, primarily dependent on the patient's weight and medical status. For adults with AN, there are a number of inpatient and outpatient psychotherapy varieties to choose from. For bulimia nervosa (BN), CBT is the preferred approach, and SSRIs, tricyclic antidepressants, and topiramate can be a helpful addition to treatment. For binge eating disorder (BED), CBT and/or BWL are

the mainstays of treatment, with lisdexamfetamine, topiramate, and SSRIs as helpful additions to treatment. Night eating syndrome (NES) can be effectively treated with CBT, sertraline, escitalopram, psychoeducation, and progressive muscle relaxation. Currently CBT for ARFID is under investigation, with preliminary findings showing positive effects. Media literacy programs show the best results for universal prevention of eating disorders in adolescents, while cognitive dissonance interventions hold the strongest support for preventing eating disorders in adolescents and emerging adults who are at elevated risk of developing eating disorders.

COVID-19 Addendum

Since drafting this chapter, Eating Disorders: Disorders of Under- and Overnutrition, the COVID-19 pandemic surged and affected how many of us eat, sleep, be active, work, shop, and socialize with others. Eating disorder treatment providers have seen increases in requests for care and are reaching out to each other on professional discussion boards for support. Some of the reasons for these increases in disordered eating symptoms could be because people who are prone to eating disorders internalize society's messages about weight and shape. There has been increased emphasis on obesity's role in the severity of COVID cases, as well as emphasis on weight gain during the pandemic [27]. Both of these messages have likely been triggering for those susceptible to AN, BN, and BED and produce more "motivation," so to say, to engage in their restrictive eating behaviors [28]. For those with AN this can lead to more severe weight loss and, in BN and BED, to more frequent binge episodes when attempts at restriction fail.

Second, particularly in the beginning of the pandemic, going into the grocery store was a very anxiety-provoking situation for most people, but for those prone to AN, food shopping is already very difficult for them, so the pressured situation we experienced in those early months was even more difficult for them and one they likely wanted to avoid completely [29]. Third, one of the few things being promoted as a safe and healthy activity during the pandemic has been to exercise. For many of us, exercise decreased during this time, but for those with restrictive eating disorder, this was likely triggering and became a point of focus as a means of controlling a very uncontrollable situation [28, 29]. Finally, social anxiety is often comorbid with the eating disorders, so as the pandemic abates, there may also be some desire to control one's weight as they re-enter the social scene/head back to school, work, etc., so they could be liked and accepted again by their friends/peers. Treatment for the eating disorders would remain the same as outlined in this chapter, with sensitivity to these particular issues.

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Nutritional Considerations Following Bariatric Surgery

24

Christopher Larson

Keywords

Bariatric surgery · Roux-en-Y gastric bypass · Sleeve gastrectomy · Nutritional deficiencies

Key Points

- Bariatric surgery is an effective treatment for obesity.
- The two most common bariatric surgical procedures are the sleeve gastrectomy and the Roux-en-Y gastric bypass.
- Postsurgical bariatric patients are advised to adhere to dietary guidelines to ensure proper healing and safe weight loss.
- Lifelong follow-up and vitamin and mineral supplementation are necessary to help avoid weight regain and potential nutritional deficiencies.

Introduction

Obesity is expected to remain a prevalent and costly disease in the United States and worldwide for the foreseeable future. By 2030, it is estimated that over 50% of the population of the United States will be obese (BMI >30 kg/m^2) and 11% will be considered severely obese (BMI >40) [1]. Traditional approaches to weight management such as dietary modification, increasing exercise, lifestyle and behavioral interventions, as well as nonsurgical options like pharmaceuticals may help patients achieve modest weight loss, but significant and sustained weight loss is rare. In those patients for whom medical management proves inadequate, bariatric surgery may be considered. Bariatric surgical procedures have been consistently shown to help obese patients achieve significant and sustained weight loss with concurrent improvement of obesity-related comorbid medical conditions and quality of life. Bariatric surgery is often referred as a "tool" to assist patients in achieving their weight-loss goals, reducing or eliminating obesity-related comorbid conditions, and improving quality of life. A 2016 study of over 1000 weight-loss surgery patients demonstrated durability of weight loss and improvement in diabetes, high blood pressure, and sleep apnea after 10 years [2].

The 1991 National Institutes of Health criteria for consideration of bariatric surgery include patients with a BMI of ≥35 with associated medical problems or a BMI of ≥40. The American Society

C. Larson (✉)
Department of Minimally Invasive Bariatric Surgery, Gundersen Health System, La Crosse, WI, USA
e-mail: CJLarson@gundersenhealth.org

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for Metabolic and Bariatric Surgery (ASMBS) has recommended that bariatric surgery be considered for patients with a BMI of 30–35 for whom other treatments have not resulted in sustained weight loss or improvement in comorbid medical conditions.

It is generally accepted that adequate nutritional evaluation and dietary guidance is vital to any comprehensive approach to the perioperative care of the bariatric surgical patient. Most bariatric surgical programs and insurance providers require that surgical candidates provide evidence of previous medically supervised weight loss attempts. In addition, a minimum of 3 months of nutrition and lifestyle education with a registered dietitian and behavioral health specialist in preparation for life after bariatric surgery is required. Before surgery many programs have adopted a low-calorie, full-liquid, or meal replacement-type diet (usually lasting from 2 to 4 weeks), ostensibly to reduce the size of the liver and improve surgical access. The potential for long-term nutritional deficiencies and weight regain is well established and underscores the need for lifelong surveillance. This chapter provides clinical guidance on nutritional considerations following bariatric surgery.

Bariatric Surgical Procedures

In 2018, it was estimated that 252,000 bariatric surgical procedures were performed in the United States. The sleeve gastrectomy (SG) and the Roux-en-Y gastric bypass (RYGB) represent the majority of the cases at 61.4% and 17%, respectively. The sleeve gastrectomy has seen a growth of 451% since 2011 [3].

Laparoscopic Sleeve Gastrectomy (SG)

By removing approximately 80% of the stomach, patients are left with a tubular, banana-shaped sleeve with a capacity of about 150 cm^3 (Fig. 24.1). The small volume of the sleeve helps to reduce dietary intake, and alterations to the gut hormone environment (reduction of ghrelin and increased release of GLP-1 and PYY) promote appetite suppression and early satiety.

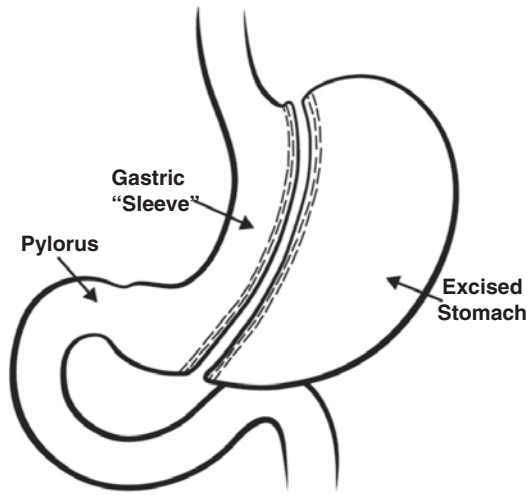

Fig. 24.1 Sleeve gastrectomy

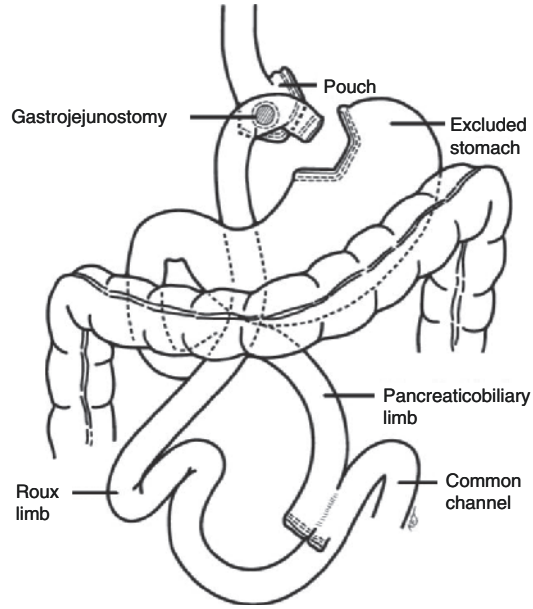

Fig. 24.2 Roux-en-Y gastric bypass

Roux-en-Y Gastric Bypass (RYGB)

The procedure begins with the transection of the stomach near the gastroesophageal junction to create a small 20–30 cm^3 pouch (about the size of a ping-pong ball). The jejunum is then transected with the distal end (Roux limb) brought up to and connected to the pouch (gastrojejunostomy). The proximal portion of the transected jejunum (biliopancreatic limb) is reconnected 50–150 cm down the jejunum (jejunojejunostomy) (Fig. 24.2).

In both procedures, the resulting restriction of dietary intake, hormonal changes, reduction of gastric acid and intrinsic factor, and, in the case of RYGB, the bypassing of preferential sites of nutrient absorption put patients at risk of nutritional deficiencies described later in this chapter.

Postoperative Dietary Recommendations

General Dietary Guidelines

Generally accepted guidelines for the progression of the early postoperative bariatric diet are often modified by individual surgeons or program-based nutritionists. Dietary recommendations attempt to promote optimal nutrition for healing during a time of significant reduction in caloric intake (<900 kcal/day) in the first 6 months following RYGB [4].

The immediate goals of the postoperative diet focus on adequate hydration and protein intake as well as the timing and composition of meals and liquids. Patients may have a difficult time adapting to new dietary recommendations. Care must be taken to educate patients on the importance of eating and drinking slowly to avoid vomiting, pain, and other gastrointestinal issues. Patients often find themselves reflexively eating too quickly, not chewing food thoroughly, or "stacking" their swallows with resulting epigastric pain or vomiting.

Progression of the postoperative bariatric diet is usually accomplished through a staged approach beginning with water and clear liquids and transitioning over time to full liquids (some programs recommend extending the full liquid phase to 3 weeks for the SG to avoid over-pressurization of the sleeve), soft foods, and finally to following well-established guidelines for healthy eating, lean proteins, complex carbohydrates, fruits and vegetables, and avoiding simple sugars or concentrated sweets. A representative progression is presented in Table 24.1 [5]. Moize et al. have developed a bariatric food pyramid to represent the dietary and lifestyle recommendations for the post-RYGB patient (Table 24.2) [6].

Specific Rules on Eating

1. Sip calorie-free or very low caloric non-carbonated fluids throughout the day with a goal of 50 oz. or more. Patients should avoid drinking fluids 10 min before a meal and 30 min after eating. Hydration is extremely important. Because of the smaller gastric volume following restrictive bariatric procedures, making hourly 4–5 oz. fluid goals throughout the day may be helpful.
2. Drink and eat slowly. Concentrate on eating and avoid distractions during meals.
3. Use small plates or bowls to avoid the temptation of taking larger servings.
4. Protein should be eaten first at meal times. Protein is essential in promoting healing and preserving muscle mass during rapid weight loss.
5. Chew food well. Carefully follow the progression of the diet and avoid the temptation to transition too quickly to "real" food.
6. Carefully introduce small amounts of new foods. Do not rely on previous "favorites" or "intuition" to guide food choices.
7. Foods should be moist and soft. Reheated foods may lose moisture and be difficult to swallow.
8. Be aware of calories from liquids such as fruit juice, protein drinks, or milk. Calorie containing fluids should be considered part of a meal.
9. Avoid using straws or swallowing air while eating or drinking.
10. Practice mindful eating, i.e., being thoughtful not only about what you are eating but also why you are eating and pay close attention to signals of fullness. Satiety may have a very abrupt onset. Learn to stop eating at the first signs of fullness.

Food Aversions and Intolerances

Food aversions and intolerances are frequently reported by bariatric surgery patients [7]. Commonly reported intolerances are to red meat, dry chicken breast, or fish; bread, pasta, or rice; and dry, stringy, or fibrous foods. Often symptoms of intolerance are associated with inadequate chewing of food or eating too quickly. Ideally, patients should be guided to carefully introduce new foods to test for individual tolerance. The rapid delivery of high osmolar foods to the small intestine may cause dumping syndrome (DS). DS is common after RYGB and has been reported in post-sleeve gastrectomy patients. DS may occur after the ingestion of simple carbohydrates or fatty foods and is characterized by abdominal cramping, pain, nausea, vomiting, and sweating. Later symptoms related to hypoglycemia may include weakness and syncope. DS may be avoided by choosing foods with less sugar and fat.

Changes in taste and food intolerances may be temporary or change over time. Patients may elect to periodically reintroduce foods.

Table 24.1 Postoperative bariatric diet [5]

Diet stage	Postoperative timing	Fluids/food	Guidelines
I	1–2 days	Clear liquids	Gastrografin swallow test for leaks on postoperative day 1; once tested, begin sips of clear liquids
		Non-carbonated; no calories	
		No sugar, no caffeine	
II *Begin supplementation: Chewable multivitamin with minerals twice daily, chewable or liquid calcium citrate with vitamin D*	3 days	Clear liquids Variety of no-sugar liquids or artificially sweetened liquids Encourage patients to have salty fluids at home Solid liquids: Sugar-free ice pops Plus full liquids ≤15 g of sugar per serving Protein-rich liquids (limit 20 g protein per serving of added powders)	Patients should consume a minimum of 48–64 fluid oz. of total fluids per day: 24–32 oz. or more of clear liquids plus 24–32 oz. of any combination of full liquids
			Nonfat milk mixed with whey or soy protein powder (limit 20 g protein per serving)
			Lactaid milk or soy milk mixed with soy protein powder
			Light yogurt, blended
			Plain nonfat yogurt; Greek yogurt
III	10–14 days[a]	Increase clear liquids (total liquids 48–64+ oz./day) and replace full liquids with soft, moist, diced, ground, or pureed protein sources as tolerated	Protein food choices are encouraged for 4–6 small meals per day; patients may be able to tolerate only a couple of tablespoons at each meal or snack. Chew foods thoroughly prior to swallowing (consistency of applesauce). Encourage patients not to drink with meals and to wait approximately 30 min after each meal before resuming fluids. Eat from small plates and advise using small utensil to help control portions
		Stage III, week 1: Eggs, ground meats, poultry, soft, moist fish, added gravy, bouillon, light mayonnaise to moisten, cooked bean, hearty bean soups, cottage cheese, low-fat cheese, yogurt	

(continued)

Table 24.1 (continued)

Diet stage	Postoperative timing	Fluids/food	Guidelines
	4 weeks	Advance diet as tolerated; if protein foods, add well-cooked, soft vegetables and soft and/or peeled fruit. Always eat protein first	Adequate hydration is essential and a priority for all patients during the rapid weight loss phase
	5 weeks	Continue to consume protein with some fruit or vegetable at each meal; some people tolerate salads at 1 month postoperative	Avoid rice, bread, and pasta until patient is comfortably consuming 60 g/day protein plus fruits and vegetables
IV	As hunger increases and more food is tolerated	Healthy solid food diet	Healthy, balanced diet consisting of adequate protein, fruits, vegetables, and whole grains. Eat from small plates and advise using small utensil to help control portions. Calorie needs based on height, weight, and age
Vitamin and mineral supplementation daily.[b] *May switch to pill form if < 11 mm in width and length after 2* months *postoperative*			

Adapted with permission from Surgery for Obesity and Related Diseases, Vol. 4/Issue 5, Mechanick et al. [5], ©2008, with permission from Elsevier

[a]There is no standardization of diet stages; there are a wide variety of nutrition therapy protocols for how long patients stay on each stage and what types of fluids and foods are recommended

[b]Nutritional laboratory studies should be monitored with bone density test at baseline and about every 2 years postoperative

Carbohydrates

At present there is no consensus regarding carbohydrate intake for patients following weight-loss surgery. Adequate carbohydrate is necessary to prevent ketosis. The Recommended Dietary Allowance intake (published by the Institute of Medicine) for carbohydrates is 130 g/day for healthy adults. Bariatric patients are encouraged to focus on complex carbohydrates and higher fiber sources such as those found in whole grains. The bariatric food pyramid suggests that carbohydrates should comprise about 40–45% of total energy intake or 100–130 g/day based on average calories per day for post-weight-loss surgery patients.

Protein

Higher protein intake can minimize the loss of lean body mass during caloric restriction and rapid weight loss following bariatric surgery. Recommendations vary with a minimum of 60 g/day ranging up to 1.2 g/kg of ideal body weight and should meet the needs of most patients [8]. Maintaining adequate daily intake of protein can be difficult for patients, especially when the new gastric volume is limited to 30 mL. Alterations in taste may lead to food aversions, and protein sources such as meats may not be well tolerated. Patients may utilize commercial protein supplement such as powders, bars, or gelatins to boost protein intake. Careful examination of product labels can help determine if

Table 24.2 Nutritional recommendations for post-gastric bypass patients [6]

Criteria	Recommendation
Try to avoid	Foods high in saturated and trans fats and cholesterol
	Foods high in sugar
	Carbonated and/or alcoholic beverages
Control intake	Servings: 2 per day
	Rice, pasta: 90 g (cooked); breakfast cereals, bread, toast: 30 g
	Legumes (lentils, peas, black and white beans, soybeans): 80 g (cooked)
	Tubers (potato, sweet potato): 85 g (cooked)
Preferential intake—Fruits, vegetables, oil	Servings: 2–3 per day of each food group
	Fruit
	Low-sugar fresh fruit (melon, watermelon, strawberry, grapefruit, apple, orange, etc.): 140 g
	High-sugar fresh fruit (grapes, apricot, banana, cherry, nectarine): 70 g
	Vegetable oil (preferably olive oil): One teaspoon
	Vegetables (any type): 85 g
Preferential intake—Meat, dairy, eggs, legumes	Servings: 4–6 per day
	Low-fat meat (chicken, beef, pork): 60 g
	Fish: White 85 g
	Low-fat or fat-free dairy products: Hard cheese, 50 g; soft cheese, 80 g; milk, 140 g; yogurt, 115 g
	Legumes (lentils, peas, black and white beans, soybeans): 80 g (cooked)
	Eggs: One large, 50 g
Everyday intake	Daily nutritional supplements
	Calcium and vitamin D
	Iron
	Multivitamin
	Vitamin B_{12}
	Ensure daily water or non-carbonated, sugar-free, caffeine-free fluid intake

Adapted with permission from Springer Nature, Moizé et al. [6]

supplements are providing high-quality protein such as whey protein isolates. Patients should be instructed to have their protein source at the beginning of their meals before consuming carbohydrates.

Micronutrients

Despite their excess caloric intake, obese individuals have high rates of micronutrient deficiencies, likely related to the abundance of nutrient-poor, energy-dense foods in the American diet. The risk of micronutrient deficiencies increases with the restricted intake and malabsorption associated with weight-loss surgery. Fortunately, most deficiencies are preventable. In order to minimize the risk of vitamin and mineral deficiencies, post-RYGB and SG patients must adhere to a lifelong regimen of vitamin and mineral supplementation and laboratory testing.

Following bariatric surgery supplementation should consist of a minimum of two adult multivitamins with iron and other minerals daily, 400–500 mg of elemental calcium, preferably as calcium citrate three times daily, a minimum of 75 μg (3000 IU) of vitamin D daily, and vitamin B_{12}, typically 500 μg/day, to achieve and maintain normal blood levels. Chewable supplements are preferred for up to 6 months postoperatively; thereafter, a wide variety of supplements are available, often in multiple forms (e.g., chewable, liquid, or sublingual). Accommodations should be made based on patient preference and tolerance (e.g., a patient may choose a chewable multivitamin that is missing adequate iron

and an alternative iron source would then be recommended). Patient choice of supplements may be influenced by cost, availability, advertising, and many other factors; providers should therefore make a habit of inspecting all vitamin and mineral products for proper dosing. Supplements often call for more than one unit (tablet, capsule) to provide the nutrient dosage referred to as a "serving size" on the nutrition label leading to confusing and potentially improper dosing. There are a number of multivitamin and mineral supplements available which are formulated to meet the specific needs of post-weight-loss surgery patients.

Patients should be counseled that lifelong vitamin and mineral supplementation and monitoring of laboratory tests is imperative to avoid deficiencies and maintain good health. Some deficiencies may take years to develop, and patients may be lulled into a false sense of security when they exhibit no immediate symptoms with sporadic intake or cessation of supplementation.

Iron and Other Minerals

Screening for iron deficiency should be performed at regular intervals following bariatric surgery. Low iron stores (hypoferritinemia) and iron deficiency anemia may occur in up to 50% of RYGB patients, less commonly in SG patients, but may occur after any bariatric procedure [9, 10]. Menstruating females are at higher risk. Common signs of iron deficiency include fatigue or lethargy, ice chewing, pallor, shortness of breath, and restless legs. Postsurgical hypochlorhydria associated with the RYGB and to a lesser degree the SG inhibits the reduction of ferric iron (Fe^{3+}) into the more readily absorbed ferrous state (Fe^{2+}). The RYGB surgically bypasses the duodenum and proximal jejunum, which are the preferential sites of absorption of iron and other nutrients.

In addition, dietary sources of well-absorbed heme iron, such as red meat, are often poorly tolerated by postsurgical patients. For some patients (men, postmenopausal women), iron needs will be met by the recommended multivitamin supplement that includes iron. Other patients will require additional iron supplementation up to 150–200 mg/day of elemental iron. Ingestion of iron and calcium supplements should ideally be separated by 4 h to avoid competitive inhibition of absorption. For patients who do not respond to increased oral supplementation, alternative treatment, such as IV iron infusion, may be necessary.

Zinc, copper, and selenium deficiencies have been reported in post-RYGB patients though the incidence is lower than that seen with iron. Routine annual screening for zinc and copper deficiency is recommended after RYGB. Screening for selenium should also be considered based on symptoms such as poor wound healing and unexplained anemia [8].

Calcium and Vitamin D

Calcium and vitamin D deficiencies are of particular concern following bariatric surgery and may cause secondary hyperparathyroidism with resulting negative effects on bone health. Preoperative obesity has been associated with substantially higher rates of vitamin D insufficiency and deficiency compared to the nonobese population [11].

Calcium is preferentially absorbed in the duodenum and proximal jejunum. Absorption of calcium is dependent on adequate levels of vitamin D and an acidic environment which makes absorption especially problematic after the RYGB. In light of this, calcium citrate is recommended for improved absorption in a hypo- or achlorhydric environment.

Vitamin D deficiency or insufficiency should be treated with increased oral doses of vitamin D_3. Significant deficiency (<20 ng/mL) in the presence of malabsorption may require treatment with 1250 μg (50,000 IU) of vitamin D_2 one to three times a week.

In the presence of decreased dietary intake or impaired absorption of calcium, normal blood calcium levels may be maintained through bone resorption of calcium and decreased urinary calcium excretion. Because of such compensatory responses, serum calcium alone is not a reliable indicator of calcium status, and other laboratory measures should be assessed, such as 24-h urinary calcium, parathyroid hormone, and alkaline phosphatase.

Vitamin B_{12} (Cobalamin)

Vitamin B_{12} deficiency in the post-bariatric surgery patient is multifactorial. Reduction in gastric acid production impairs the ability to cleave vitamin B_{12} from bound protein. Production of intrinsic factor is impaired; it is produced by parietal cells of the stomach and is necessary for absorption of vitamin B_{12} in the terminal ileum. Vitamin B_{12} deficiency symptoms include paresthesia of the hands and feet and may occur in spite of normal serum B_{12} levels. With the complex pathway of normal B_{12} absorption disrupted, bariatric surgery patients may utilize passive absorption of vitamin B_{12} by taking oral crystalline B_{12} (350–1000 μg daily) or intranasal B_{12} (500 μg weekly). If B_{12} levels fail to respond, intramuscular injection of 1000 μg/month may be used.

Vitamin B_1 (Thiamin)

Thiamin is a water-soluble vitamin, and deficiency can therefore occur quickly. In the bariatric surgery patient, reduced intake and episodes of nausea and vomiting may rapidly deplete the body's limited store of thiamin. Some multivitamins may not provide the recommended ≥12 mg of thiamin daily; therefore, a B-complex supplement providing 50–100 mg daily should be used. Clinicians should be aware of early symptoms of deficiency such as muscle cramping, paresthesia, gait abnormalities, and potential Wernicke encephalopathy or beriberi. Symptoms may resolve with oral doses of 100 mg/2–3 times daily; however, IV doses may be necessary for more severe cases. Of note, the administration of glucose can be harmful and should be avoided if thiamin deficiency is suspected.

Alcohol

Post-weight-loss surgery patients are more susceptible to the effects of alcohol. It is absorbed more readily and eliminated from the body less efficiently after both RYGB and SG [8]. More research is needed into the effects of alcohol on post-bariatric surgery patients, but it is clear that small amounts of alcohol may have magnified effects with resulting inebriation and impairment, especially following RYGB. Avoiding alcohol during rapid weight loss is advised, and strictly limiting or abstaining from alcohol thereafter is encouraged. Providers should inquire about alcohol intake at all patient visits and make appropriate referrals when needed.

Weight Regain

Obesity is a disease that often proves resistant to treatment. While bariatric surgery has proven to be an effective treatment for obesity, weight regain remains a significant concern. The causes of this are not well defined but are, in part, related to patients returning to presurgical lifestyles which encourage weight gain. The positive effects of weight-loss surgery (reduced hunger, early satiety) and negative feedback (abdominal discomfort, DS) may diminish with time allowing patients to tolerate a greater variety and larger volume of food. Patients may discover that they can "graze," i.e., eat many small

frequent meals throughout the day, leading to excessive calorie intake. As the rapid weight loss of the first 6 months wanes, early excitement and enthusiasm for exercise and lifestyle changes may subside. Patients report that the positive feedback from friends and family becomes less frequent. Patients can be reminded to look at other positive lifestyle benefits (being able to tie their shoes, walking up stairs without becoming winded) and improvement in comorbid medical conditions as evidence of the benefits of sustained weight loss.

At 1-year postoperative, the median percent excess weight loss (%EWL) has been reported to be 66.5% for the RYGB and 56% for the SG [12]. It is not unusual for patients to experience a slight weight gain (10–15 lbs) from their nadir as they adjust to a new and sustainable lifestyle. Of greater concern is the patient whose weight continues to creep up slowly over time. Patients and clinicians should monitor weight closely. Early intervention is critical when significant weight gain is detected as it may be a harbinger of the return of comorbid medical conditions or impair the ability to be physically active. Patients who regain weight may feel shame and perceive themselves as failures making them reluctant to return for follow-up appointments. Appropriate referral to a multidisciplinary team, including a registered dietitian, behavioral health specialist, and bariatrician, should be considered. Pharmacologic treatment may be useful in some patients. Significant weight regain may also be related to changes in the surgical anatomy, such as stretching of the pouch or gastrojejunal anastomosis, or the development of a gastrogastric fistula. In such cases, patients should be referred back to their bariatric surgical team.

Conclusion

In those patients for whom medical management proves inadequate, bariatric surgery may be considered. The procedure has been consistently shown to help obese patients achieve significant and sustained weight loss with concurrent improvement of obesity-related comorbid medical conditions and quality of life. Bariatric surgery is often referred as a "tool" to assist patients in achieving their weight-loss goals, reducing or eliminating obesity-related comorbid conditions, and improving quality of life.

It is generally accepted that adequate nutritional evaluation and dietary guidance is vital to any comprehensive approach to the perioperative care of the bariatric surgical patient. The potential for long-term nutritional deficiencies and weight regain is well established and underscores the need for lifelong surveillance. This chapter provides clinical guidance on nutritional considerations following bariatric surgery.

Though some bariatric surgery patients remain under the care of a dedicated bariatric surgery team, studies have shown dramatic drop-offs in patient attendance at follow-up appointments over time, with rates of attendance as low as 10% at 36 months [13]. Many of these patients will continue to have contact with primary care providers or specialists. Routine surveillance of nutritional status, including regular laboratory testing for potential deficiencies, monitoring and appropriately adjusting vitamin and mineral supplements, and regular weight checks, can allow for early intervention if problems occur.

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Nutrition and the Assessment of Sarcopenia

25

William J. Evans and Robert R. Wolfe

Keywords

Sarcopenia · D_3-creatine dilution · Dietary protein requirement · Anabolic resistance · Essential amino acids

Key Points

- Sarcopenia should be defined as the age-related decrease in skeletal muscle mass.
- In older people, muscle mass (but not lean body mass) is strongly associated with health-related outcomes such as risk disability, falls, hip fracture, and mortality.
- Anabolic resistance is age-related and is defined as a decreased postprandial rate of muscle protein synthesis compared to younger subjects.
- Aging is associated with a substantial decrease in energy needs but an increase in dietary protein requirement.
- Supplements or proteins that are rich in essential amino acids can overcome anabolic resistance and should be a component of a healthy diet for those over 65 years.

Introduction

A reduction in lean body mass and an increase in fat mass are the most striking and consistent changes associated with advancing age. Skeletal muscle [1] and bone mass are the principal, if not exclusive, components of lean body mass that decline with age. The term "sarcopenia" (from the Greek: *sarx* for flesh, *penia* for loss) was used by Evans and Rosenberg [2] and originally described by Evans and Campbell [3] and further defined [4] as age-related loss of muscle mass. This loss of muscle results in decreased strength, metabolic rate, aerobic capacity, and, thus, functional capacity. Subsequently, sarcopenia can more specifically be defined as a subgroup of older persons with low lean body mass

W. J. Evans (✉)
Department of Nutritional Sciences and Toxicology, University of California, Berkeley, CA, USA
e-mail: william.evans@berkeley.edu

R. R. Wolfe
Donald W. Reynolds Institute on Aging, University of Arkansas for Medical Sciences, Little Rock, AR, USA

Division of Geriatrics, Duke University Medical Center, Durham, NC, USA
e-mail: rwolfe2@uams.edu

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(LBM), usually defined as being two standard deviations below the mean LBM of younger persons (usually age 35 years) [5]. Sarcopenia has become recognized as an important geriatric condition and a key precursor to the development of frailty [6, 7]. The original description of sarcopenia was that, like osteopenia (low bone density), it predicts risk of a bone fracture and loss of muscle mass and is a powerful predictor of late-life disability.

Sarcopenia very likely begins in early adulthood [8] with atrophy and loss of type II muscle fibers [9, 10] and continues throughout life as a result of complex interaction of environmental and genetic causes. The etiology of sarcopenia is complex. Skeletal muscle is among the most plastic of tissues and, as a post-mitotic tissue, undergoes constant turnover through changes in muscle protein synthesis and breakdown. Although an important contributor to sarcopenia is a loss of motor units, alterations in muscle protein metabolism play a critical role in the trajectory of sarcopenia with advancing age. Among factors that may contribute to a reduced rate of muscle protein synthesis with advancing age are increased body fatness and insulin resistance, reduced levels of physical activity, a reduction in circulating testosterone and growth hormone, inflammation, and the presence of chronic disease. This chapter will focus on nutritional influences on skeletal muscle and body composition with a particular focus on macronutrients, dietary protein (and amino acids), energy, and carbohydrates.

Muscle Mass and Lean Body Mass

Assessment of Muscle Mass

The measurement of muscle mass in humans is difficult; most of the available methods require assumptions that may not always be valid and have variable degrees of accuracy and difficulty. In particular, the assessment of total body skeletal muscle mass has, until recently, been problematic. Skeletal muscle is a significant, but not the only, component of LBM. In most clinical trials [5, 11, 12], lean mass is incorrectly referred to as muscle mass. The use of FFM as a surrogate assessment of muscle mass has resulted in erroneous conclusions on the importance of skeletal muscle in development of late-life dysfunction and risk of chronic disease.

Lean Body Mass

The use of LBM as a surrogate for muscle mass relies on assumptions that the muscle is a constant proportion of LBM in all populations and does not change with advancing age. A number of tools are available for assessing LBM, including measuring body density by underwater weighing or whole-body plethysmography, determining total body water (TBW), using bioelectrical impedance, or using dual X-ray absorptiometry (DXA). DXA is, currently, the most widely used to estimate LBM. Lean mass includes muscle mass, water, organ weight, and all other non-bone, non-fat soft tissue (Fig. 25.1). Therefore, DXA does not measure muscle mass specifically. Baumgartner et al. [5] using DXA demonstrated that low lean mass of the arms and legs (appendicular lean mass) was associated with worse functional status. A meta-analysis by Schaap et al. [13] found that various measures of muscle size (both lean mass and muscle cross-sectional area by CT and BIA) were not associated with functional decline, while poor muscle strength was associated with decline. Although the use of DXA to assess muscle mass is precise and its feasibility and safety are well-known, DXA is inaccurate for measuring muscle mass since DXA does not, in practice, provide a reliable measurement of skeletal muscle mass.

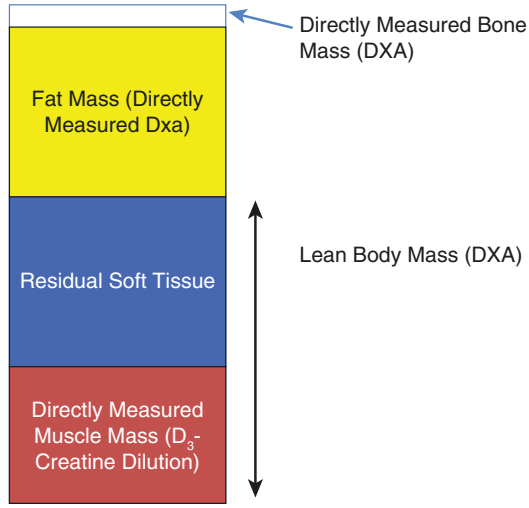

Fig. 25.1 Body composition using DXA and D_3-creatine dilution to measure muscle mass. Importantly, muscle mass is only one component of lean body mass (LBM) which includes blood, viscera, and body water. LBM is not a surrogate measurement of muscle mass

Lean Body Mass and Functional Capacity

A meta-analysis [13] of longitudinal observational studies in older people (≥65 years), conducted between 1976 and 2012, examined body composition (BIA, DXA, CT) and physical functional capacity. The authors concluded that "low muscle mass was not significantly associated with functional decline." They also concluded that the role of muscle mass in the development of functional decline was unclear but was "much smaller than the role of fat mass and muscle strength." The loss of skeletal muscle mass, per se, is only weakly associated with functional outcomes in older people and very likely a result of using the measurement of lean mass as a proxy for muscle mass rather than using a direct measurement of muscle mass.

Indeed, this lack of a strong association between lean mass (as a surrogate measurement of muscle mass) and outcomes in elderly people has led to several consensus definitions of sarcopenia that include measures of muscle strength and/or physical performance in addition to measures of lean mass alone [14]. Using DXA-derived appendicular lean mass from multiple cohort studies in older people, Cawthon et al. [15] reporting for the Foundation for the National Institutes of Health Biomarkers Consortium Sarcopenia (FNIH) described specific cut points in lean mass that were associated with muscle weakness (grip strength). While the results showed that specific levels of low lean mass were associated with weakness, the association of low lean mass with slow walking speed was inconsistent. Because of the weak association between lean mass and outcomes, alternative definitions of diagnostic criteria for sarcopenia have incorporated various measures of strength or function [16–19]. As per the consensus definition from FNIH sarcopenia project [20], cut points for weakness are grip strength <26 kg for men and <16 kg for women and for low lean mass, appendicular lean mass adjusted for body mass index <0.789 for men and <0.512 for women.

Measurement of Skeletal Muscle Mass Oral Creatine Dilution

An accurate measure of muscle mass can be obtained with the D_3-creatine (D_3Cr) dilution method. It assumes that about 98% of the total body creatine is sequestered in skeletal muscle and that creatine

is turned over in the muscle through the conversion of creatine to creatinine. Importantly, the measurement of D_3-enrichment in urinary creatinine (Crn) does not require dietary control and relies on a single-spot, fasted urine sample taken 48–96 hours after dosing [21]. Because of the relatively slow turnover of intramyocellular Cr (~1.7%/day), subsequent longitudinal measurements require a pre-dose urine sample as well as a post-dose sample to correct for residual D_3-Cr. This method has been validated in rats and humans [21].

Creatine pool size provides an indicator of functional muscle mass independent of lipid and fibrotic tissue, both of which increase with advancing age [22] and reduce the accuracy of the measurement of purely anatomic muscle mass using radiographic imaging or DXA. This method has low subject burden as a subject simply swallows a capsule and produces a fasting urine sample later [23]. There is no limit to how many repeat measurements can be made as long as a urine sample is collected prior to subsequent doses of D_3-creatine to correct for baseline enrichment of urine D_3-creatinine.

In a large cohort study of MrOS trial, muscle mass was measured in 1382 men (mean age 84.2 yrs.) along with DXA lean mass [24]. Those with the lowest muscle mass/weight by D_3Cr dilution have the highest risk of incident mobility limitation and injurious falls and much worse physical performance and lower strength than those with higher muscle mass. These associations were not explained by confounding factors such as age, comorbidities, or activity level. In the same study, DXA-based measures of lean mass had much weaker (if any) associations with these outcomes. This is the first large cohort study with a side-by-side comparison of DXA estimates and D_3Cr muscle mass measurements on outcomes related to functional capacity and disability. No significant relationship was observed between muscle mass and appendicular lean mass. In this population, muscle mass was also associated with risk of disability as assessed by activities of daily living and instrumental activities of daily living and mortality [25]. In addition, there was no longitudinal change in DXA lean mass over 1.6 years, but there was a 5.7% decline in muscle mass and a reduction in habitual gait speed and grip strength [26]. Without a measurement of muscle mass and using only DXA evidence for a lack of change in LBM, the conclusions on the causes of the longitudinal reduction in function would be quite different. This substantial 3.6% annualized loss of the muscle was previously unreported in this age population and points to the need for a better understanding of nutritional strategies as a countermeasure. The relationship between body fatness, muscle mass, and functional outcomes was also explored in this cohort of elderly men. Sarcopenic obesity has been described as an additive or synergistic effect of low lean mass and high amount of body fatness on functional capacity and risk of disability [27]. However, when muscle mass is measured accurately, body fatness has very little (if any) additive effect on function or other health-related outcomes [28]. Sarcopenic obesity is likely an anachronistic term resulting from measurement error.

Energy Needs During Aging: Effects on Sarcopenia

Energy requirements decrease progressively with advancing age. Total energy expenditure (TEE) in the ninth decade of life averages 2249 ± 413 and 1781 ± 315 kcal/day for men and women, respectively [29]. This is a significant decrease from the energy requirements in the eighth decade of life in men (2482 ± 476 vs. 2208 ± 376 kcal/day) but not in women (1892 ± 271 vs. 1814 ± 337 kcal/day). The investigators reported that energy expenditure from physical activity was lower in women, and the lack of change in TEE over 10 years was, at least in part, due to little change in physical activity in women. Data from the Baltimore Longitudinal Aging Study [1] showed an age-related decrease in basal metabolic rate (BMR) that was accompanied by a similar reduction in skeletal muscle mass. The authors concluded that muscle mass (rather than other components of LBM) was primarily responsible for the decreased BMR. Decreasing BMR along with decreasing average levels of physical activity results in a significant decrease in energy needs with advancing age. A simple reduction in total food intake to maintain body weight results in a decreasing protein and micronutrient intake along with a continuing decrease in muscle mass (sarcopenia). As a result, older men and women need to consume more nutrient-dense, but not energy-dense, foods.

Increased body fatness and changing body fat distribution is one of the most often measured features of advancing age. Using computed tomography (CT), Borkan et al. [30] first revealed differences in total fat and, particularly, fat distribution, in older people. They reported fatty infiltration of tissues, particularly skeletal muscle. Goodpaster et al. [31] reported that aging is associated with increasing intramuscular fat, increased insulin resistance, and decreased force production in the muscle. Data from the longitudinal Health ABC study show that in older people, weight gain is almost entirely the result of increased body fat with very little increased LBM. Villareal et al. [32] showed that 96% of obese men and women over the age of 70 years were classified as frail.

These data show that older people with obesity have reduced functional capacity, fatigue, slow walking speed, and reduced levels of physical activity. Being overweight or obese in middle age also results in a substantial increased risk of disability [33]. Compared to young people, weight loss among older men and women results in an exaggerated loss of lean mass and strength. In older women, weight loss is associated with increased rates of hip-bone loss and a twofold greater risk of subsequent hip fracture, irrespective of current weight or intention to lose weight [34]. The authors concluded that, "these findings indicate that even voluntary weight loss in overweight elderly women increases hip fracture risk."

With an already low energy requirement, a reduction in energy intake for weight loss may result in nutrient deficiencies, particularly protein. Decreased energy intake increases dietary protein needs, and an 80 kg older woman with an energy requirement of 2000 kcal/day, consuming a 500 kcal/day deficit diet to lose weight, would need to consume about 25% of her daily energy as protein to get the 1.2 g protein/kg. However, for older people with obesity, weight loss can improve quality of life and functional capacity [33].

Skeletal Muscle Protein Metabolism

Muscle Protein Turnover

The rate of loss of the muscle with aging is variable but averages between 0.5 and 1.0% of muscle mass per year after age 70 [34]. The physiological basis for loss of muscle over time is an imbalance between the rates of muscle protein synthesis and breakdown.

In the muscle, protein turnover serves to replace older muscle fibers that have lost their peak strength of contraction with newer, more efficient fibers [35]. For this reason, muscle strength is directly related to muscle protein turnover in older individuals [36]. Skin has a relatively rapid rate of protein turnover, and a small increase in the rate of breakdown relative to the amino acids needed for new skin proteins cannot be derived entirely from skin protein breakdown because there is a certain obligatory rate of oxidation of amino acids. Eleven of the 20 amino acids in body proteins can be produced in the body, but the other nine are essential and must be derived from the diet, creating a potential bottleneck for muscle protein replacement.

Muscle Protein as the "Reservoir" of Amino Acids

The net breakdown of muscle protein is the primary source of essential amino acids required to maintain a balance between protein synthesis and breakdown. Muscle protein is a reservoir of stored amino acids that can be drawn upon in the absence of dietary intake. In contrast to vital tissues and organs that generally have a limited capacity to endure a net loss of protein, a significant percentage of muscle protein can be lost without endangering survival. Thus, there is a net release of both essential and non-essential amino acids from the muscle in the post-absorptive state that maintains an adequate amino acid supply for the synthesis of protein in vital tissues and organs. Under normal conditions the net loss of muscle protein in the post-absorptive state is restored by a net uptake of those amino acids

in the postprandial state. Over the course of the day, the period of net release of amino acids from the net breakdown of muscle protein in the post-absorptive state is balanced by the net uptake of amino acids in the postprandial state, such that there is no net change in the amount of muscle protein. In the case of the progressive loss of the muscle with aging, the overall balance between protein synthesis and breakdown is negative, meaning that the net gain in muscle protein in the fed state is insufficient to compensate for the net loss of protein in the post-absorptive state.

Mechanisms Responsible for Net Muscle Protein Loss

A principal dilemma in aging is that the imbalance between muscle protein synthesis and breakdown can be very small, yet when extrapolated over a whole year can become significant. If we take a midpoint average of 0.75% of muscle loss per year [34] and an average muscle mass of an older individual of 25 kg [24], then approximately 0.19 kg of the muscle is lost per year. Expressed in conventional units of measurement of the fractional synthetic rate (FSR) of muscle protein (%/hour), the imbalance between protein synthesis and breakdown over the entire year corresponds to only 0.00002%/hour, as compared to an average muscle protein synthetic rate of 0.0005 +/− 0.00002 (SEM) %/hour [37]. The total difference in FSR necessary to explain the loss of muscle mass with aging is only equal to the standard error of the mean of the measured value of FSR in human subjects. Thus, it would be very difficult to measure a difference in the basal rates of muscle FSR between young and elderly subjects, even if the loss of the muscle with aging over time is due entirely to reduction in the basal rate of synthesis. Thus, no measurable difference in basal muscle protein synthetic rates between young and elderly subjects has been detected [38, 39], but these results must be interpreted with caution.

Given the inherent difficulty of determining the metabolic basis for the loss of muscle mass with aging by measuring the basal rate of protein synthesis, greater insight into the mechanisms underlying the loss of muscle protein with aging can be gained by considering changes that occur in the regulation of muscle protein metabolism in various circumstances. There are two principal ways in which muscle protein metabolism is regulated: signaling through mTORC1 (mechanistic target of rapamycin complex) [38] and the availability of amino acid precursors of protein synthesis [39]. While the two processes are distinct, they are intimately related.

Anabolic Resistance

Consumption of dietary protein results in the absorption of amino acids and the activation of protein synthetic processes throughout the body, particularly muscle protein synthesis [40]. There is a direct relationship between the amount of dietary protein intake and the net gain in body protein in young healthy individuals [41]. Anabolic resistance refers to circumstances in which dietary protein has a diminished stimulatory effect on the net production of new muscle protein. Critical illness [42] or the response to the severe trauma of a major burn injury [43] provide clear-cut examples of anabolic resistance. Aging is also one of the factors leading to anabolic resistance.

As much as 30–35% of total caloric intake as protein may prove to be beneficial in older adults [40]. Although this level of dietary protein intake may be impractical for many older individuals, the age-related decrease in energy need makes a greater relative amount of high-quality protein an important consideration. For this reason, dietary supplements that stimulate muscle protein synthesis may play an important role in protein nutrition in the elderly. Data from the Health ABC study [44] strongly suggest that inadequate dietary protein intake may result in an acceleration of sarcopenia in older subjects. Tieland et al. [45] demonstrated that compared to placebo, consumption of an additional 15 g of high-quality protein at breakfast and lunch results in increased strength and physical performance in a group of frail older men and women.

Nutritional Support for Sarcopenia Prevention

Dietary Supplements and Protein Nutrition in Elderly

Dietary supplements of nutrients that act as pharmaceutical agents (i.e., nutraceuticals) to increase muscle mass and improve function have been researched extensively. The following may have at least some experimental support in relation to (*1*) muscle mass/protein metabolism (leucine, hydroxyl β-methylbutyrate (HMB), creatine, vitamin D, ursolic acid, and phosphatidic acid) and (*2*) strength or endurance capacity (HMB, carnitine, creatine, nitrates, and β-alanine) [46]. Of these potential nutraceuticals, HMB, a metabolite of leucine, probably has the most scientific support for a beneficial effect on the muscle in aging. Ingestion of 3 g of HMB has been shown to stimulate muscle protein synthesis and inhibit muscle protein breakdown [47]. Longer-term studies have also found a benefit of HMB. A recent meta-analysis included 15 randomized controlled trials that involved 2137 subjects. There was evidence that HMB increases skeletal muscle mass and function, although the effect sizes were small [48]. HMB supplementation has especially been promoted as reducing age-related loss of muscle mass [49]. However, the magnitude and physiological significance of these effects are small. For example, the loss of lean body mass was attenuated in elderly subjects confined to bed rest for 10 days, but this did not translate to improved retention of physical function [50].

The reason that the effect size of HMB is small is that the magnitude of the stimulation of protein synthesis is limited by the extent to which the efficiency of the reincorporation of essential amino acids from protein breakdown can be increased. In the absence of dietary intake of protein, protein breakdown is the only source of EAAs since they cannot be produced in the body. Normally, about 85% of EAAs released by muscle protein breakdown are directly reincorporated into protein, and about 15% are oxidized [51]. The only EAAs available for an increased rate of muscle protein synthesis are the EAAs that would otherwise have been oxidized. This means that only about 15% of EAAs from protein breakdown are potentially available for an increased production of muscle protein mediated by an increased activation of mTORC1. Other tissues compensate for limited intracellular availability of EAAs by drawing EAAs from the blood that have been released as a consequence of net muscle protein breakdown. While the net release of EAAs from the muscle into the blood helps maintain protein homeostasis throughout the body, this role of muscle protein further reduces the amount of EAAs available for muscle protein synthesis, and thus only a limited increase in muscle protein synthesis is possible in the absence of consumption of EAAS. This discussion leads to the inevitable conclusion that increasing dietary consumption of EAAs via high-quality proteins or dietary supplements is essential for the reversal of age-related decrements in muscle mass and function.

Essential Amino Acids as Dietary Supplements

The importance of the EAA component of dietary protein has been known for more than 100 years. The quality of a protein as determined by the Digestible Indispensable Amino Acid Score is determined by the amount of EAAs per gram of protein [52]. It is often impractical for elderly individuals to consume sufficient dietary protein to maximize beneficial responses in light of a reduced energy requirement. Consumption of dietary sources of high-quality protein, such as meat and fish, may be limited in aging individuals by cost, changes in food preferences, difficulty with chewing and swallowing, and decreased cooking ability. Thus, consumption of a dietary supplement of EAAs is a reasonable approach to meeting optimal EAA intake levels. Co-ingestion of non-essential amino acids is not necessary for the full anabolic response to supplemental EAAs [53], so an EAA supplement can be consumed in a condensed physical volume that does not impact the metabolic response to the next meal [54]. In addition, absorption of ingested free amino acids is complete [55]. Importantly, when

EAAS stimulate protein synthesis, the non-essential amino acids that are incorporated into the newly synthesized protein come from more efficient reutilization. As a result, urea and ammonia production may fall after consumption of EAA, thereby lessening the potential adverse effects of excessive nitrogen intake that can occur in critical illness or other conditions in which kidney function might be impaired. This may be particularly important for older, institutionalized men and women with an extremely low level of physical activity and energy need. In this case, even modest decreases in appetite and food intake may have severe adverse consequences [56].

The first report of the beneficial effect of an EAA-based dietary supplement appeared in 2000 [57], and since then more than 90 clinical trials have documented various benefits of dietary EAA supplements. Most importantly, dietary supplements of EAAs have a powerful anabolic effect. On a gram per gram basis, EAAs elicit three to four times the anabolic effect of whey protein [58], which is the most effective intact dietary protein supplement [59]. EAA supplements have been particularly useful in improving physical function in the elderly [60–62]. While the loss of physical function due to 10 days of bed rest in elderly people was not ameliorated by consumption of HMB [50], EAA supplementation in the same experimental paradigm significantly reduced, and even eliminated in some cases, decrements in the functional measures assessed [63].

Insulin and Protein Nutrition

Despite the well-known anabolic effects of insulin, it has been a challenge to determine the role of insulin in regulating protein metabolism and how resistance to the action of insulin on glucose metabolism affects protein metabolism. The difficulty in investigating the physiological role of insulin in relation to protein metabolism stems from the suppressive effect of insulin on the plasma concentrations of amino acids, including the EAAs [64]. A decrease in the availability of EAA precursors of protein synthesis reduces the rate of protein synthesis, irrespective of the prevailing insulin concentration [65]. As a result, an increase in insulin concentration in blood generally results in the inhibition of protein synthesis [59]. The interpretation of the role of changes in insulin concentration on protein metabolism is further complicated by changes in counter-regulatory hormones that help maintain a constant blood glucose level but that also could potentially affect protein metabolism. Finally, changes in plasma insulin concentration affect both plasma glucose and free fatty acid (FFA) levels, both of which could impact the rate of protein synthesis.

The isolated effect of insulin on muscle protein synthesis has been assessed in human subjects by the infusion of insulin directly into the femoral artery [66]. This approach can produce local hyperinsulinemia in the muscle without affecting peripheral levels, thereby avoiding the complication of systemic responses to an increase in insulin concentration. With this experimental paradigm, local hyperinsulinemia-stimulated muscle protein synthesis [66, 67], and larger increases in insulin concentration, also suppressed muscle protein breakdown [67]. The stimulation of muscle protein synthesis by insulin was mediated physiologically by increased muscle blood flow and thus delivery of EAAs [67].

Insulin resistance is common in aging and includes decreases in both glucose uptake by the muscle and the suppression of hepatic glucose production [68]. Impaired responsiveness to the anabolic action of insulin may also contribute to the loss of muscle mass and strength with aging. Increasing capillary perfusion increases the delivery of EAAs to muscle tissue, thereby increasing muscle protein synthesis [64]. This study highlights the difference between insulin resistance with regard to glucose as opposed to protein metabolism with aging. While the normal responsiveness of muscle protein synthesis was restored by increased capillary perfusion and delivery of EAAs to the muscle, the diminished effectiveness of insulin-stimulated glucose uptake was not improved [69]. Therefore, insulin resistance is likely to be the most important reason for the large decrease in lean mass and muscle protein FSRseen in older men and women [70].

Conclusion

Sarcopenia is the age-related loss of skeletal muscle mass. New data using a direct and accurate measure of total body muscle mass suggests that loss of muscle mass is strongly associated with age-related risks of disability, falls, hip fracture, and mortality. The etiology of sarcopenia is complex and is linked to age-related decreases in circulating testosterone and growth hormone, insulin resistance, and reduced levels of physical activity, each of which have effects on reducing postprandial rate of muscle protein synthesis. Dietary protein requirements increase and energy needs decrease with advancing age despite a decrease in muscle and lean mass. The result is that many older people consume relatively low-protein diets as they reduce their energy intake to maintain body weight. Inadequate protein intake has been identified as a potential risk factor for accelerated loss of muscle mass in older people. Essential amino acids (EAAs) have a powerful effect on stimulating muscle protein synthesis. High-quality protein, rich in EAAs, should be a central component of a diet aimed at preventing sarcopenia. Protein supplements enriched with EAAs may also be a strategy to stimulate muscle protein synthesis for those with a poor appetite or those attempting to maintain a lower energy intake. We recommend 20–30 g/day of EAAs consumed as 10–15 g amounts during regular meals. Importantly, there is no evidence that an increase in dietary protein or increased use of protein supplements has any harmful effects in elderly people and are likely to improve both muscle and bone health.

Consideration of a single definition of sarcopenia as the age-related loss of skeletal muscle mass may help to focus on public health strategies specific to nutritional status and muscle metabolism and the maintenance of muscle mass to prevent disability and loss of independence (Fig. 25.2).

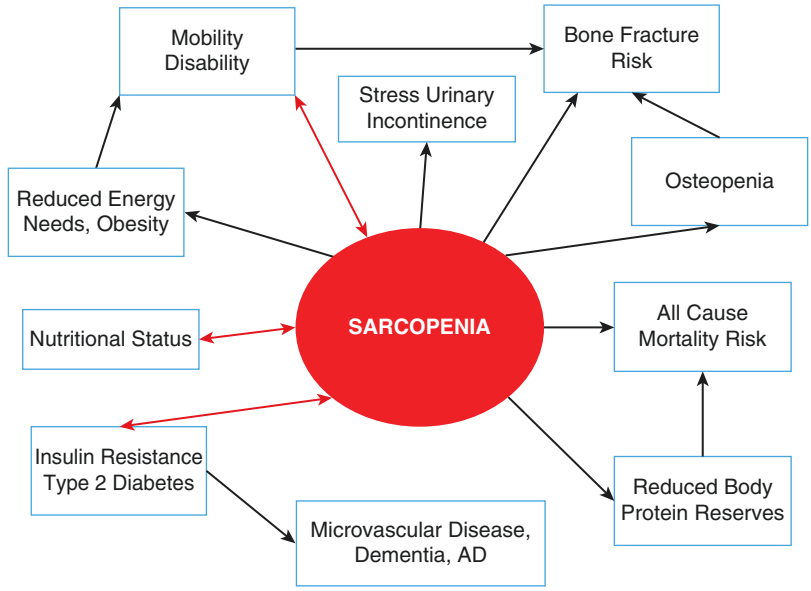

Fig. 25.2 Sarcopenia is central to a number of age-related diseases and conditions. Black lines indicate a direct effect of muscle, and red lines suggest a more complex relationship in both directions. For example, low muscle mass is associated with reduced levels of physical activity. Low level of physical activity has a direct influence on the rate of muscle protein synthesis, resulting in an accelerated rate of loss of muscle

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Suggested Further Readings

Cawthon PM, Orwoll ES, Peters KE, Ensrud KE, Cauley JA, Kado DM, et al. Strong relation between muscle mass determined by D_3-creatine dilution, physical performance and incidence of falls and mobility limitations in a prospective cohort of older men. J Gerontol A Biol Sci Med Sci. 2019;74:844–52.
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Drug Interactions with Food and Beverages

26

Garvan C. Kane, Sheila M. Wicks, Temitope O. Lawal, Nishikant Raut, and Gail B. Mahady

Keywords

Alcohol · Caffeine · Drug metabolism · Cranberry · CYP3A4 · Garlic · Ginger · Grapefruit · Statins Tyramine

Key Points

- Acidic beverages aid in the absorption of antifungal drugs.
- Cranberry supplements may enhance the effects of warfarin.
- Dairy and calcium supplements can reduce drug absorption and effects.
- Grapefruit juice, alcohol, and caffeine may interfere with drug metabolism.
- Garlic enhances anticoagulant effects and reduces protease inhibitor levels.
- Vitamin K-rich foods impair anticoagulant effects of warfarin.

Introduction

Proper adherence to drug regimens is important for optimizing clinical outcomes and reducing the risk of adverse events. This is especially important for patients with chronic diseases, where adherence levels may be a low as 50%. For proper administration of medications, patients should always be encouraged

G. C. Kane
Division of Cardiovascular Disease, Department of Internal Medicine, Mayo Clinic, Rochester, MN, USA

S. M. Wicks
Department of Clinical and Molecular Medicine, Rush University, Chicago, IL, USA

T. O. Lawal
Department of Pharmacy Practice, University of Illinois at Chicago, Chicago, IL, USA

Department of Pharmaceutical Microbiology, University of Ibadan, Ibadan, Nigeria

N. Raut
Department of Pharmacy Practice, University of Illinois at Chicago, Chicago, IL, USA

G. B. Mahady (✉)
Division of Cardiovascular Disease, Department of Internal Medicine, Mayo Clinic, Rochester, MN, USA

Department of Pharmacy Practice, University of Illinois at Chicago, Chicago, IL, USA
e-mail: mahady@uic.edu

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to follow the label instructions carefully. In general, some medications should be taken with a full glass of water, some must be taken with food, while others should be taken on an empty stomach [1–3].

Patients should consult with a physician or pharmacist to determine if there are any foods that should be avoided while taking their medications [1–6]. Patients frequently ask about the best time to take their medicine relative to mealtime or whether they should take it with or without food? However, patients rarely ask about what specific foods should be avoided while taking their medications. In some instances, patients will be instructed to take their medication with a particular food or beverage to aid palatability (and hence compliance), minimize local irritation to the gastrointestinal tract, or aid in drug absorption. More importantly, there are many incidences when the consumption of specific foods in combination with certain medications presents a problem by interfering with the absorption, metabolism, or excretion of these drugs [1–6]. If these instances go unrecognized, therapeutic drug levels may become too high or too low leading to unmet therapeutic effects and possible drug-related adverse events.

This chapter highlights some of the main instances where concomitant ingestion of particular foods or beverages can interfere with medication action and then reviews how a better understanding of these interactions can sometimes be used to aid in patient management.

Medications to Be Taken on an Empty Stomach

Generally speaking, food slows absorption by reducing the drug's concentration as a result of simple dilution (see also Food–Drug interactions Table 26.1). However, in the majority of cases, the overall degree of final absorption is largely unaffected, with modest if any clinical effects. Food intake may have other effects on drug absorption: stimulation of gastric and intestinal secretions may aid drug dissolution, and fat-stimulated release of bile salts promotes the uptake of lipophilic compounds. However, in specific cases, for example, with levothyroxine, bisphosphonates, alendronate, and risedronate, the drugs should be taken first thing in the morning on an empty stomach with plain water.

While not technically a drug, iron supplements will also have much better absorption if taken on an empty stomach. However, while food typically cuts in half the amount of iron absorbed, it may be needed to minimize gastric irritation.

Specific Examples of Food–Drug Interactions

There are many examples of food–drug interactions. Some of the most important ones include the combination of grapefruit juice with many of the anticonvulsant, antihypertensive, antiarrhythmic, antihyperglycemic, and antipsychotic drugs. In addition, the anticoagulant, warfarin, interacts with many foods and beverages, with some foods increasing its anticoagulant effects, while others reduce the therapeutic effects of warfarin. Furthermore, dairy products and calcium can inhibit the adsorption of many drugs including antibiotics, and garlic products may reduce the therapeutic effects of antiretroviral drugs.

A more extensive list of specific food–drug interactions is described in Table 26.1.

Effects of Vitamin K on Warfarin Anticoagulation

With the increase in aging populations and cardiovascular diseases, the likelihood of thromboembolic events requiring the use of anticoagulants, such as warfarin, has also increased. Older patients often have comorbidities that require multiple drug therapy, thus increasing potential interactions with warfarin. The anticoagulant effect of warfarin is mediated through inhibition of the vitamin K-dependent coagulation factors II, VII, IX, and X. One key feature in the stability of the warfarin anticoagulant effect is week-to-week differences in the content of vitamin K in the patient's diet. Foods, particularly

Table 26.1 Drug–food interactions[a]

Drug	Food interaction	References
Acebutolol	Grapefruit ↑ DE	[5, 6]
Acetaminophen	Alcohol ↑ AE	[5, 8]
	Caffeine ↑ DE	
Amiodarone	Grapefruit ↑ DE	[6]
Amlodipine	Grapefruit ↑ DE	[6]
Aliskiren	Grapefruit ↑ DE	[6]
Artemether	Grapefruit ↑ DE	[6]
Atenolol	Grapefruit ↑ DE	[6]
Atorvastatin	Grapefruit ↑ DE	[5, 6]
	Alcohol ↑ AE	[5]
Barnidipine	Grapefruit ↑ DE	[6, 7]
Buspirone	Grapefruit ↑ DE	[6, 7]
Carbamazepine	Grapefruit ↑ DE	[5, 6]
	Alcohol ↑ AE	
Celecoxib and other NSAIDs	Alcohol ↑AE	[5]
Cefotetan	Alcohol ↑ AE	[5]
Cilostazol	Grapefruit ↑ DE	[6]
Ciprofloxacin	Dairy, Ca, Mg, Fe ↓ DE	[1]
Clomipramine	Grapefruit ↑ DE	[6]
Clozapine	Caffeine ↑ AE	[5, 8]
	Alcohol ↑ AE	[5]
Cyclosporine	Grapefruit ↑ DE	[6, 9]
Diazepam	Grapefruit ↑ DE	[5, 6]
	Alcohol ↑ AE	[5]
Disopyramide	Grapefruit ↑ DE	[6]
Doxycycline	Dairy, Ca, Mg, Fe ↓ DE	[1]
Ebastine	Grapefruit ↑ DE	[6]
Etoposide	Grapefruit ↑ DE	[6]
Felodipine	Grapefruit ↑ DE	[6, 9]
	Grape juice/red wine ↑ DE	[1]
Fexofenadine	Orange or grapefruit ↑ DE	[1, 6]
	Apple ↓ DE	
Fluvoxamine	Caffeine ↑ AE	[8]
Furafylline	Caffeine ↑ AE	[8]
Griseofulvin	Alcohol ↑ AE	[5]
Fe supplements	Food ↓ effect	[10]
Idrocilamide	Caffeine ↑ AE	[8]
Isocarboxazid	Tyramine ↑ AE	[10]
Isoniazid	Alcohol ↑ AE	[5]
	Tyramine ↑ AE	[10]
Isosorbide dinitrate	Alcohol ↑ DE	[5]
Isradipine	Grapefruit ↑ DE	[6]
Ketamine	Grapefruit ↑ DE	[6]
Levofloxacin	Dairy, Ca, Mg, Fe ↓ DE	[1]
Lithium	Caffeine ↓ DE	[8]
Loratadine	Grapefruit ↑ DE	[6, 7]
Linezolid	Alcohol, caffeine, tyramine ↑ AE	[5, 8]
Lovastatin	Grapefruit ↑ DE	[6]

(continued)

Table 26.1 (continued)

Drug	Food interaction	References
Methadone	Grapefruit ↑ DE	[6]
Mercaptopurine	Dairy, Ca, Mg, Fe ↓ DE	[1]
Metronidazole	Alcohol, ↑ AE	[5]
Mexiletine	Caffeine ↑ AE	[8]
Midazolam	Grapefruit ↑ DE	[6]
Minocycline	Dairy, Ca, Mg, Fe ↓ DE	[1]
Nicardipine	Grapefruit ↑ DE	[6]
Nifedipine	Grapefruit ↑ DE	[6]
	Grape juice ↑ DE	[1]
Nimodipine	Grapefruit ↑ DE	[6, 7]
Nisoldipine	Grapefruit ↑ DE	[6]
	Alcohol ↑ AE	[5]
	Grapefruit ↑ DE	[6]
Phenelzine	Tyramine ↑ AE	[5]
Pranidipine	Grapefruit ↑ DE	[6]
Propafenone	Grapefruit ↑ DE	[6]
Quinidine	Grapefruit ↑ DE	[6]
Quinolones	Caffeine ↑ AE	[8]
Saquinavir	Grapefruit ↑ DE	[1, 3, 4, 6]
	Garlic ↓ DE Grape juice↑ DE	
Sertraline	Grapefruit ↑ DE	[5, 6]
	Alcohol ↑ AE	
Sildenafil	Grapefruit ↑ DE Grape juice↑ DE	[1, 6]
Simvastatin	Grapefruit ↑ DE	[6]
Sulfa drugs	Alcohol ↑ AE	[5]
Tacrolimus	Grapefruit ↑ DE	[6]
Terfenadine	Grapefruit ↑ DE	[6]
Tetracycline	Dairy, Ca, Mg, Fe ↓ effect	[1]
Theophylline	Caffeine ↑ DE	[8]
Thyroid hormone	Food ↓ effect	[10]
Tolvaptan	Grapefruit ↑ DE	[6]
Tranylcypromine	Tyramine ↑ AE	[10]
Triazolam	Grapefruit ↑ DE	[6]
Verapamil	Grapefruit ↑ DE	[6]
Warfarin	Vitamin K-rich foods ↓ DE	[3, 11, 12–15]
	Garlic ↑ DE Grapefruit ↑ DE	
	Cranberry ↑ DE	
	Green tea ↓ DE	
	Soy ↓ DE	
	Ginger ↑ DE	
Zaleplon	Grapefruit ↑ DE	[6]
Zolpidem	Alcohol ↑AE	[5]

Ca calcium, *Mg* magnesium, *Fe* iron, *AE* adverse effects, *DE* drug effects

[a]This list is not meant to be exhaustive but merely highlighting some of the main food and beverages that may give rise to a clinically significant interaction with particular drugs

those high in vitamin K, include vegetable oils, asparagus, broccoli, brussels sprouts, cabbage, lettuce, parsley, peas, pickles, and spinach. Many dietary supplements, including multivitamin preparations and herbal products, are also high in vitamin K which may also affect coagulation. While the clinical effect of increased dietary vitamin K can be overcome with increased warfarin, it is the variability of the clinical anticoagulant effect that is of greatest importance. Indeed, in cases where a patient's warfarin control is quite unstable, a supplement of modest daily vitamin K (e.g., 60–80 μg) may help in achieving a more stable warfarin effect.

Monoamine Oxidase Inhibitors and Tyramine

Monoamine oxidase (MAO) inhibitors are commonly used in the treatment of depression and phobic anxiety disorders. They are being increasingly replaced by safer alternatives due to a number of potentially dangerous interactions with foods containing high levels of tyramine (e.g., beer, ale, red wine, soy, aged cheeses, smoked or pickled fish or meat, anchovies, yeast, and vitamin supplements). Ingested tyramine is normally metabolized by the enzyme MAO in the bowel wall and liver. MAO inhibitors inhibit the metabolism of tyramine that can lead to a sudden and significant release of norepinephrine, resulting in a severe hypertensive crisis.

Calcium Impairs Absorption of Certain Antibiotics

Calcium-rich foods, such as dairy products and tofu, even milk added to tea or coffee, can deliver enough calcium to significantly impede the absorption of several antibiotics, including tetracycline, minocycline, doxycycline, levofloxacin, and ciprofloxacin [13]. To improve their absorption, these medications should be taken 1 hour before or 2 hours after calcium, magnesium, and iron supplements or dairy products.

Ginger Enhances Anticoagulant Effects

Ginger (the rhizome of *Zingiber officinale* Roscoe) is a widely used condiment, food, and herbal medicine. It is used as a digestive aid, to treat inflammation, for morning sickness, but it also has antiplatelet and antimicrobial effects. Ginger therefore has the potential to interact with anticoagulants. In the scientific literature, there are a few reports of an increase in the International Normalized Ratio (INR) in patients taking ginger root, ginger tea, and other herbal medicines containing ginger, in conjunction with warfarin [14–16]. The INR is an alternate measure of the common coagulation test known as prothrombin time (PT) and was introduced by the World Health Organization. A normal INR is approximately 0.9–1.1 and is elevated to between 2 and 3.5 when patients are on warfarin therapy, so an elevation following ginger supplementation indicates that ginger has anticoagulant effects. One longitudinal study showed that concurrent administration of warfarin with a ginger product resulted in a statistically significant increase in bleeding episodes [16].

It is well known that the cytochrome P450 (CYP450) isoenzymes are important for metabolizing a wide range of medications, including ginger and/or its chemical components This action may be due to mutual competitive inhibition, mechanism-based inhibition, or nonselective inhibition of CPYs. These effects of ginger on the activity of CPYs may result in alterations in the pharmacokinetics and pharmacodynamics of co-administered drugs [16].

Garlic Enhances Anticoagulant Effects and Reduces Protease Inhibitor Levels

Garlic, known scientifically as *Allium sativum* L., is both a food and a dietary supplement, and its beneficial effects on health are well documented [3, 4]. Garlic contains phytochemicals that may influence the pharmacokinetic and pharmacodynamic behaviors of prescription drugs, including warfarin and protease inhibitors. Clinical reports show a possible interaction between garlic (primarily as a dietary supplement) and warfarin [3, 4]. Some case studies reported that the ingestion of garlic with warfarin may increase the INR, while other reports showed no effect. However, since it is well known that garlic decreases platelet aggregation, there may be an increased risk of bleeding with warfarin [3]. In addition, garlic is well known to have antimicrobial activities and may prevent intestinal flora from producing vitamin K thus potentiating the effects of anticoagulants. Synergistic pharmacodynamic effects have been observed after the ingestion of garlic or garlic-containing supplements with fluindione, chlorpropamide, and NSAIDs, and pharmacokinetic interactions have been observed with both acetaminophen and lisinopril [3, 4]. In addition, garlic and garlic supplements have a significant impact on the efficacy of protease inhibitors used to treat human immunodeficiency virus (HIV). For example, there is a significant decrease in maximal plasma levels and the mean area under the curve (AUC) of saquinavir after co-administration of a garlic product for 3 weeks. However, no changes in the single-dose ritonavir pharmacokinetics were observed after 4 days [4].

Soy Reduces Anticoagulant Effects

Soy beans, known scientifically as *Gycine max* L., are fermented and then used as part of a wide array of Asian cuisine and soy-based products. These fermented products are well known to contain high levels of vitamin K that may interact with anticoagulants. Clinical reports and studies have shown that the administration of warfarin along with soy protein, soy milk, or other soy products may decrease the INR in patients [2, 17].

Specific Examples of Food–Beverage Interactions

Use of Acidic Beverages to Aid Drug Absorption

The absorption of the oral broad-spectrum antifungal drugs, ketoconazole and itraconazole, is dependent on an acidic environment. If gastric acid production is low (achlorhydria), either due to a manifestation of the patient's medical condition (e.g., AIDS gastropathy) or their use of acid-suppression therapy, then the absorption of these drugs is compromised [18]. These weakly alkaline drugs dissolve poorly in the relatively higher pH in the proximal small intestine and absorption is low. In such instances, patients should be advised to take their ketoconazole or itraconazole with an acidic beverage to boost drug availability by as much as 50% (Table 26.2) [19].

Citrus Juice Inhibits Drug Metabolism

Drug interactions with grapefruit juice (*Citrus paradisi*), and other fruits derived from grapefruits, were first characterized more than 20 years ago [9]. Both grapefruit and grapefruit juice, as well as *Citrus aurantium* (Seville oranges) and *C. grandis* (pomelo), interact with a number of prescription drugs, interfering with their metabolism and increasing the risk of dose-dependent side effects [6, 9]. It is estimated that > 85 drugs may interact with grapefruit due to an inhibition of their intestinal

Table 26.2 The pH of selected commercially available beverages that may affect drug absorption

Beverage[a]	pH	Beverage	pH
Coca-Cola Classic	2.5	Diet Coca-Cola	3.2
Cranberry juice	2.5	Diet Pepsi	3.2
Pepsi	2.5	Orange juice	3.3
Rockstar Energy Drink	2.5	Grape juice	3.3
Red Bull	2.7	Mountain Dew	3.3
Canada Dry Ginger Ale	2.8	Tropicana grapefruit juice	3.4
Dr. Pepper	2.9	7-Up	3.4
Sprite	2.9	Tropicana orange juice	3.8
Grapefruit juice	2.9	Black tea	4.1

[a]Those medications in the left column tend to aid in ketoconazole absorption

metabolism, causing an increase in their peak plasma concentrations and the risk of adverse events [9]. The compounds responsible for these interactions include the flavonoids and furanocoumarins.

Sufficient quantities of these compounds are present in a typical glass of grapefruit juice (or any part of the grapefruit) to irreversibly inhibit a key-metabolizing enzyme (CYP3A4) in the intestinal wall, although no effects are seen on the activity of CYP3A4 present in the liver [7]. Interestingly, oral antidiabetic medications including glybenclamide, glyburide, and repaglinide, as well as L-thyroxine, are not metabolized through CYP3A4 and therefore are not affected by the ingestion of grapefruit, orange, or apple juices. Furthermore, fruit juice–drug interactions appear to be transient, and the effect is significantly reduced within a few hours of ingestion, so that intake of the drug more than 4 hours after ingestion of the fruit juice reduces the risk of interaction by more than 60% [6]. In addition, large amounts of the juice, more than 300 ml/day, need to be consumed daily before such interactions are observed. However, it appears that orange juice may significantly interact with aliskiren, beta-blockers, fexofenadine, and fluoroquinolones by inhibiting the organic anion transporting polypeptide (OATP1A2 and 2B1) [9]. Furthermore, apple juice has been reported to decrease the concentrations of fexofenadine and atenolol in the plasma and may reduce oral bioavailability by up to 70% [6].

Multiple studies suggest that grapefruit and grapefruit juice inhibit the activity of CYP3A4, an enzyme that metabolizes >65% of drugs. The inhibition of CYP3A4 causes a range of dose-dependent effects, and both desirable and undesirable clinical effects can be observed. Grapefruit and other citrus juices also inhibit P-glycoprotein and a number of other metabolic enzymes and transporters. The extent to which individuals are affected by these juices is largely genetically determined and is related to the extent and relative distribution of isoforms of this enzyme in the intestine. Thus, the responses are often quite variable between individuals, with patients with the highest intestinal expression of CYP3A4 experiencing the greatest grapefruit juice–drug interactions. While there are broad ethnic differences, for example, African Americans are more affected than Caucasians, prediction of the scope of the effect in a particular individual is not yet possible in the clinic; however with increasing pharmacogenomic analyses, this may be possible in the future.

The drugs most affected by grapefruit juice include the dihydropyridine calcium antagonists: felodipine, pranidipine, nisoldipine, and nimodipine. Any possible interactions with other agents, such as amlodipine, cardizem, and verapamil, are not likely to be of clinical significance. The HMG-CoA reductase inhibitors, such as lovastatin and simvastatin, and to a lesser extent atorvastatin, all have a significant interaction with grapefruit juice as they are all substrates for the CYP3A4 and P-glycoprotein (P-gp) [6, 9]. Other statins including fluvastatin, pitavastatin, pravastatin, and rosuvastatin are not substrates for CYP3A4 and do not appear to be affected. Lee et al. [20] have challenged the validity of medical advice suggesting that grapefruit juice should not be used in combination with statins. In their review of the clinical trials of grapefruit juice– statin interactions, they concluded that one daily

glass of grapefruit juice increases the blood simvastatin and lovastatin concentrations by ~260% when taken concomitantly, but by only about 90% if taken 12 hours apart, and grapefruit juice increases atorvastatin blood concentrations by ~80% (whenever taken). When grapefruit juice and statins are taken together, the reduction in LDL-cholesterol and risk of heart disease is significantly greater than when statins are given alone. Drinking grapefruit juice in moderation (one glass per day) may therefore be beneficial and not adverse to health [20]. The increased risk for rhabdomyolysis, the most serious and potentially fatal side effect of statin use, would only minimally increase when statins are administered with grapefruit juice. However, there are no studies to this effect [20]*;* therefore, until such studies are done, it might be prudent to err on the side of caution as most patients using statins may also be taking other drugs.

Other medications with a significant interaction with grapefruit juice include the immunosuppressants (cyclosporin and tacrolimus), the antihistamines (terfenadine, ebastine, and loratadine), the antimicrobials (artemether and saquinavir), the neuropsychiatric drugs (diazepam, midazolam, triazolam, buspirone, sertraline, carbamazepine, clomipramine, zaleplon, and methadone), cilostazol, and sildenafil. Interestingly, orange juice also appears to impact the oral effects of fexofenadine and celiprolol, both of which are substrates for the solute carrier organic anion transporter 1A2 (SLCO1A2). The flavonoids hesperidin and naringin have been identified as the compounds responsible for the effect on SLCO1A2. Naringin also modulates the activity of the organic anion transporting polypeptide and P-glycoprotein that causes a significant decrease in the oral bioavailability of pravastatin and pitavastatin [2, 21].

In summary, ingestion of grapefruit and other citrus fruits can significantly inhibit the metabolism of many medications spanning a variety of clinical fields. All forms of grapefruit (i.e., the whole fruit, fresh fruit juice, and frozen concentrate) are associated with the food–drug interactions. In general, the subset of patients in whom these juices may have the greatest effect are those who at baseline display the greatest amounts of intestinal metabolism and hence the lowest rates of drug bioavailability. In day-to-day practice, this group of patients is the most difficult to identify, and this inhibition of metabolism can lead to manyfold increases in circulating drug levels; this places these patients at risk for dose-dependent side effects. Unfortunately, due to a variety of both patient and grapefruit factors (perhaps explained by changes in the constituents of grapefruit with different crops and preparations), this effect is unpredictable and cannot be used clinically. Until these issues are defined, it seems prudent to dissuade patients from combining grapefruit juice with any of the abovementioned medications, particularly when they are taking them for the first time or in high doses.

Effect of Alcohol on Drug Action

Both acute and chronic excessive consumption of alcohol impart many effects on drug therapy [5]. Alcohol consumption may delay gastric emptying and thus slow the onset of absorption of many medications. Over time, heavy alcohol consumption may also lead to chronic altered bowel motility. Chronic consumption of excessive quantities of alcohol may result in cirrhosis and an associated impairment of hepatic drug metabolism. Alcohol is a known substrate for the cytochrome P450 isozyme CYP2E1, and, depending on the frequency of alcohol intake, it can also be either an inducer or inhibitor of CYP2E1. In the acute setting, alcohol competes for this enzyme and may reduce the metabolism of medications normally metabolized by CYP2E1 (e.g., warfarin, phenytoin, and rifampicin).

In chronic alcohol consumption, there is a five- to tenfold increase in CYP2E1 levels, which may increase the metabolism of these drugs over time [5]. CYP2E1 is also one of the minor pathways of acetaminophen metabolism, with the end product being a toxic metabolite. Therefore, chronic alcohol use greatly predisposes to acetaminophen toxicity. Cefotetan, griseofulvin, isoniazid, metronidazole, nitrofurantoin, and sulfa drugs mimic disulfiram by also inhibiting acetaldehyde dehydrogenase, a key

enzyme in the metabolism of alcohol. Hence, consumption of alcohol by many patients taking these antimicrobials is associated with greatly increased concentrations of acetaldehyde and symptoms of tachycardia, flushing, vomiting, confusion, and hypotension.

Red wine has also been shown to cause inhibition of intestinal CYP3A4, albeit to a lesser extent than grapefruit juice. Hence, a clinically significant effect of red wine on medications normally metabolized in the intestine by CYP3A4 would likely be uncommon. However, in rare patients (those with the highest intestinal CYP3A4 concentrations), red wine may carry the same risks as grapefruit juice for dose-dependent side effects.

In addition, alcohol intake is an independent risk factor for the exacerbation of GI bleeding in patients with concomitant use of NSAIDs [5]. The adverse effects may be due to degeneration of the gastric mucosa, development of esophageal varices, or a reduction in clotting factors due to chronic alcohol ingestion leading to chronic alcohol liver disease and cirrhosis. The risk of GI bleeding increases in individuals consuming three or more drinks per day, in combination with ibuprofen or aspirin, while hepatotoxicity may occur in these individuals when acetaminophen is consumed.

Effect of Caffeine on Drug Action

Caffeine is one of the most commonly used drugs worldwide and is most often consumed through coffee, tea, soda, energy drinks, and many other carbonated beverages [8]. These beverages are discussed in Chaps. 27, 28, and 31 of this book in greater detail. Acting as a central nervous system stimulant, caffeine ingestion leads to elevation in mood, a reduction in fatigue, and an increased facility for work [8]. Excessive caffeine intake can result in increases in heart rate, cardiac arrhythmia, delirium, and seizures. In addition to its stimulant action and effects on the cardiovascular system, caffeine has specific effects on drug metabolism by induction of the CYP1A2 enzyme system responsible for the metabolism of certain drugs [8]. However, it is likely that there are only a few medications that undergo a clinically significant interaction with usual doses of caffeine; of particular importance are medications with a narrow margin between when they are therapeutic and toxic (e.g., clozapine, lithium, and theophylline). The consumption of caffeine should be minimized in patients taking these medications. Clozapine, an atypical antipsychotic used in the treatment of schizophrenia, is one such medication. There are a number of reported cases of the presence of dose-dependent clozapine adverse events in patients consuming large quantities of caffeine (5–10 cups of coffee per day). It should be noted that psychiatric populations frequently have high caffeine consumption. Also noted is that ingestion of large quantities of caffeine may lead to a reduction in lithium levels and a decrease in its therapeutic effect.

Green Tea Reduces Anticoagulant Effects

Beverages and dietary supplements that contain green tea also contain vitamin K and may therefore reduce the effect of warfarin and other anticoagulants. Green tea leaves contain high levels of vitamin K; however, the vitamin K levels in brewed beverages are much lower; thus only large amounts (1500–3500 mL/day) are reported to decrease the INR [9].

Cranberry Increases Anticoagulant Effects

Cranberries, known scientifically as *Vaccinium macrocarpon*, are very popular worldwide as a food or beverage, as well as an herbal supplement for treatment of digestive disorders and urinary tract infections. In the scientific literature, there are a few reports of an interaction between cranberry and

warfarin, but this interaction remains controversial [9, 11, 22–24]. In one case report, administration of cranberry together with warfarin increased the International Normalized Ratio and caused significant bleeding [9]. There is also one report of a very serious interaction in which a patient drinking approximately two cups of cranberry juice daily for 6 weeks purportedly died as a consequence of this interaction [11]. Increases in the INR (up to 28%) have been reported when cranberry is administered with warfarin. However, it is important to remember that the case studies have not been supported by controlled clinical trials. For example, Lilja et al. [22] investigated the effects of cranberry juice on simultaneous administration of R- and S-warfarin, tizanidine, and midazolam as drug probes for the CYP liver isozymes CYP2C9, CYP1A2, and CYP3A4 in a randomized crossover study. Ten healthy volunteers were administered 200 mL of cranberry juice or water three times daily for 10 days. On day 5, they ingested 10 mg of racemic R- and S-warfarin, 1 mg tizanidine, and 0.5 mg midazolam, with juice or water, followed by monitoring of drug concentrations and thromboplastin time. The results show that for a one-time dose of these three drugs, cranberry juice did not increase the peak plasma concentration or area under concentration–time curve (AUC) of any of the drugs or their metabolites, but slightly decreased (7%) the AUC of S-warfarin. Thus, cranberry juice did not change the anticoagulant effect of warfarin. Daily ingestion of cranberry juice for 10 days did not inhibit the activities of any of the liver enzymes responsible for drug metabolism. The study concluded that a pharmacokinetic mechanism for the cranberry juice–warfarin interaction seems unlikely [22]. However, the limitations of this study are that it does not take into account repeated daily drug administration or the suggestion that many food–drug interactions may take 2–4 weeks to be observed. It has been suggested that consumption of 1–2 L of cranberry juice per day or the equivalent of cranberry juice concentrate in supplements for an extended time period (~3–4 weeks) may temporally alter the effect of warfarin; however, the complete avoidance of cranberry juice by warfarin users may not be justified based on the current published studies [23, 24].

Conclusion

This chapter has reviewed some of the most common drug interactions with food and beverages. In general, patients should carefully follow the the label instructions for proper administration of all medications. Some medications should be taken with a full glass of water, some must be taken with food, while others should be taken on an empty stomach. Patients should consult with a physician or pharmacist to determine if there are any foods that should be avoided while taking their medications. Patients often ask what time of the day to take their medications, and if they should take them with food, but need to be informed if there are specific foods that they should avoid when taking some medications. In some instances, patients will be instructed to take their medication with a particular food or beverage to aid palatability (and hence compliance), to minimize local irritation to the gastrointestinal tract, or to aid in drug absorption. However, importantly, there are many incidences when the consumption of specific foods in combination with certain medications presents a problem by interfering with the absorption, metabolism, or excretion of these drugs. If these instances go unrecognized, there may be significant divergence of therapeutic drug levels and hence therapeutic effects and possible drug-related adverse events.

By acting on gastric motility, pH, and drug metabolism, food and beverages can have a variety of effects on the absorption and metabolism of medications, as well as on many vitamins and minerals, with the clinical significance ranging from passing interest to concern for significant reductions in drug action, as is seen with garlic and saquinavir, as well as serious adverse events, as seen with cranberry and warfarin. For some food–drug interactions, such as grapefruit juice, that affect drug metabolism through the cytochrome P450 isoenzymes, there is huge variability from one person to the next

and the risks of dangerous interactions are only present in a few. With further understanding and perhaps profiling of patients for their gene expression of metabolic enzymes, it may be possible to identify those most at risk for both beverage–drug and drug–drug interactions. In the meantime, it is best for patients to take their medications with a glass of water unless otherwise advised.

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Suggested Further Readings

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Part VI

Food and Nutrient Health Effects

Coffee Consumption and Its Impact on Health

27

Valentina Guercio

Keywords

Coffee · Caffeine

Key Points

- Coffee contains large numbers of bioactive chemicals, many of which are antioxidants.
- Moderate coffee drinking may decrease total mortality and the risk of cardiovascular disease, stroke, type 2 diabetes, and the metabolic syndrome.
- Coffee is associated with a lower risk of liver and endometrial cancer, but there is no evidence that it affects the risk of other types of cancer.
- Coffee is associated with a lower risk of Parkinson's disease but is not associated with risk of dementia and Alzheimer's disease.
- Overall, drinking up to 5 cups of coffee per day appears to provide some limited health benefits.
- Coffee appears to be associated with a modestly increased risk of several adverse pregnancy outcomes.

Introduction

Coffee is the second most commonly consumed beverage in the world after tea. The most prominent component of coffee is caffeine (2–4% of the content of coffee). However, the beverage contains more than 2000 other chemicals, including many bioactive compounds with potential effects on health. The amount of such chemicals present in a cup of coffee is highly variable and depends on the type of coffee, the brewing method, and the cup size [1].

Coffee drinking is highly correlated with smoking which is an important determinant of mortality. Accordingly, it is especially important to adjust for smoking when estimating the relationship between coffee intake and health outcomes. The lack of correct adjustment for smoking is possibly a reason why in the past coffee consumption was often considered unfavorable to health, but more recent epidemiological evidence has revealed many potential favorable effects of moderate coffee intake.

V. Guercio (✉)
Didcot, Oxfordshire, UK

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Total Mortality

The association of coffee drinking with total and cause-specific mortality has been investigated in many prospective cohort studies. For example, the National Institutes of Health–AARP Diet and Health Study investigated the relationship between coffee intake and mortality risk among about 400,000 men and women [2]. During about 13 years of follow-up, 33,700 men and 18,800 women died. Coffee drinking showed a clear inverse association with total mortality.

The overall findings of cohort studies have been summarized in several meta-analyses [3, 4]. After adjustment for smoking and other potential confounders, consumption of coffee shows an inverse association with risk of death. The lowest risk is seen at an intake of between about 2 and 5 cups per day with a reduction in risk of about 10 to 15%. Similar findings were seen in different subgroups irrespective of gender, age, weight, alcohol drinking, or smoking.

Cardiovascular Disease

The effect of coffee on risk factors for cardiovascular disease (CVD) and on the incidence and mortality of CVD has long been debated [5].

Blood Pressure and Blood Lipids

Hypertension is a strong risk factor for both stroke and coronary heart disease (CHD). Consumption of caffeine has been linked to a short-term rise in blood pressure [6]. In patients with hypertension who drank coffee, a slight blood pressure increase followed the intake of 2–3 cups of coffee in the first 3 hours, but with no long-term effects and no evidence of increased CVD risk [7]. In a meta-analysis of four cohort studies, among 196,000 participants of whom 41,200 had hypertension, coffee consumption was not associated with an increased risk of hypertension. Indeed, the findings suggest that a coffee intake above 3 cups per day may reduce risk [8]. By contrast, a meta-analysis of clinical trials, among non-hypertensive participants, found a slight increase of 2–2.4 mmHg in systolic blood pressure and of 0.8–1.2 mmHg in diastolic blood pressure after 4 cups/day of coffee [9]. Overall, there appears to be very little relationship between drinking coffee and long-term rise in blood pressure or risk of hypertension.

A meta-analysis of 5 studies showed no evidence of an increase in blood lipids in drinkers of filtered coffee [10].

Cardiovascular Disease

Older studies suggested that coffee intake could increase the risk of CHD and stroke. However, this was not seen in recent studies, possibly because of a more accurate adjustment for smoking and other potential confounders [5].

Meta-analyses that focused on CVD have pooled data from dozens of cohort studies that have included several million subjects and tens of thousands of cases, both fatal and nonfatal. The findings provide solid evidence for a protective effect of coffee consumption on the risk of CVD [4, 11]. A habitual intake of 3 cups per day may reduce risk by about 17%.

The association between coffee and CHD risk is inconsistent. Some meta-analyses have reported a beneficial effect of protective association of 1.5 to 3.5 cups of coffee per day with risk on CHD risk [11, 12].

Stroke

Findings for stroke are similar to those for CVD. This is seen for both deaths and incidence of the disease. The findings from meta-analyses indicate that persons who drink about 3 cups of coffee per day have a 20% lower risk of stroke [11, 12].

Diabetes and the Metabolic Syndrome

A meta-analysis was carried out of 30 cohort studies that included 1.2 million participants of whom 53,000 developed type 2 diabetes. Risk of developing diabetes was reduced by 7% for each extra cup per day of regular coffee [13]. Similar results were seen for decaffeinated coffee suggesting that coffee may be protective against type 2 diabetes independent of its caffeine content.

The metabolic syndrome is a combination of elevated blood sugar, high blood pressure, abnormal levels of blood lipids, and a large waist circumference. It is a major risk factor for type 2 diabetes and CHD. A meta-analysis of 11 studies with a total of 160,000 participants reported that habitual coffee drinkers had an approximately 13% decreased risk of developing the metabolic syndrome [14].

Cancer

A meta-analysis of 12 cohort studies concluded that coffee consumption is associated with a reduced risk of liver cancer. Each additional cup per day lowers risk by 15% [15]. The substances in coffee that may be responsible for this action include chlorogenic acid and other antioxidants.

A recent meta-analysis assessed the relationship between coffee intake and risk of endometrial cancer. The analysis included 12 cohort studies and 8 case-control studies (with 11,700 and 2700 cases, respectively). Coffee intake was associated with a 26% lower risk of endometrial cancer [16].

The International Agency for Research on Cancer (IARC) evaluated the relationship between coffee drinking and more than 20 other cancers. No association has been demonstrated between coffee drinking and risk of cancer of the bladder, pancreas, or prostate [17]. Unfortunately, the IARC was not able to draw clear conclusions regarding the relationship between coffee and other types of cancer because of the scanty evidence.

The bottom line is that coffee may help protect against cancer of the liver and endometrium, but there is no evidence that it increases the risk of other types of cancer [17].

Neurological Diseases

Dementia is a common disease in the elderly. Investigators have looked at whether coffee affects risk. A meta-analysis was carried out that included 8 cohort studies. In total, there were 7500 cases of dementia diagnosed among 329,000 subjects. No association was seen between coffee consumption and dementia risk. A narrower focus on subjects with Alzheimer's disease came to the same conclusion [18].

There appears to be a protective association between coffee intake and risk of Parkinson's disease. This was shown in a meta-analysis of observational studies which reported a 25% lower risk when comparing the highest and lowest intake [19].

Pregnancy and Breastfeeding

During the last trimester of pregnancy, caffeine metabolism and elimination is greatly slowed. Caffeine freely passes the placental barrier; the fetus does not express the enzymes to inactivate it, and caffeine metabolites may accumulate in the fetal brain. A meta-analysis of 53 studies found that an increment of 100 g caffeine intake (equivalent to about 3 cups of coffee per day during the pregnancy) was associated with a significant increased risk of spontaneous abortion, stillbirth, and low birth weight, but not with preterm delivery [20]. While the evidence is not conclusive, coffee drinking should be limited during pregnancy. Thus, a caffeine intake below 200 mg/day (less than 2 cups of coffee) is recommended for pregnant women [21].

Caffeine is found in breast milk after ingestion of coffee. There is no clear information on the effect of caffeine on breastfed babies, except for irritability. However, caffeine is metabolized very slowly by young children; thus an accumulation is possible after high maternal ingestion. A low consumption of coffee during breastfeeding is therefore recommended.

Conclusion

The relationship between coffee consumption and a range of several health effects has been extensively investigated in many epidemiological studies, especially prospective cohort studies. Moderate coffee drinking may decrease total mortality and risk of cardiovascular disease and stroke. Coffee appears to have little or no association with hypertension and does not lead to a rise in blood pressure or blood lipids. It is likely that coffee drinking is also protective against type 2 diabetes and the metabolic syndrome.

Coffee consumption is associated with a lower risk of liver and endometrial cancer, but there is no evidence that it increases the risk of other types of cancer.

Finally, there seems to be beneficial effects of coffee consumption on Parkinson's disease, but not with other neurological diseases, such as dementia and Alzheimer's disease. Coffee consumption appears to be associated with a modestly increased risk of adverse pregnancy outcomes.

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Health Effects of Tea Consumption

28

Mamoru Isemura, Monira Pervin, Keiko Unno, Kieko Saito, and Yoriyuki Nakamura

Keywords

Tea · Green tea · Oolong tea · Black tea · Catechin · Epigallocatechin gallate

Key Points

- Tea is manufactured from the leaves of the Theaceae plant (*Camellia sinensis*).
- Various types of brewed tea are consumed worldwide and the types of tea vary with respect to clinical benefits.
- Tea exhibits beneficial effects on cancer, obesity, metabolic syndrome, type 2 diabetes, cardiovascular disease, and possibly some neurodegenerative diseases.
- A major component of tea catechins is (−)-epigallocatechin gallate. It may be responsible for many of the biological effects of tea.

Introduction

Tea is the world's most popular beverage after water. Green, black, and oolong teas are all obtained from the leaves and buds of the Theaceae plant (*Camellia sinensis*) when the leaves are served following no fermentation, full fermentation, or a semi-fermentation process, respectively [1]. The three primary tea products are probably not equal with respect to health benefits. A search of the PubMed database carried out for the last 10 years is suggestive of the popularity of tea in human health research. This search (May 23, 2020) of "green tea," "black tea," and "oolong tea" yielded 5,692, 1,374, and 328 citations, respectively. Tea contains various constituents with potential health promoting effects, such as caffeine, polyphenols, vitamins, γ-aminobutyric acid, and theanine.

Tea polyphenols or catechins have been suggested to protect against cancer, obesity, metabolic syndrome (MetS), diabetes mellitus (DM), cardiovascular disease (CVD), and neurodegenerative diseases [2–5]. Tea consumption may also have antibacterial, antiviral, hepatoprotective, and microbiota-modulating effects [2–5]. Among the catechins, (−)-epigallocatechin gallate (EGCG, Fig. 28.1) appears to be the chemical with the greatest biological activity, with green tea containing the highest amount of EGCG. Black and oolong teas contain some EGCG as well as additional bioactive catechin

M. Isemura (✉) · M. Pervin · K. Unno · K. Saito · Y. Nakamura
Tea Science Center, University of Shizuoka, Shizuoka, Japan
e-mail: isemura@u-shizuoka-ken.ac.jp; gp1747@u-shizuoka-ken.ac.jp; unno@u-shizuoka-ken.ac.jp; saitok@u-shizuoka-ken.ac.jp; yori.naka222@u-shizuoka-ken.ac.jp

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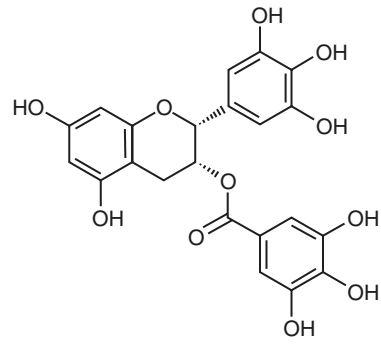

Fig. 28.1 Chemical structure of EGCG

derivatives formed during fermentation, such as theaflavins, thearubigins, theasinensins, and chaflosides. This chapter mostly focuses on the human health promoting effects of consumption of green tea and/or green tea catechins (GTC).

Green Tea Benefit for Obesity and Metabolic Syndrome

The MetS is a group of associated variables including elevated levels of body mass index (BMI), body fat, waist circumference, blood pressure, triglyceride, blood glucose, and hemoglobin A1c concentrations and reduced levels of high-density lipoprotein-cholesterol (HDL-C). The results of several epidemiological studies suggest that tea is a preventive agent for MetS, but confirmatory studies are required [4].

A cross-sectional population-based survey saw an inverse association of green tea consumption with MetS and some of its components. The high tea consumers (≥3 cups/day) exhibited lower BMI and waist circumference, but diastolic blood pressure was not affected [6]. After adjusting for confounding factors, higher tea consumption had a significant inverse association with MetS. In a study of 6,500 adults, an inverse association was observed between tea intake and MetS markers [7]. A more recent systematic review and meta-analysis of six observational studies concluded that there was a significantly reduced risk of MetS for individuals consuming more tea [8]. However, a study of 5,100 adults in Poland reported that tea consumption was related to some components but not to MetS [9]. The conflicting results could have been confounded by differences in the base diet and genetic background of these Polish subjects.

A recent pooled analysis of six human trials showed that consumption of GTC-containing beverages (540–588 mg GTC/beverage) for 12 weeks significantly reduced total fat area, visceral fat area, subcutaneous fat area, body weight, BMI, and waist circumference and improved blood pressure. Further analyses of pre-MetS and MetS studies indicated significantly improved MetS in the GTC consumers [10]. These encouraging findings indicate, therefore, that daily consumption of GTC reduces abdominal fat and improves MetS.

The anti-obesity effects of green tea have been investigated in 24 human studies published between 2002 and 2013 [11]. Five out of 11 trials in Asian populations showed significant weight loss of 1–2 kg, and three out of 13 trials in Western populations resulted in notable weight loss ranging from 1 to 9 kg. A randomized, double-blind, crossover, and placebo-controlled clinical trial in which green tea extract (GTE) was given to overweight or obese women for 6 weeks showed that it resulted in a significant 4.8% reduction in low-density lipoprotein cholesterol (LDL-C) and a 25.7% increase in leptin [12]. However, there was no significant effect on total cholesterol, triglycerides, and HDL-C.

In addition, a beneficial effect of green tea in overweight or obese peoples was demonstrated by a meta-analysis of 21 papers that included 1700 overweight or obese subjects. Green tea significantly decreased total plasma cholesterol (about −3.38 mg/dL) and LDL-C levels (about −5.29 mg/dL), but with no effect on plasma triglyceride and HDL-C levels [13].

Generally, regular consumption of green tea, and EGCG commonly found in GTE, seems to provide benefits for improved weight management and MetS management. These improvements probably contribute to reductions in CVD risk.

Benefits of Green Tea for Cardiovascular Disease

Many studies have investigated the relationship between tea consumption and risk of CVD. Two of the studies mentioned above reported that GTE or green tea lowers LDL-C [12, 13].

According to a comprehensive review by Yang et al., tea may help reduce the risk of CVD and related diseases [2]. The evidence for this is as follows:

(a) A meta-analysis of 14 prospective cohort studies showed an inverse association between tea consumption and risk of stroke.
(b) A systematic review and meta-analysis of ten human trials observed that tea reduces systolic and diastolic blood pressure.
(c) A multiethnic study saw inverse associations between tea consumption and both coronary artery calcification and incidence of cardiovascular events.
(d) The Shanghai Men's Health Study reported an inverse association between green tea consumption and CVD mortality among non-smokers.

Other studies have provided additional weight to these findings. People consuming ≥5 cups/day of green tea (vs <1 cup/day) had a lower mortality of approximately 18–25% for both heart disease and CVD [14]. Similarly, a study of 101,000 Chinese adults revealed that habitual tea drinkers had a 15–22% reduced risk of atherosclerotic CVD incidence, atherosclerotic CVD mortality, and all-cause mortality [15]. The findings also revealed that at age 50, habitual tea drinkers had 1.4 more years free of atherosclerotic CVD and 1.3 years longer life expectancy [15].

Taken as a whole, these results strongly indicate that green tea consumption is associated with reduced risk of CVD and related diseases.

Benefits of Green Tea for Type 2 Diabetes Mellitus

Epidemiological studies have detected antidiabetic effects of green tea [1, 3]. For example, a large cohort study on 17,400 Japanese published in 2006 showed type 2 DM among drinkers of green tea of ≥6 cups/day was improved relative to those who drank <1 cup/week [16]. Similarly, an analysis of a large cohort study from eight European countries revealed that tea consumption was inversely associated with the type 2 DM incidence which was improved for drinkers of ≥4 cups/day compared to non-drinkers [17]. Remarkably, the result from an analysis indicated that replacing sugar-sweetened beverages with tea can lower type 2 DM incidence by 22%, whereas substituting fruit juice or milk did not alter type 2 DM incidence significantly [18].

Additional evidence for the beneficial effects of tea on type 2 DM comes from the following two studies. A hospital-based case-control study in Vietnam showed an inverse association of tea consumption with risk of type 2 DM; persons drinking >2 cups/day had a lower risk than those drinking <1 cup/day [19]. A Japanese intervention study on 60 subjects with mild hyperglycemia demonstrated

that ingestion of GTE reduced the blood level of hemoglobin A1c, an indicator of glucose control and a marker used to diagnose DM [20].

However, several studies failed to show this effect [21, 22]. For example, the results of a cohort study which monitored 47,000 participants aged 30–69 indicated no association between the intake of tea and the risk of type 2 DM [21]. These conflicting results indicate that the possible antidiabetic benefit of tea needs to be further investigated.

Benefits of Green Tea for Neurodegenerative Diseases

Evidence suggests that tea has benefits for neurodegenerative disorders such as Alzheimer's disease (AD), dementia, cognitive impairment, and depressive symptoms. For example, a cross-sectional survey of 2,015 persons aged ≥65 in China demonstrated that the age-gender-standardized prevalence rates of dementia, AD, and vascular dementia were lower in green tea consumers [23]. However, a prospective study of 1,840 Japanese Americans in the USA failed to see an association for tea consumption with AD [24].

In the case of Parkinson's disease, a meta-analysis of eight studies including 345,000 participants found an inverse association and decreased smoking-adjusted risk by 26% when consumption was increased by 2 cups/day [25].

A small randomized, single-blind study reported that consumption of matcha tea (a kind of green tea), compared to placebo, significantly improved attention abilities and psychomotor speed in response to stimuli [26]. However, another double-blind, randomized controlled study failed to observe a favorable effect on cognitive function after green tea (2 g/day) was consumed for 1 year [27].

Benefits of Green Tea for Cancer

Recent epidemiological studies, systematic reviews, and dose-response meta-analyses indicate that long-term and high-dose consumption of green tea reduces the risk of various types of cancer [1, 3, 4]. For example, in a study of Hong Kong Chinese men, habitual green tea consumption significantly reduced the risk of prostate cancer in a dose-dependent manner for intake of EGCG [28]. The possible beneficial effect of green tea consumption on cancer is also suggested by a pooled analysis of eight cohort studies in Japan which concluded that moderate consumption of green tea reduced woman's risk of total cancer [14]. Another cohort study indicated that green tea drinkers had reduced risk of hematologic neoplasms including acute myeloid leukemia and follicular lymphomas compared with the non-drinkers of green tea [29].

Conversely, some studies have failed to demonstrate such risk reduction, and therefore more research is needed to better understand the utility of green tea for cancer prevention [1]. It also should be noted that the inconsistencies in results may be due to several different factors, such as quantity of tea consumption, tea temperature, smoking, alcohol consumption, intestinal flora, and genetic polymorphisms [3].

Intervention studies can provide much useful information on the chemopreventive effects of tea in humans. Two Japanese studies showed that green tea extract is an effective supplement for the chemoprevention of metachronous colorectal adenomas [30, 31]. Similarly, a recent randomized clinical study carried out in Korea reported that among 143 patients the incidence of this adenoma was significantly lower in the group given 0.9 g/day GTE for a year than in the control group [32].

In an intervention study carried out in Italy on 30 men with high-grade prostate intraepithelial neoplasias, the proportion of men who developed prostate cancer was far lower in those treated with 600 mg of GTC daily for 12 months compared with those given a placebo [33].

Green Tea Effects May Be Variable in Different People

There are many complicating factors with respect to the effect of green tea consumption on human health. While EGCG is probably one of the more important catechins associated with the health benefits of green tea, the amount of EGCG in different green tea products is variable [34]. The ability of the EGCG in tea leaves to be solubilized is related to the time of brewing which varies between individuals, with longer brewing times resulting in greater EGCG content in the tea. Before the EGCG and other catechins reach the bloodstream, there is considerable potential for these phenolic compounds to be modified by the gut microbiome [2]. All of these factors complicate a "one tea fits all" approach. However, one can generally suggest a safe upper limit of 3 to 5 cups of green tea per day with little risk of deleterious effects.

Summary

Green tea has several potential health benefits with respect to weight management, type 2 DM, CVD, cancer, and possibly cognitive function. EGCG is probably the compound most responsible for the benefits of green tea consumption. Consumption of up to 3 to 5 cups per day can be recommended in clinical practice.

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Dietary Fat: The Good, the Bad, and What Is Best?

29

Philip A. Sapp, Kristina S. Petersen, and Penny M. Kris-Etherton

Keywords

Dietary fat · Fatty acids · Saturated fatty acids · Monounsaturated fatty acids · Polyunsaturated fatty acids · *Trans*-fatty acids

Key Points

- Fatty acids (FAs) differ by the structure of their hydrocarbon chain containing no double bonds (saturated, SFA), one double bond (monounsaturated, MUFA), or multiple double bonds (polyunsaturated, PUFA).
- Essential fatty acids (EFA) cannot be synthesized by human beings. These are PUFA (omega-6 and omega-3 fatty acids) and must be consumed in the diet or taken as a supplement. These fatty acids decrease risk of heart disease and other chronic conditions.
- Some foods contain *trans*-fatty acids (TFA), naturally occurring and industrially produced. The process of partial hydrogenation of unsaturated fatty acids (PHOs) creates TFA. TFA increases risk of heart disease.
- Most SFA increase low-density lipoprotein-cholesterol (LDL-C), a causal factor for atherosclerotic cardiovascular disease.
- When MUFA and PUFA replace SFA in the diet, lipids/lipoproteins are improved, which reduces the risk of CVD.
- Recommended healthy eating patterns are low in SFA and higher in unsaturated fat and/or carbohydrate from whole grains, although will vary in total fat based on the macronutrient substituted for SFA. Importantly, a healthy eating pattern can be individualized to accommodate dietary preferences as a strategy to promote adherence.

Introduction

The Internet is littered with misinformation about macronutrients, foods, and diets. This has created many misconceptions about dietary fat and how it impacts health. In addition, there is much confusion about including foods containing fat in healthy diets. Many patients obtain their health information from

P. A. Sapp · P. M. Kris-Etherton (✉)
Department of Nutritional Sciences, The Pennsylvania State University, University Park, PA, USA
e-mail: PZS5199@psu.edu; PMK3@psu.edu

K. S. Petersen
Department of Nutritional Sciences, Texas Tech University, Lubbock, TX, USA
e-mail: Kristina.Petersen@ttu.edu

T. Wilson et al. (eds.), *Nutrition Guide for Physicians and Related Healthcare Professions*, Nutrition and Health, https://doi.org/10.1007/978-3-030-82515-7_29

non-evidence-based sources and are misinformed about dietary recommendations, in general, and guidelines for fat intake. Typical questions healthcare professionals ask about dietary fats are as follows:

- What are the bad fats?
- What are the good fats?
- Can a very low-fat diet be healthy?
- Can a high-fat diet be healthy?

Types of Fat

General Characteristics

Fatty acids (FAs) are organic molecules composed of a carboxyl group, methyl group, and a hydrocarbon chain of varying lengths. FAs can be saturated ($-CH_2-CH_2-$), monounsaturated ($-CH_2-CH=CH-CH_2-$), and polyunsaturated containing more than one double bond. The carbon-to-carbon bonds are in the cis-formation (almost always), but food processing can create carbon-to-carbon bonds in the *trans*-formation. Saturated (SFA), monounsaturated (MUFA), and polyunsaturated (PUFA) fatty acids are present in foods primarily as triglycerides.

Saturated Fatty Acids

Dietary sources of SFA include red meat, full-fat dairy products, fish, poultry, and all fats and oils, with tropical oils (coconut and palm and palm kernel) being the highest. SFA are solid at room temperature. The structural features of SFA are important for maintaining the structure/function of plasma membranes and lipid bilayers. Common SFA found in foods are stearic (18:0), palmitic (16:0), myristic (14:0), and lauric (12:0) acid, with palmitic acid being the major SFA in the Western diet.

Unsaturated Fatty Acids

Dietary sources of MUFA and PUFA are mainly plant-based, although they are also present in animal sources. MUFA are found in many plant foods such as nuts, seeds, and liquid oils, as well as animal foods, such as meats, dairy products, and eggs. The most common MUFA is oleic acid (18:1, n-9). Foods rich in PUFA are safflower, corn, and soybean oils as well as nuts and fish/seafood. The most common PUFA are linoleic acid (18:2, n-6) and alpha-linolenic acid (18:3, n-3). Longer-chain PUFA, i.e., eicosapentaenoic acid (EPA [20:5, n-3]) and docosahexaenoic acid (DHA [22:6, n-3]), are present in lesser amounts in the diet. Unlike SFA, MUFA and PUFA are liquid at room temperature. Essential fatty acids are linoleic acid (an omega-6, or n-6, fatty acid) and alpha-linolenic acid (an omega-3, or n-3, fatty acid).

N-6 and N-3 Fatty Acids

The classification of either n-3 or n-6 is based on the first double bond being on the 3rd (n-3) or 6th (n-6) carbon from the methyl terminus. The common long-chain n-3 FAs are EPA and DHA. The most abundant n-6 FA is linoleic acid (LA) and the most prevalent n-3 fatty acid is alpha-linolenic acid (ALA).

N-3 and n-6 FAs have many health benefits (*see Dietary fat and health)*. Fish and shellfish, particularly fatty cold-water species, are rich in EPA and DHA (salmon, albacore tuna, mackerel, and oysters). Fish oil supplements are a source of EPA and DHA. Non-animal sources of DHA and EPA are

seaweed and algae. ALA is found primarily in plant-based foods like walnuts, flaxseeds, and chia seeds as well as canola oil and soybean oil. Sources of LA are nuts, seeds, and most vegetable/liquid oils.

Sterols, Stanols, and Cholesterol

Sterols, also referred to as steroid alcohols, are comprised of a four-ring steroid structure, a double bond, and one or more hydroxyl groups [1]. Stanols are nearly identical, but the four-ring steroid structure is saturated. The majority of cholesterol in the body is synthesized in the liver and is an integral component of plasma membranes as well as steroid hormones (i.e., testosterone and estrogen) and cholecalciferol (vitamin D) synthesis. Cholesterol is found in animal foods like eggs, shrimp and other shellfish, and organ meats. Phytosterols (both sterols and stanols) are found in plant cell membranes. Structurally similar to cholesterol, they block the absorption of dietary cholesterol in the intestine.

Trans-Fatty Acids

Most unsaturated fatty acids (UFA) occur naturally in the *cis* configuration, but some *trans*-fatty acids (TFA) are formed by biohydrogenation in ruminant animals. TFA are also produced by partial hydrogenation of vegetable oils. This creates a *trans* isomer that solidifies the vegetable oil at room temperature. This process prevents PUFA oxidation that increases the shelf life of processed foods. In response to the many adverse health effects of TFA, the FDA banned adding partially hydrogenated oils (PHOs) (that contain TFA) to any processed foods after June 2018 (see Dietary fat and health).

Triacylglycerols

Triacylglycerols (TAGs) or triglycerides are comprised of a glycerol backbone with three FAs (SFA, MUFA, or PUFA) attached via ester bonds [1]. TAGs make up approximately 95% of dietary fat [1]. During fat digestion lingual, gastric, and pancreatic lipases cleave the FA into diacylglycerols or monoacylglycerols for absorption into the enterocyte. These can be repackaged into TAGs and assembled into chylomicrons for transport in the plasma to target tissues such as the muscle and adipose tissue where they can be metabolized or stored.

Circulating Lipoproteins

Lipoproteins transport the bulk of dietary lipids through the circulation to target tissues. The hydrophobic core of lipoproteins contains triglycerides and cholesteryl esters, and the outer bilayer membrane is made up of phospholipids, free cholesterol, and protein molecules (apolipoproteins), with the different lipoprotein classes having one or more apolipoproteins. Lipoprotein classes are defined by their density, size, and characteristic constituent apolipoprotein(s). The key lipid constituents that affect CVD risk are TAG and cholesterol, which are transported in the plasma principally in chylomicrons and very low-density lipoproteins (specifically TAG), and LDL and HDL (specifically cholesterol). An elevated TAG level increases risk for CVD, and elevated cholesterol carried in LDL increases CVD risk whereas a high HDL-C decreases risk.

Chylomicrons are produced postprandially in the intestine as a vehicle for dietary fat absorption and transport. The peripheral tissues (cardiac, skeletal, adipose, etc.) remove TAGs from chylomicrons resulting in chylomicron remnants (CR), which are taken up by the liver [2]. Hepatocytes

produce TAG-rich very-low-density lipoproteins (VLDL), which contain Apo B-100 as their main structural apolipoprotein. VLDL transports TAGs to target tissues for storage and energy utilization. VLDL are converted to cholesteryl ester-rich intermediate-density lipoproteins (IDL) and low-density lipoproteins (i.e., LDL-C) via hydrolysis of triglycerides by lipoprotein lipase and hepatic lipase. IDL and LDL are smaller than VLDL and have a greater proportion of cholesterol and protein because TAGs have been removed by peripheral tissues.

Low-density lipoprotein cholesterol (LDL-C) is the primary transporter of cholesterol in the body, and its major structural apolipoprotein is Apo B-100, the ligand for hepatic LDL receptor-mediated LDL clearance. LDL particles range in size and density, which affect their function. All LDL-C are atherogenic; however, the LDL particle size affects the susceptibility and likelihood of the particle becoming trapped in the arterial wall [3]. Compared to larger LDL particles, small-dense LDL particles bind more avidly to glycosaminoglycans in the artery wall where they are taken up into the subintimal space and are more likely to be trapped. All LDL particles that are trapped in the artery wall release cholesterol and promote atherogenesis. Despite more small, dense LDL being trapped, more cholesterol is released by each larger LDL particle (despite fewer being trapped). Thus, large and small LDL particles cause similar vessel wall injury because large LDL particles release more cholesterol per particle, while small LDL particles contain less cholesterol and more particles are trapped so the net atherogenic effects are equal. Small-dense LDL particles are potentially more susceptible to oxidation, and oxidized LDL-C may bind to scavenger receptors on macrophages thereby promoting atherosclerosis [2, 4]. Therefore, all LDL-C (i.e., all LDL regardless of particle size) are considered to be an independent causal risk factor for coronary artery disease [5].

High-density lipoprotein-cholesterol (HDL-C) is also comprised of cholesterol and phospholipids and the main structural protein is Apo A-1. HDL particles have several anti-atherogenic properties. Most notably, HDL particles remove cholesterol from cells and tissues and deliver it to the liver for excretion by two different pathways. First, through a process of reverse cholesterol transport, HDL removes cholesterol from macrophages thereby preventing foam cell formation and atherogenesis. Another pathway of cholesterol transport to the liver by HDL is via its cholesteryl ester exchange for TAG from VLDL and LDL by cholesteryl ester transfer protein (CETP) followed by receptor-mediated hepatic LDL (and cholesteryl ester) uptake. Other anti-atherogenic properties of HDL include reducing inflammation, LDL oxidation, and thrombosis formation (by inhibiting coagulation factors), as well as inducing endothelium-dependent vasodilation [6].

There is a robust evidence base from epidemiological studies, clinical trials, animal studies, and in vitro experiments that HDL-C is cardioprotective and is inversely associated with cardiovascular morbidity and mortality [5, 7]. However, there is some evidence that not all HDL particles confer protection against CVD. HDL is a heterogeneous particle; subspecies contain apolipoprotein E and or apolipoprotein CIII. Interestingly, HDL particles that contain apolipoprotein E promote reverse cholesterol transport, whereas the presence of apolipoprotein C III abolishes these effects [8]. Further research is needed to understand which HDL particles confer the greatest benefits against CVD and how these can be increased with lifestyle and pharmacologic interventions. To date, the CETP inhibitor drugs that have increased HDL-C markedly have not demonstrated cardiovascular benefits without side effects. Therefore, despite considerable initial promise, CETP inhibition provides insufficient cardiovascular benefit for routine use [9].

Non-high-density lipoprotein-cholesterol (non-HDL-C) is calculated by subtracting serum HDL-C from total cholesterol and is an estimate of all cholesterol and triglycerides present in chylomicrons, CR, VLDL, IDL, and LDL-C [10]. Thus, non-HDL-C includes all atherogenic cholesterol in contrast to LDL-C measurement, which only accounts for the cholesterol contained in the LDL particles (roughly 75% of cholesterol carried by non-HDL-C). Moreover, LDL-C is usually calculated, not directly measured, and therefore may not provide the most accurate measure of atherogenic cholesterol. Finally, non-HDL-C is more strongly associated with ASCVD risk compared to LDL-C [11].

Dietary Fat and Health

Dietary fat, one of the three macronutrients, is necessary for survival. The composition of our dietary fat has specific effects on circulating lipoproteins. Different FAs can be associated with both health benefits and adverse health outcomes. Specific FAs elicit changes in circulating lipids/lipoproteins, and long-term consumption of certain FAs increases risk of developing cardiometabolic diseases. Diets containing a greater percentage of SFA are associated with increased risk of CVD, diabetes, obesity, metabolic syndrome, and non-alcoholic fatty liver disease [12–14]; unsaturated fatty acids, in contrast, confer many health benefits.

When MUFA/PUFA are substituted for SFA, improvements in lipids/lipoproteins and vascular health are observed [14]. A diet containing a greater proportion, or ratio, of MUFA/PUFA:SFA is associated with reduced risk of CHD, metabolic syndrome, and hyperglycemia [15]. Additionally, n-3 PUFA, notably, marine-derived n-3 PUFA, have unique cardioprotective benefits, which has led to extensive research and the development of pharmaceuticals to treat specific diseases.

Trans-Fatty Acids

Although there were concerns about the negative health consequences of TFA in the 1980s, it was not until 1990 that Mensink and Katan reported that TFA increased LDL-C and decreased HDL-C in healthy subjects [16]. A subsequent meta-analysis of 12 controlled trials confirmed these findings reporting adverse effects of TFA on both LDL-C and HDL-C, thereby increasing risk of CHD [17].

The pooled relative risk from two observational studies showed a 2% increase in calories from TFA was associated with a 23% increased incidence of CHD [17]. A more recent dose-response meta-analysis of cohort studies estimated that the risk of CVD was increased 16% for each 2% increase in daily energy from TFA [18]. Collectively, the epidemiological and clinical research showing that TFA increased CHD risk led first to food labeling guidelines by the Food and Drug Administration, then removal of the Generally Recognized as Safe (GRAS) status for partially hydrogenated oils, and finally a ban on their addition to foods [19]. In the United States, consumption of TFA significantly decreased from 2.6% of total energy in the 1990s to 1.1% of total energy in the late 2000s, and serum TFA levels declined more than 50% from 2000 to 2009 [20, 21].

SFA/MUFA/PUFA

Current guidelines recommend consuming <10% of calories from SFA due to their adverse effects on lipoproteins (from clinical trial evidence) and associations with CVD (from epidemiological studies) [22, 23]. The 2020 Dietary Guidelines Advisory Committee concluded that there is strong evidence to support the replacement of SFA with PUFA based on consistent findings demonstrating risk reduction for both CHD events and CVD mortality [24]. Clinical trials assessing the effects of SFA on serum lipoproteins consistently show increases in LDL-C and HDL-C [25, 26]. Over the last few decades, epidemiological studies evaluating the relationship between dietary SFA and cardiometabolic health have reported inconsistent findings, which are largely explained by the statistical methods used and whether the replacement macronutrient was considered [27].

An epidemiological study beginning in the late 1950s showed a positive relationship between dietary SFA and heart disease leading to the hypothesis that SFA *causes* cardiovascular disease [28]. Zhu and colleagues conducted a dose-response meta-analysis on dietary FA and CVD in cohort studies and determined SFA intake was not associated with CVD [18]. However, this analysis only examined the relationship between SFA and CVD without assessing the replacement nutrient for SFA,

which was likely refined carbohydrates (CHO) based on data about usual American consumption patterns. In a prospective cohort analysis, of over 126,000 US adults followed for up to 32 years, isocaloric replacement of 5% of energy from SFA with either PUFA (predominate dietary source is n-6) or MUFA was associated with a reduction in risk of total mortality by 27% and 13%, respectively. Similarly, replacing 5% of energy with unsaturated fatty acids (both PUFA and MUFA) reduced CVD mortality by 20% [29]. In addition, replacement of 5% of energy from SFA with whole grain CHO, MUFA, or PUFA was associated with a 9, 15, and 25% reduced risk of CHD, respectively [30].

In alignment with epidemiological findings, a recent Cochrane systematic review of 15 clinical studies, including over 59,000 participants, found that lowering SFA intake, regardless of the replacement macronutrient (PUFA, MUFA, or CHO), reduced combined cardiovascular events (cardiovascular death, cardiovascular morbidity, and unplanned cardiovascular interventions) risk by 21% [31]. However, there was not a significantly lower risk of all-cause mortality, cardiovascular mortality, or any of the secondary outcomes; findings are likely explained by the lack of statistical power due to the insufficient number of events and relatively short duration of follow-up.

Clinical trial evidence demonstrates that replacing SFA with MUFA, PUFA, or CHO significantly reduces LDL-C. Replacing 1% of dietary energy from SFA with the same percentage of energy from PUFA, MUFA, and CHO is estimated to lower LDL-C by 2.1, 1.6, and 1.3 mg/dL, respectively [32]. Whole grain CHO sources lower LDL-C more than refined grains [33]. A meta-analysis of randomized controlled trials showed that replacing SFA with whole grains, compared to refined grains, led to a greater reduction (3.5 mg/dL) in LDL-C [34].

Full-fat dairy products are a rich source of SFA with dairy fat being comprised of nearly 60% SFA (an 8-ounce glass of whole milk contains 8 g fat and 5 g is SFA). Dairy fat-derived SFA may not have the same effect on circulating lipoproteins as other animal-based SFA. Observational data suggest that dairy fat containing SFA is not associated with increased risk of CVD [35]. However, macronutrient replacement analyses show that CVD risk is reduced when MUFA, PUFA, and whole grains are consumed in place of dairy fat-derived SFA. Interestingly, a meta-analysis of three cohorts estimated that the replacement of 5% energy from dairy fat with equal energy from other animal fat increased CVD risk by 6% [35]. Dairy fat-derived SFA increased LDL-C less than other animal fats containing SFA; however, dairy fat-derived SFA are more atherogenic than UFA [35, 36]. The findings described here indicate that dairy fats pose some risk of CVD, but this is less than that associated with other animal fats containing SFA. For that reason, it is recommended that intake of dairy foods should be fat-free, low-fat dairy products.

N-3 Fatty Acids (ALA, EPA, and DHA)

Large, randomized controlled trials of prescription EPA + DHA and/or EPA (840–4000 mg/day) show reduced risk of CVD in healthy individuals and those with diabetes or elevated triglycerides (135–499 mg/dL) [37]. Two trials, VITAL and ASCEND, evaluated EPA + DHA for primary prevention of CVD and did not find a significant reduction in the primary endpoints (combination of coronary and ischemic outcomes). It is important to note, however, that in the VITAL trial, 460 mg of EPA + 380 mg DHA significantly reduced fatal (50%) and nonfatal heart attacks (28%) and in the ASCEND trial, 465 mg of EPA + 375 mg DHA resulted in a 19% reduction in CVD death, each of these being secondary endpoints [38, 39]. In VITAL, individuals consuming 1 ½ servings of fish per week at baseline had a 19% reduction in major cardiovascular events, while those with a baseline fish consumption greater than 1 ½ servings/week did not have a significant reduction in cardiovascular events [38]. The REDUCE-IT trial evaluated 4 g/day (2 g two times/day) of a purified form of EPA (icosapent ethyl) for secondary prevention of CVD in statin-treated individuals with elevated triglycerides. There was a 25% reduction in the primary endpoint, a composite of unstable angina, nonfatal

stroke, nonfatal heart attack, and CV death, compared to the placebo group [40]. A recent meta-analysis of 13 trials (including VITAL, ASCEND, and REDUCE-IT) found a dose-response effect of marine-based n-3 on reducing risk of total CVD, CVD death, myocardial infarction, and total CHD [41]. Collectively, these studies demonstrate the importance of the n-3 fatty acids, EPA + DHA, for primary prevention of CHD and underscore the need to increase intake of these fatty acids in the population. There are also important benefits of a prescription dose of icosapent ethyl for secondary prevention of CVD, excluding stroke.

The 2020–2025 Dietary Guidelines for Americans recommend consuming 8 ounces of seafood per week, which provides approximately 250 mg EPA+DHA/day [23, 42]. The AHA recommends 1 to 2 servings (3.5 oz/sv) of fish per week, with emphasis on fatty fish [42]. If recommendations for n-3 intake cannot be achieved from food sources, an over-the-counter supplement may be considered in consultation with a healthcare provider. Over-the-counter supplements are not regulated by the Food and Drug Administration but are typically safe although sometimes the quantity of EPA/DHA in the product falls short of what is listed on the label.

Observational studies demonstrate a moderately lower risk for CVD with increased alpha-linolenic acid (ALA) consumption, but the relationship is not as consistent or strong as for EPA and DHA [43]. However, a meta-analysis of five cohort studies estimated that a 1 g/day increase in ALA was associated with a 10% reduction in CHD death, and a systematic review of RCTs reported that a higher intake of ALA was associated with a 5–9% reduction in CVD, although this was nonsignificant [43, 44].

Dietary Patterns

The focus of this chapter is on the effects of individual FAs and FA classes on circulating lipoproteins as well as overall health. However, foods contain a mixture of different fatty acids in varying proportions and generally have a predominant fatty acid class. As such, the focus of current dietary recommendations is on food-based healthy eating patterns. The 2020–2025 Dietary Guidelines for Americans recommend a healthy US style, a healthy Mediterranean style, and a healthy vegetarian/vegan style eating pattern [23]. In addition, the Dietary Approaches to Stop Hypertension (DASH) eating pattern also is recommended by many health organizations [45]. These dietary patterns are all low in SFA (<10% kcal), sodium, and added sugars and emphasize fruits, vegetables, nuts, seeds, legumes, whole grains, plant protein or lean/low-fat unprocessed animal protein, and liquid oils. In addition, these dietary patterns limit SFA by including MUFA/PUFA or fiber-rich whole grain CHO foods in place of food sources of SFA thereby affecting the total fat content of the diet. Although the total fat content of these dietary patterns can vary depending on the replacement macronutrient, they nonetheless align with the current dietary reference intake (DRI) for total fat (20–35% of total calories).

The fat content of many commonly consumed dietary patterns exists on a spectrum ranging from very-low fat (Ornish diet: <10% of total calories), low fat (10–20% of total calories), moderate fat (20–35% of total calories), and high/higher-fat (35–70% of total calories) to very-high fat (keto diet: >70% of calories from fat) diets. The topic of how low-carbohydrate diets influence plasma lipid profiles is discussed in further detail in Chap. 18. Clinical trials of these dietary patterns show that the effects on lipids/lipoproteins generally reflect their fatty acid profile (see Dietary fat and health). The effects of fatty acids on lipids and lipoproteins are due to their quantitative contribution on an energy basis in the diet. The key is for SFA to be low, and as total fat increases in the diet, the emphasis should be on unsaturated fat. As a result, all healthy dietary patterns, defined as meeting nutrient and food-based recommendations, provide <10% of calories from SFA, regardless of total fat content. Therefore, healthy lower-fat diets are higher in fiber-rich whole grain CHO, while healthy higher-fat diets are higher in MUFA and PUFA.

Summary

Healthy eating patterns meet food-based dietary guidelines, achieve nutrient adequacy, and meet recommendations for SFA (<10% of calories), sodium, and added sugars. A healthy eating pattern can vary in total fat, which depends largely on the differences in the amounts of unsaturated fatty acids and CHO that are substituted for SFA. The evidence that supports recommendations for SFA is based on the well-documented adverse effects of SFA on LDL-C and CVD risk and beneficial effects of unsaturated fats and CHO from whole grains. The core precept of contemporary dietary guidance specific to fatty acids is to replace SFA with PUFA, MUFA, or CHO (from whole grains) to decrease CVD risk.

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Demystifying Dietary Sugars

30

J. Bernadette Moore and Barbara A. Fielding

Keywords

Sugar · Sugar-sweetened beverages · Sugar tax · Obesity · Agave · Fructose

Key Points

- High dietary intakes of sugars increase energy intake, body weight, and the risk of tooth decay.
- High consumption of sugar-sweetened beverages increases risk for type 2 diabetes.
- Sugar naturally present in intact foods produces less of a glycemic response than added or free sugars.
- Health effects of specific sugars on metabolism beyond excess energy are not clear.
- Fiscal policies may help in reducing intake of sugar-sweetened beverages and high-sugar snacks.

Introduction

An extensive body of evidence now links excess consumption of sugar to obesity and dental caries. High intakes of sugar-sweetened beverages specifically are associated with increased risk for type 2 diabetes [1]. This is a particular concern for adolescents and young adults who typically consume the highest percentage of their daily calories from sugar-sweetened beverages (>9% in the USA [2, 3]). The confluence of evidence has led to the updating of dietary recommendations related to the consumption of added/free sugars by many public health advising bodies across the world. Moreover, some countries have implemented fiscal (sugar tax) or other policy measures aimed at reducing sugar consumption and preventing obesity. While there is now increased public awareness of the recommendations to reduce sugars and sugar-sweetened beverages in our diets, there remains confusion over terms such as "total sugar," "added sugars," and "free sugars" found on food labels and used by public health officials. In addition, there are misunderstandings about the relative risks or healthfulness of different types of sugars found in foods and terms such as "raw" and "natural" that are used in their marketing. One example of this problem is "raw" agave nectar, a syrup derived from the agave

J. B. Moore (✉)
School of Food Science & Nutrition, University of Leeds, Leeds, UK
e-mail: j.b.moore@leeds.ac.uk

B. A. Fielding
Department of Nutritional Sciences, University of Surrey, Guildford, UK
e-mail: b.fielding@surrey.ac.uk

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plant commonly found in health food stores and widely used in foods and beverages. Sales of this product are increasing as a result of its marketing as a natural and low glycemic alternative sweetener to "refined" sugar and high-fructose corn syrup [4]. However, as detailed below agave is, in reality, a highly refined syrup with a higher fructose content than high-fructose corn syrup [5]. The aim of this chapter is to demystify these terms for the healthcare professional and give a balanced overview of the role of dietary sugar in obesity and metabolic health.

Types of Sugar

Chemical Classification

Conventionally, the term "sugars" encompasses chemically the monosaccharides (glucose, fructose, galactose) and disaccharides (sucrose, lactose, maltose). These are the lowest molecular weight carbohydrates. Carbohydrates are biomolecules made up of carbon, hydrogen, and oxygen and an important source of energy in the diet. Glucose, fructose, and galactose are six-carbon hexoses with the chemical formula $C_6H_{12}O_6$ and are the building blocks of disaccharides as well as longer oligo- and polysaccharides. The word saccharide is derived from the Greek word for sugar.

Disaccharides are the product of a condensation reaction between two monosaccharides. The most common disaccharide is sucrose, often called table sugar, which is produced naturally in plants from glucose and fructose. It is extracted and refined, most commonly from sugarcane and sugar beets, but also corn, agave, palm, and numerous other plants and grains (the latter called malt). Glucose and fructose are also found in their free form in fruits, plant juices, and honey. Starch, the principal storage carbohydrate in plants, is a polysaccharide comprised of many glucose monomers. As fruits ripen, their starch breaks down increasing the free sugar content of the fruit and its sweetness.

Maltose is a disaccharide of two glucose molecules and an intermediate of starch hydrolysis found in germinating grains and seeds. Lactose, or "milk sugar," is a disaccharide of glucose and galactose that is intrinsic to milk and dairy-based products, but also an important part of human breast milk, a topic discussed at greater length in Chap. 3.

"Total" versus "Added" or "Free" Sugars

Currently, most countries require the declaration of "total sugar" on the nutrition facts labels of packaged foods. Total sugar on labels includes sugars occurring naturally in foods and beverages, such as lactose, as well as sugars added by the manufacturer during processing and preparation.

However, dietary guidelines recommending limiting sugar intakes refer either to "free sugars" (World Health Organization, UK) or "added sugars" (USA, Australia). In recognition of the role of the food matrix on health effects discussed further below, these terms are similar in excluding the sugars present in intact fruits and vegetables as well as lactose naturally present in milk and milk products. The difference between the terms free and added sugars is that the definition of free sugars includes the sugars in juiced or pureed fruit and vegetables, whereas these are excluded from the definition of added sugars (definitions have been summarized in Table 30.1).

Therefore, in the USA where the reporting of added sugars (under total sugars) on food labels has now been mandated [6], a 250 ml glass of 100% orange juice that contains 26 g of total sugar will list 0 g of added sugars on the label while still containing 26 g of free sugars. This is problematic because in terms of the health risks of dental caries, weight gain, and type 2 diabetes associated with intake of dietary sugar, there is consensus that public guidance and intake monitoring should focus on free sugars [7]. Moreover, as the US Food and Drug Administration's definition of added sugars excludes fruit purees, the increased use of these as sweetening ingredients has been touted by some in the food industry as a strategy for circumventing the "added sugar label hurdle" [8]. Fruit (and vegetable)

Table 30.1 Definitions of relevant sugar-related terms [11]

Term	Definition
Sugars[a]	Conventionally describes chemically the monosaccharides (glucose, fructose, galactose) and disaccharides (sucrose, lactose, maltose). Sugars include those occurring naturally in foods and drinks or added during processing and preparation
Total sugars	Currently required for nutrition facts labels on packaged foods in most countries worldwide. Includes sugars occurring naturally in foods and beverages and those added during processing and preparation
Added sugars	A required subline under "total sugars" for US food labels from 2020 [6]. Defined as "Syrups and other caloric sweeteners used as a sweetener in other food products. Naturally occurring sugars such as those in fruit or milk are not added sugars" [12]; the term "added sugars" in the USA also excludes sugars in juiced or pureed fruits and vegetables that are included in the WHO definition of free sugars
Free sugars	"All monosaccharides and disaccharides added to foods by the manufacturer, cook, or consumer, plus sugars naturally present in honey, fruit juices, and syrups" [13]. Under this definition, sugars present in intact fruits and vegetables and lactose naturally present in milk and milk products are excluded
Monosaccharides	The simplest form of carbohydrates including the three primary hexoses (six-carbon simple sugars): glucose, fructose, and galactose; these are the monomers that make up naturally occurring di-, oligo-, and polysaccharides
Disaccharides	Product of condensation reaction between two monosaccharides; includes sucrose, lactose, maltose
Sucrose	A crystalline disaccharide of fructose and glucose found in many plants, predominantly sugarcane and sugar beets. It is extracted and refined and used widely as table sugar
Lactose	A disaccharide of glucose and galactose. It is often called "milk sugar" because 100% of "total sugars" in milk are lactose

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[a]Examples of sugars commonly found as ingredients: sucrose, fructose, glucose, dextrose, maltose, lactose, trehalose, brown sugar, turbinado sugar, demerara sugar, raw sugar, cane sugar, fruit sugar, invert sugar, corn sweetener, corn syrup, high-fructose corn syrup, malt syrup, glucose syrup, glucose-fructose syrup, honey, molasses, date syrup, agave syrup, rice syrup

puree is often the reason for high free sugar content in foods for infants and toddlers [9], and fruit purees are also often found in yogurts that can contain a surprisingly high amount of free sugars [10].

Sugars versus Complex Carbohydrates in the Context of Real Food

Although the chemical structure and biological handling of sugars are indistinguishable regardless of source, the food matrix greatly impacts the metabolic effects of sugar. For example, intact fruit provides much greater satiety and a lower glycemic effect than its comparable fruit juice [7]. For this reason, sugars contained within the cell walls of fruit are not "counted" as added sugars. Whereas high fruit and vegetable intakes are associated with beneficial effects on body weight, increased fruit juice consumption contributes to weight gain and the risk of dental caries. Current pediatric recommendations underscore that 100% fruit juice offers no nutritional benefits over whole fruit; indeed, juice is lacking the protein and fiber found in whole fruit and intakes should be limited [14]. While 100% fruit juices may provide some essential nutrients, they can also provide almost as much sugar as carbonated soft/fizzy drinks, and frequent consumption of acidic fruit juices have been shown in meta-analysis to contribute to tooth erosion in children [15]. In contrast, higher consumption of milk has been associated with lower risk for tooth erosion [15]. Although some studies have suggested that lactose may be less cariogenic than other sugars, there is also a pH effect with the food matrix components in unsweetened dairy products providing a buffering capacity that is protective to tooth enamel [16].

When glucose is consumed as a sugar-sweetened beverage or as fruit juice, absorption into the blood is rapid, and although plasma concentrations of glucose are partly determined by the balance between the arrival of ingested glucose into the blood and uptake into tissues, a compensatory decrease in endogenous (hepatic) glucose production (EGP) also influences plasma glucose levels. Stable isotope techniques have shown that in people with type 2 diabetes, a reduced suppression of EGP significantly contributes to the higher plasma glucose concentrations compared to healthy controls after an oral glucose tolerance test (Fig. 30.1). Thus, postprandial glycemia is dependent on the degree of hepatic insulin sensitivity.

As noted previously, complex carbohydrates, such as starch, are composed of a series of glucose monomers. However, starch and the equivalent glucose load are not necessarily equal with regard to glucose-raising potential. One of the reasons for this is that in real life, starch is usually eaten as part of a mixed meal, with slower gastric emptying than after a drink. We can take potato mashed with butter as an example. This food produces a much lower glucose spike than does a comparable amount of available carbohydrate in a sugar-sweetened beverage (Fig. 30.2). We can see that the glucose in plasma directly attributable to glucose from the drink has returned to baseline by 270 min, whereas the glucose in plasma directly attributable to glucose from the potato meal is still above baseline by the end of the study at 360 min. If consumed with its skin, some lean protein, and vegetables, the

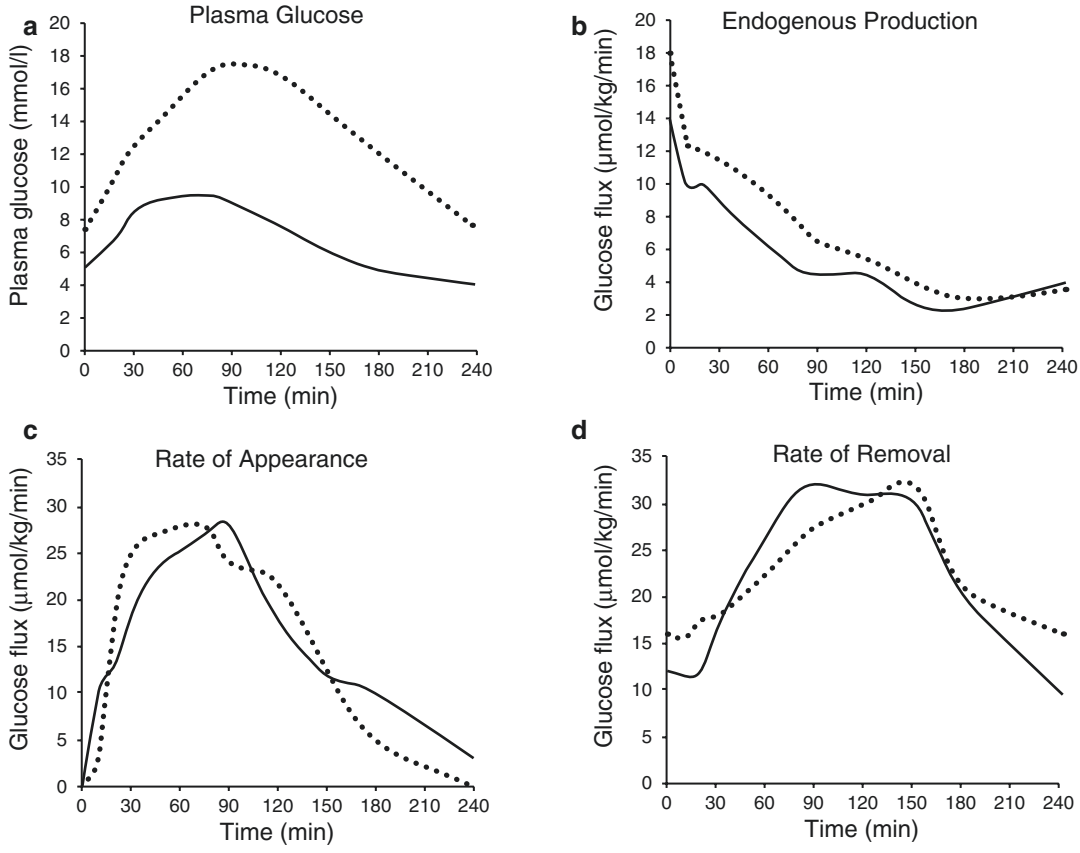

Fig. 30.1 Glucose fluxes contributing to plasma glucose concentrations in healthy people (solid line) and people with type 2 diabetes (*dashed line*) after an oral glucose tolerance test (OGTT, 75 g glucose). (**a**) plasma glucose concentrations; (**b**) rate of endogenous (hepatic) glucose production; (**c**) rate of glucose appearing in the blood from the drink; (**d**) rate of glucose removal from the blood. (Data taken from Lund and colleagues [17])

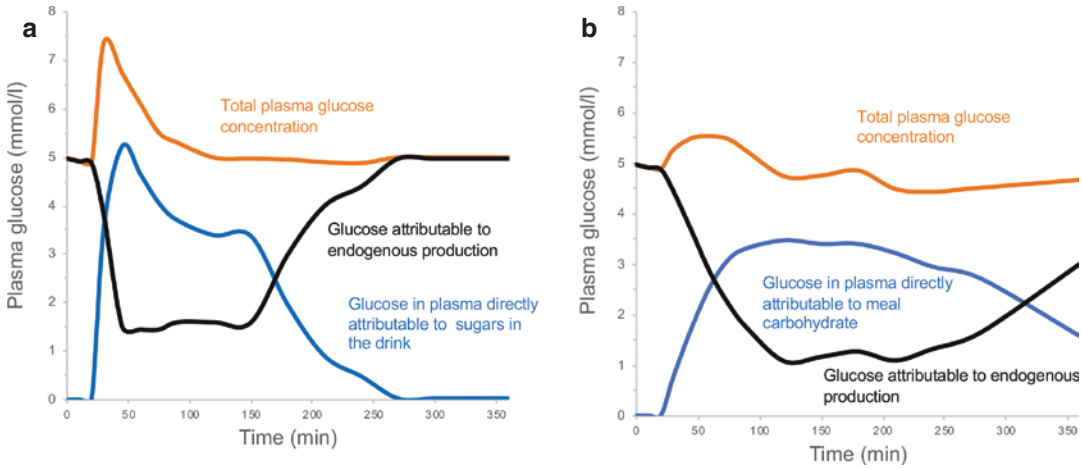

Fig. 30.2 Determinants of plasma glucose concentrations in healthy individuals after either: (**a**) a drink containing 35 g glucose, data estimated from [18, 19]; or (**b**) a comparable amount of available carbohydrate in a serving of mashed potato containing 20 g fat from butter, author's (BAF) unpublished data

response would be even further blunted. Moreover, while the composition of a meal influences the glycemic response, recent large-scale precision nutrition studies have demonstrated both that numerous factors influence the postprandial response and that there is tremendous inter-individual variability even to the same foods [20, 21]. Therefore, simplistically representing potatoes, rice, bananas, or other whole plant foods in terms of spoonfuls of sugar, as occasionally depicted, is very misleading.

Sugar, Obesity, and Metabolic Health

Public Health Recommendations

In recent years numerous public health advisory bodies have updated and strengthened their guidelines around dietary sugar intake (Table 30.2). The scientific basis for restricting the consumption of free sugars to a maximum of 10% of total dietary energy came from two independent meta-analyses commissioned by the World Health Organization (WHO) and the UK's Scientific Advisory Committee on Nutrition. These concluded that there is a causal relationship between a high-sugar diet and obesity [22, 23]. However, with respect to type 2 diabetes, the strongest evidence is seen for a relationship with the consumption of sugar-sweetened beverages specifically, rather than for total sugars [23]. Nonetheless, with obesity, a leading risk factor for cardio-metabolic disease, reducing dietary sugar intake is presumed to be beneficial for anyone wishing to mitigate risk of developing cardiovascular disease, type 2 diabetes, and fatty liver.

There has been a staggering global tripling of the population classified as obese since 1975. In an attempt to reduce this rising tide, the WHO has proposed different economic policies. The most common of these is a tax on sugar-sweetened beverages. Both modelling and studies evaluating the impact of sugar tax have indicated that purchases or sales decrease significantly with taxation amounts of around 8 to 10% [27]. A modelling study based on UK dietary habits concluded that a 20% price increase on "high sugar snack foods" in the UK would have substantially more impact on the average weight change of adults than would a similar price increase on SSBs [28]. We have previously cautioned that fiscal policies aimed at reducing consumption of sugar might be useful, but they fail to incentivize the consumption of healthy foods. Ultimately, tackling obesity and diet-related disease

Table 30.2 Organizational recommendations for the consumption of dietary sugars [11]

Organization (Year)	Recommendations
World Health Organization (2015)	Intakes of free sugars should be reduced to less than 10% of total energy intake in both adults and children [24]
UK Scientific Advisory Committee on Nutrition (2015)	The average population intake of free sugars should not exceed 5% of total dietary energy for those aged 2 years or over [23]
US Department of Health and Human Services (2015)	Consume less than 10% of calories per day from added sugars [12]
Australian National Health and Medical Research Council (2013)	Limit intake of foods and drinks containing added sugars such as confectionary, sugar-sweetened soft drinks, and cordials, fruit drinks, vitamin waters, energy and sports drinks [25]
European Food Safety Authority (2010)	At the time EFSA concluded the available evidence was insufficient to set an upper limit for intake of sugars. However, this is currently being reviewed with an aim of setting "a tolerable upper intake level for total/added/free sugars if the available data allow it," with publication anticipated in 2021 [26]

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requires a sustained group of initiatives aimed at reducing health inequalities [29]. More recently, evidence is accruing of "a perfect storm" with a higher mortality rate when the coronavirus disease COVID-19 infects people with obesity [30].

Common Sources of Sugar and Marketing

Major challenges for consumers who wish to cut down their intake of sugars include both the ubiquity of sugars in foods and the myriad ways that sugars are either disguised or marketed. While the majority of the public anticipate that sugar will be in cakes and confectionary, they underestimate the sugar content of perceived healthy foods such as yogurts, under the so-called health halo effect [31]. Added sweeteners are found in numerous foods consumers might not expect such as peanut butter, baked beans, and many sauces and condiments. Moreover, added sugars are often missed by consumers on ingredient lists because of the variety of names that mono- and disaccharides may be disguised under. Although we list 25 names in the footnote of Table 30.1, we caveat this is not a comprehensive list. In more recent years the marketing of "natural sugars" has become problematic. When surveyed, consumers stated preferences are for honey, agave, and date syrups and "raw cane sugar," with table sugar the least popular. Their preferred sweetening ingredients were based on the "natural" sugars being perceived as "healthier" and/or less processed [32].

For example, agave nectar or syrup is marketed as a natural sweetener but is processed almost identically to high-fructose corn syrup (HFCS); and it contains approximately 84% fructose, whereas HFCS generally contains either 42 or 55% fructose [11]. It is noteworthy that whether sourced from sugarcane, sugar beets (common in the European Union), agave, or corn, extracting sugars from these fibrous plants requires a similar amount of (extensive) processing to produce even raw sugar. Regardless of source or name, the dominant compounds in all sweeteners are monosaccharides and disaccharides; it is these substances that lead to a significant increase in the energy density of foods that contain added sugar (Table 30.3). However, the unwitting consumer just sees "agave" on the ingredients list and may assume the product is healthier than a product listing sugar as an ingredient. Recent research has underscored that chemical or alternative names for sugars found on ingredient labels is not always helpful for consumers; 30–50% of them, when surveyed, incorrectly identified sucrose, fructose, and dextrose as being non-caloric sweeteners [33].

Table 30.3 Energy and sugars found per 100 g in common dietary sweeteners[a] [11]

Sweetener	Energy (kcal)	Water (g)	Total sugars (g)	Sucrose (g)	Glucose (g)	Fructose (g)
White sugar	385	0.02	99.8	99.8	0.0	0.0
Brown sugar	380	1.34	97.0	94.6	1.4	1.1
Honey	304	17.1	82.1	0.9	35.8	40.9
Molasses	290	21.9	74.7	29.4	11.9	12.8
Maple syrup	260	32.4	60.5	58.3	1.6	0.5
Agave syrup	310	22.9	68.0	0.0	12.4	55.6
Golden syrup	298	20.0	79.0	32.8	23.1	23.0
HFCS	281	24.0	75.7	nr	nr	nr

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HFCS high-fructose corn syrup, *nr* not reported
[a]Data taken from the U.S. Department of Agriculture Food Data Central database [34] and the Public Health England Composition of Foods Integrated Dataset [35]

Sugar-Sweetened Beverages

Sugar-sweetened beverages are hot or cold drinks sweetened with any kind of added sugar. In many cases they have no other nutritive value. They include carbonated sweet drinks (often called soda), fruit drinks, sports drinks, energy drinks, sweetened waters, and coffee and tea beverages with added sugar and are a leading source of dietary sugar in many countries. The evidence for a causal relationship between consumption of sugar-sweetened beverages, obesity, and consequent metabolic dysfunction has been well summarized [23], but an independent effect on the risk of type 2 diabetes has been surprisingly difficult to prove [36]. Despite public health messages and guidelines to reduce intake, worldwide longitudinal studies have not shown significant decreases in recent years although some trends in the right direction have been observed [37]. Underlying reasons for high consumption of sugar-sweetened beverages are complex, varying by age, sex, race/ethnicity, geography, socioeconomic status, and associated with less healthy behaviors [38]. Moreover, replacement of sugar-sweetened beverages with sugar-free (diet) alternatives has not led to a reduction of energy intake.

Is Fructose Worse for Health?

There are two sides to fructose; on the one hand, refined fructose is marketed as a naturally occurring fruit sugar that can be consumed in smaller quantities than other sugars to achieve the same sweet taste. It is also metabolized differently than glucose and is not recognized by the beta-cell. But on the other hand, although fructose does not directly elicit an insulin response, it can do so indirectly by conversion to glucose. Using stable isotope tracers, it has been calculated that 26% of fructose carbons are converted to glucose when 0.5 g/kg was consumed with a mixed meal and 19% are converted in the presence of a mixed meal that also contains glucose [39]. However, fructose is predominantly metabolized by the liver to products such as glycerol and fatty acids, leading to significantly greater postprandial hypertriglyceridemia than glucose when consumed in supraphysiological amounts in acute studies [40]. The use of hypercaloric, supraphysiological doses in intervention trials has been a major confounding factor, and the matter of whether or not hepatic lipogenesis and non-alcoholic fatty liver disease pathogenesis in humans occur independently of excess energy remains unresolved [41]. There is only a limited amount of evidence that hypercaloric fructose and glucose diets have similar effects on liver fat and liver enzymes in healthy adults [42].

Fructose has been scrutinized in part because intakes of HFCS have increased dramatically in parallel with the increase in obesity and metabolic disease in the USA since its introduction in 1967 [40].

As alluded to previously, its name is in fact a misnomer as HFCS generally contains either 42 or 55% fructose—much less than agave nectar at 84%. Metabolically, the fate of the glucose and fructose monomers in HFCS is no different from the monomers of glucose and fructose derived from sucrose (after cleavage by the enzyme sucrase in the intestine) or the syrups produced from sugarcane or sugar beet. In the European Union, where syrups are typically derived from sugar beet, these sugars are found on food labels as glucose-fructose syrup, fructose-glucose syrup, or isoglucose, depending on the ratio of monomers [40]. Interestingly, these ingredients and the very popular baking ingredient "golden syrup" (Table 30.3) have yet to be as demonized by consumers as HFCS, despite the fact that they all contribute equally to excess energy intake. The point remains, nonetheless, that fructose is almost never consumed in isolation, and to date proving an adverse metabolic effect of specific sugars at typically consumed levels that is independent of their contribution to excess energy has been difficult.

Conclusion

High intakes of dietary sugars have fueled the obesity pandemic. The overconsumption of sugar-sweetened beverages has an associated higher risk for developing type 2 diabetes. Worldwide differences in the terminology of added, free, and total sugars and the guidelines relating to dietary sugar have likely hindered progress in understanding how to reduce the high global consumption. Significant misunderstandings exist, among consumers and health professionals alike, about the relative healthfulness of different sugars and sweeteners. While the free sugars in fruit juice and fruit purees produce sharp spikes in blood glucose levels, intact fruit has a reduced glycemic response because the sugars are contained within cell walls and the accompanying fiber slows the rate of digestion. Fruit also contains micronutrients and phytochemicals that are more beneficial to health. Although fiscal policies may help in reducing intake of sugar-sweetened beverages and high-sugar snacks, it is imperative that important confounding factors, such as social inequalities, are taken into consideration.

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Suggested Further Readings

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Energy Drinks and Human Health: Information, Implications, and Safety

31

Jessica R. Szczepanski, Ted Wilson, and Frances R. Ragsdale

Keywords

Energy drinks · Caffeine · Taurine · Ginseng · Guarana · Red Bull · Monster · Rockstar

Key Points

- Energy drinks (EDs) have become a popular beverage option in spite of their ability to maintain unclear and inconsistent ingredient contents as well as identity.
- Market value ($53.01 billion 2018) of EDs continue to increase worldwide and is expected to rise steadily (>$86 billion 2026). Sales in the United States alone reached an all-time high of over $3.4 billion in 2019, with an almost 4% increase in total sales volume.
- Caffeine is the primary active ingredient in EDs. Other stimulant ingredients commonly identified in EDs include taurine, ginseng, and guarana.
- Adverse effects appear to be associated with caffeine toxicity, although it is difficult to document adverse effects in controlled study conditions.

Introduction

Energy drinks (EDs) have traditionally appealed to physically active individuals, even those who are not extreme competitors but simply recreational athletes attempting to enhance their sport performance or fuel their training regimen, although nonathletes also use them. Caffeine, the main ingredient in EDs, is touted as one of the best-tested ergogenic aids to enhance sport performance. The marketing of EDs offer consumers "a lifestyle in a can," and their use is associated with extremely demanding and exciting lifestyles as lived (in popular imagination) by professional athletes and famous musicians. Consumers are promised increased energy, improved mood, superior cognition, speedier reaction time, enhanced athletic performance, etc. Red Bull was one of the first EDs in the marketplace and became available in the United States in 1987. By the mid-2000s, over 500 EDs were being sold around the world [1].

J. R. Szczepanski (✉)
Department of Health Sciences, Northern Arizona University, Flagstaff, AZ, USA
e-mail: Jessica.Szczepanski@nau.edu

T. Wilson · F. R. Ragsdale
Department of Biology, Winona State University, Winona, MN, USA
e-mail: twilson@winona.edu; fragsdale@winona.edu

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These products include Monster, Rockstar, and a plethora of other beverages, each with its own "proprietary mix" of ingredients. EDs are sweetened beverages with a "proprietary mix" of ingredients – caffeine, carbonation, minerals, vitamins, and stimulants such as taurine, ginseng, and guarana. Some EDs use artificial sweeteners in place of sugar (sucrose), while others have purposefully diverged from synthetic ingredients to alternative substitutes – such as honey, agave nectar, or high-fructose corn syrup – in place of sugar (sucrose). Most, if not all, ingredients of EDs have purported "health benefits," but rules and regulations limit the ability to make too many FDA-approved claims. The research and documentation of positive physiological changes following consumption of EDs such as Red Bull are difficult to quantify [2–4]. This chapter describes ED marketing, content, and health considerations.

Defining Energy Drinks: Intent Is to Be Difficult

Marketing Strategy and Target Audience

The US release of Red Bull in 1987 marked the beginning of the modern caffeinated energy drink (ED) [5]. The initial marketing strategy emphasized EDs as dietary supplements to young adult males with the image of a macho, masculine athlete that an average man could achieve to escape the conformity of his nine-to-five job and follow his dreams, selling to a "jock identity" [6]. Several brand names such as Full Throttle, No Fear, Brawls, Red Bull, Monster, and Rockstar all appeal to this population. This marketing strategy created brand name recognition and established a pool of celebrities ready to endorse ED products. In order to attract females to this market, brand names like Vixen, Go Girl, and Enviga appeared with a campaign to suggest ED consumers should strive to be "all that SHE can." Manufacturers again targeted young women, especially athletes, as their audience. Collectively, this population of ED consumers became known as "young transitionals" – young adults who appeared to have sufficient spending money as well as ample time to play and party [7]. One of the latest populations ED manufacturers appear to be advertising to is older baby boomers. With celebrity endorsements (John Ratzenberger who plays the Cliff Clavin character from the TV series Cheers) to advertisements appearing in senior specific publications (AARP magazine), the ED industry has shifted its marketing strategy from young adults to older adults [8].

The ambiguous nature of the "energy drink" definition is also a marketing strategy, where the loosely coined term can refer to any caffeinated beverage with other ingredients that are purported to provide the consumer with an extra boost of energy [9]. All labeling for products distributed as dietary supplements must comply with the Dietary Supplement Health and Education Act of 1994, although these rules and regulations are quite lax and do not require specifics such as caffeine content. Other definitions for EDs minimize the use of the term "caffeinated" and substitute the more generic term "stimulant" to refer to the presence of caffeine, ginseng, gingko, guarana, theobromine, theophylline, or even sugar.

Sales of all EDs continue to increase significantly (7.5% increase from 2017 to 2018) [10], which contrasts considerably with the slow and steady decline of soda sales [11]. Taking into consideration differences in the size of a single serving (8.4–12 oz.), EDs cost about four times more than soda (12 oz.). Despite the high price as well as the unidentified health benefits and potential health risks of EDs, consumers are still ingesting these beverages in substantial quantities. Red Bull continues to be the most popular ED with the company grossing $10.9 billion worldwide in 2012. Red Bull and Monster are the top selling EDs in the United States; they sold $3.4 billion (43% of market sales) and $3.1 billion dollars (39% of market sales), respectively, in the first half of 2013 [11]. Rockstar is the third most popular brand in the United States, with 10% of the market share. In 2013, the consumption of EDs worldwide exceeded 5.8 billion liters [12]. EDs are the second most common dietary

supplement used by young adults in the United States; over 30% of this population consumes these beverages daily [13]. With both sales and consumption of EDs continually rising, it is imperative to understand the implications and safety of these products.

Composition of Energy Drinks

In general, energy drinks (EDs) contain caffeine and sugar as well as a mixture of amino acids, electrolytes (minerals), vitamins, and herbs (i.e., ginseng and gingko) designed to be palatable to the diet and taste buds of the western world. Most EDs have a slight medicinal taste, so manufacturers oftentimes suggest consuming the beverages cold for optimal flavor. A majority of EDs are consumed like soft drinks. A more detailed description of some ED ingredients may be helpful to better understand them.

Caffeine

Caffeine is a methyl xanthine that is quickly metabolized and absorbed within about 20 minutes of consumption. Once in the bloodstream, the half-life of caffeine is highly variable (2–10 hours), depending on individual metabolism, lifestyle, and habits [14, 15]. The average consumption of caffeine by the US adult population is between 110 and 260 mg/day, making most of the country a major potential marketplace for EDs [16]. At this level, caffeine has also been shown to enhance physical and mental performance by postponing fatigue, increasing muscle efficiency, and improving oxygen utilization [17, 18]. Caffeine has also been shown to enhance psychomotor function [19, 20].

The caffeine content of EDs is highly variable (6–242 mg/serving) [21]. Based on the serving size of these beverages (8.4–12 oz.), the amount of caffeine in EDs is well within the range of ordinary coffee, tea, or carbonated soda (134–245 mg/serving; 48–175 mg/serving; 65 mg/serving, respectively). Most ED manufacturers designate an 8–12 oz. serving size, similar to the original Red Bull packaging. Recently, some companies have created 16 oz. packages containing "two servings"; in reality, this volume is to be consumed immediately upon opening since the container typically cannot be resealed. Even so, the amount of caffeine in this volume is still similar to two large espresso coffees. EDs now come in all sizes, including 24 oz. packages with tops that can be resealed.

Excess caffeine may cause irritability, which can create feelings of anxiety, restlessness, nausea, and gastrointestinal distress to name a few. Furthermore, caffeine intoxication is medically defined as consumption over 400 mg. A lethal dose of caffeine is estimated to be 10 g [22], a level that far exceeds the caffeine content of a single serving of Red Bull by a factor of at least 20. The lack of an absolute understanding of caffeine consumption and its function within as well as implications for the human body is surprising given the global popularity of this stimulant.

Sugar

In addition to caffeine, many EDs contain considerable amounts of sugar (21–34 g/8 oz. serving) [23], although some brand names can also be found in a "diet" form in which artificial or other nonnutritive sweeteners are used. As stated earlier, some manufacturers have also diverged from synthetic ingredients to alternative substitutes – such as honey, agave nectar, or high-fructose corn syrup – in place of sugar; these products still contain simple carbohydrates associated with "extra energy," but this comes at a cost to the consumer. The current Dietary Guidelines for Americans recommend no more than 10% of total calories come from added sugar, which includes all nutritive sweeteners such as sucrose

and alternative substitutes [16]. Considering the amount of sugars in an 8 oz. serving, an ED provides about 4–7% of total calories in added sugar for an individual following a 2000 calorie/day diet; this is a substantial contribution to the 10% recommendation. Currently, only one study has compared the influence of original Red Bull and "diet" Red Bull; results indicated a significant difference in glycemic response between the high-calorie and low-calorie drinks, but there were no cardiovascular or renal differences observed between the two groups [2].

Taurine

Taurine is a naturally occurring amino acid. Aside from being synthesized by the body, taurine can also be consumed in the diet, primarily from animal sources (i.e., meat, poultry, dairy products). Supplementation of as much as 3000 mg/day is considered safe [24]. The approximate amount of taurine in a typical ED is about 1000 mg/8 oz. serving. Taurine plays a role in neuroprotection and neurotransmission as well as cardiovascular function. Its primary cellular actions occur through modulation of intracellular calcium through several mechanisms. Taurine may be beneficial in skeletal muscle performance as well as in care of cardiovascular disease or anxiety due to its purported antioxidant activity, but these benefits are not detected at levels delivered in EDs. Other studies have suggested that taurine in conjunction with caffeine can enhance mental performance, although cognitive improvements specific to this combination have not been demonstrated [25–27].

Electrolytes (Minerals)

Several EDs now contain electrolytes (minerals), primarily sodium, as a means to enhance physical performance. Electrolytes play a role in regulation of neurological and muscular function, hydration, pH balance, and blood pressure, therefore improving sport performance through these mechanisms. Although electrolytes are considered essential for optimal physical performance and the amounts found in EDs are comparable to sports drinks (Red Bull, 11 mg potassium, 140 mg sodium/12 oz. serving; Gatorade, 45 mg potassium, 160 mg sodium/12 oz. serving), current nutritional guidelines for athletics and sport performance do not recommend consumption of EDs in place of sports drinks [28]. The combination of other ingredients found in EDs (i.e., caffeine, taurine, herbs) raises considerable concern for overall safety of these beverages during competition and training [29, 30].

Vitamins

The B vitamin complex is a set of eight vitamin compounds and is another prototypical ingredient found in many EDs. For example, the concentration of B vitamins in Red Bull is over the Recommended Dietary Allowances (RDA) and Adequate Intakes (AIs) set by the Institute of Medicine of the National Academy of Sciences. According to manufacturers, the amount of B vitamins provided in the product will allow the consumer to "fly or sail through the day" [7]. A typical ED (8 oz./serving) contains about 350–500% of the RDA/AI of vitamin B_6 and 100–200% of both B_{12} and B_3 [30].

In general, vitamin B_{12} is involved in blood cell and nerve development at the systemic level as well as DNA synthesis at the cellular level. There is no reliable information concerning the tolerable upper limits (UL) for vitamin B_{12} for adults or youth [30]. Vitamin B_6 is involved in basic cellular metabolism as well as heme and nerve development. The UL for vitamin B_6 is 100 mg/day for adults. Niacin (B_3) is also associated with basic cellular metabolism. The UL for niacin is 35 mg/day for adults. A single case of hepatotoxicity due to excess niacin has been reported in a young adult after the consumption of 10 EDs and is the smallest reported dose for niacin toxicity [31].

Because B vitamins are involved in metabolism, manufacturers of EDs can continue to attract their energetic and active target audience by adding these compounds to their ingredient list. Apart from vitamin B_{12}, most B vitamins are not stored in the body when consumed in excess, but rather overdoses are eliminated in the urine following discontinued use. This notion that overdoses are excreted leads the public to believe excess B vitamins in EDs are safe for consumption.

Herbal Ingredients

Several different and distinct herbal ingredients can be found within EDs. One common herb is ginseng, which is an extract from the *Panax ginseng* plant that has long history in traditional medicine as a means to enhance immunity, improve mood, and increase energy [32–34]. The plant extract is typically processed prior to its marketable form. Ginseng and some of its metabolites may even enhance mental cognition. The amount of ginseng varies considerably in EDs (2–200 mg/8 oz. serving) [35], and the actual physiological influence of ginseng when consumed in an ED has yet to be determined [36].

Another herbal ingredient commonly found in EDs is guarana, which is derived from the berries of the *Paullinia cupana* plant. These berries contain about twice as much caffeine as a comparable amount of coffee beans. The compound also contains other xanthine alkaloids, including theobromine and theophylline. The amount of guarana added to EDs varies considerably, ranging from 1.4 to 300 mg/12 oz. serving [35]. Most functions of guarana mirror, and are commonly thought to be from, the effects of caffeine; some physiological effects include increased antioxidant activity, improved mental cognition, and enhanced metabolism. However, some scientists conclude that the slower metabolism of guarana comparative to caffeine may provide more sustained effects [37]. Other minor ingredients typically present in trace amounts in EDs include gingko, L-carnitine, glucuronolactone, creatine, L-theanine, and extracts of the Acai berry.

Health Considerations

Promises and Performance

Slogans from energy drink (ED) campaigns, such as "Giving wings to people and ideas," "Unleash the beast," "…made to help hard working people," and "Designed for those who lead active lifestyles," all make strong promises [5, 38, 39]. Some studies do suggest that EDs may improve physical performance, alertness (psychomotor performance), and mental cognition as well as elevated mood [2, 17, 25, 26]. The amount of caffeine in a single serving of ED has been associated with improved mental cognition and enhanced mood [25, 26]. Yet, there is little concrete evidence that the combined ingredients in EDs, aside from caffeine, contribute to any of these effects [40].

Implications and Safety

As with all beverages that contain caffeine, EDs are not suitable for all consumers; deaths have been reported worldwide [41]. ED manufacturers have issued warnings against excessive consumption of their products, and most of these beverages have additional warning labels on their packages against consumption by children, women who are pregnant or breastfeeding, and individuals who are sensitive to caffeine. Although the actual wording varies considerably, all of these warnings are predominantly based on caffeine consumption guidelines. The recommendations for caffeine consumption

among youth and adolescents are <100 mg/day and 2.5 mg/kg/day, respectively [42]. Yet, over half of ED sales continue to be to children and individuals under the age of 26 [43].

According to the FDA, there were a total of 2598 cases with 224 adverse events and 0 fatalities associated with ED consumption in 2018. Furthermore, data from poison control centers indicate that most ED calls are associated with consumption by children under the age of 5 [44]. Most of the adverse effects attributed to EDs are due to an excessive intake of caffeine, regardless of the consumer age [45, 46]. Common adverse effects include anxiety, insomnia, restlessness, nausea, vomiting, seizure, and tachycardia that can result in cardiac arrest. As stated earlier, a lethal dose of caffeine is estimated to be 10 g; any consumption at or above this level causes toxicity. Caffeine toxicity may include anxiety, headaches, restlessness, nausea, vomiting, seizure, and cardiovascular incidences such as cardiac arrest [22]. The curious fact concerning most documented fatalities is the medical crisis occurred at caffeine levels much lower than the lethal threshold. An overdose of caffeine from EDs would mean consumption of 10–30 servings, depending on the specific ED consumed. With youth and adolescents, there is concern that these individuals lack the comprehension to avoid excessive caffeine intake. In particular, youth and adolescents may be extremely vulnerable to adverse effects of caffeine, especially those involving critical thinking and impulse control concerning discrimination of risks associated with reckless behaviors [47].

Further concerns about youth and adolescent ED consumers come when EDs are mixed with alcohol. Although many cocktails mix caffeine with alcohol, these beverages fit perfectly into extreme playing and partying associated with the ED lifestyle. The dangerous mixture of caffeine and alcohol is thought to diminish overall perception of drunkenness and facilitate excess consumption.

A review of the literature using PubMed with the key words “energy drink” yielded 694 citations for the period 2000 to 2020. Of these, only 19 reports were associated with EDs alone and adverse events or fatalities from cardiac, psychiatric, or neurological conditions. Among young adults, the incidence of sudden fatal cardiac events following the consumption of EDs is extremely low. Most ignorant consumers experience traumatic consequences with excess consumption simply due to caffeine-sensitivity. Of the 19 reports in the review of literature, of which there were 9 deaths, extenuating circumstances including excessive exercise and ED consumption or excessive alcohol and ED consumption triggered fatal cardiac events. The cardiac events and fatalities included atrial fibrillation, cardiomyopathy, supraventricular tachycardia, spontaneous coronary artery dissection, and hypertension; all of these conditions were likely correlated to caffeine-sensitivity or overdose, and not necessarily overall ED consumption [48]. Information from the US National Poison Data System found only 0.2% of all calls (over 2.3 million in total) were related to EDs including the effects of EDs and alcohol or other additives; of these inquiries, only an extremely small portion were for EDs alone [45]. Most reports were for abuse of EDs by male youth and adolescents and were nonfatal [46].

Conclusion

Energy drink (ED) sales and consumption continue to rise worldwide, and it is expected by the year 2026, ED sales will exceed $86 billion. Current consumption trends in the United States indicated a substantial rise from 2003 to 2016 among youth and adolescents (0.2% to 1.4%) as well as young adults (0.5% to 5.5%) and middle-aged adults (0.0% to 1.2%). Strong marketing strategies as well as athletic and media sponsorships continue to attract consumers of all ages. Several brands with catchy names (i.e., Red Bull, Monster, Rockstar) continue to provide suggestions of an “extra burst of energy” from caffeine for the tired and weary target audience. Apprehensions continue to be expressed regarding excess consumption of EDs with and without alcohol, especially by youth, adolescents, and young adults. EDs are here to stay, so patients and clients may ask about their safety as part of clinical practice. With the definition of these beverages and their physiological effects being unclear and inconsistent, it may be extremely challenging to provide solid and concrete answers at this time.

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Alcohol Consumption and Health

32

Ted Wilson and Norman J. Temple

Keywords

Alcohol drinking · Alcohol-related disorders · Coronary heart disease · Alcohol and mortality

Key Points

- Many cohort studies have reported that (compared with nondrinkers) a moderate alcohol consumption (one or two drinks per day) reduces the risk of coronary heart disease (CHD) and of several other health disorders. The lowest risk of CHD is seen at an alcohol intake of under 100 g/week (one drink per day), but possibly less.
- As alcohol intake increases, so does the risk of cardiovascular disease, especially stroke and heart failure.
- Alcohol creates many social problems, such as violence and accidents, as well as negative health effects, most notably those related to cancer and fetal alcohol syndrome.
- Risk for various health disorders increases sharply in heavier drinkers, defined as more than four drinks per day.
- Life expectancy is longest when alcohol intake is between zero and one drink per day. As alcohol intake increases, life expectancy falls.
- The healthiest level of drinking is a maximum of one drink per day. The more common limit of one to two drinks per day may be a little too high, but during pregnancy alcohol should not be consumed.
- The global COVID-19 pandemic was associated with an increase in isolation and alcohol consumption and alcohol-related health risks.

Introduction

The widespread consumption of alcoholic beverages and their potentially conflicting health impacts makes a discussion of this topic vitally important for physicians and other healthcare professionals. Alcohol (ethanol) consumption in large quantities is strongly linked to dramatic negative health

T. Wilson
Department of Biology, Winona State University, Winona, MN, USA
e-mail: twilson@winona.edu

N. J. Temple (✉)
Centre for Science, Athabasca University, Athabasca, AB, Canada
e-mail: normant@athabascau.ca

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consequences. The acute effects of alcohol consumption on behavior, motor function, and health risks are plainly observed in an emergency room on a Saturday night. The long-term effects of moderate consumption – years or decades rather than hours – are much less clinically obvious. The biological effects of a drink are mostly related to its alcohol content, alcohol metabolites, and the other substances found in alcoholic beverages (i.e., sugars and polyphenolic compounds). This chapter briefly reviews the health effects of alcohol consumption and then makes recommendations that physicians may give to their patients.

A Look at Alcoholic Beverages

In the USA, a drink is defined as containing 14 g or 0.4 fluid ounces of alcohol. The equivalent beverage volumes that contain one drink are quite variable (Fig. 32.1) [1]. For example, beer can have an alcohol content of between 3% and 9%; this means that a 12 oz. (355 ml) bottle or can provides between 0.6 and 1.8 drink equivalents (8.4 to 25.2 g alcohol). Containers of alcoholic beverage in the USA are required to state the alcohol content. When one considers the wide range of bottle sizes, glass sizes, and percent alcohol content, it is little wonder that consumers are often confused; this can play an important role in overconsumption.

Alcohol is not technically a nutrient but is a source of calories (7 cal/g) in the form of acetate that is directly oxidized to ATP or used for fatty acid synthesis. One drink therefore delivers about 98 kcal of energy from alcohol. Alcohol is primarily metabolized in the liver. Alcohol dehydrogenase converts ethanol into acetaldehyde which is then converted by acetaldehyde dehydrogenase into acetate. The acetate can then be converted to fatty acids or oxidized to carbon dioxide in the mitochondria.

Most alcoholic beverages have additional calories because of their content of carbohydrates. Typically, a glass of wine or a can of beer contains about 100–140 kcal. However, this can be quite variable; a sweet wine, for example, may have 240 kcal per glass, while some brands of "light beer" are low in sugar and therefore have few nonalcoholic calories. A can of light beer may therefore have as little as 110 kcal.

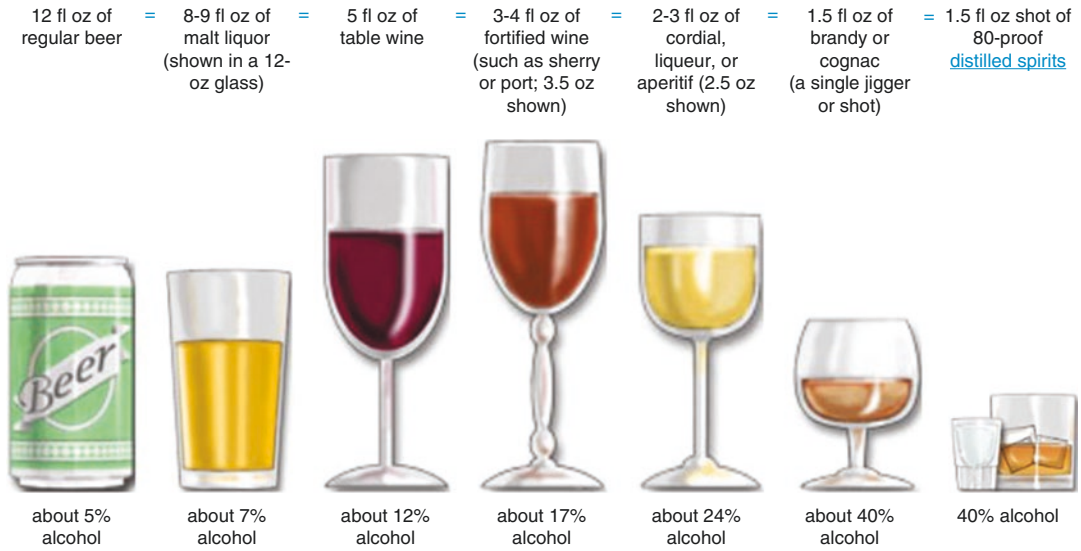

Fig. 32.1 Equivalent beverages volumes that provide the US definition of one "drink" containing 14 g of alcohol [1]. (Reprinted from National Institute on Alcohol Abuse and Alcoholism. National Institutes of Health. US Department of Health and Human Services [1])

Appreciating the quantity of alcohol consumed is important for making clinical recommendations. The majority of Americans consume alcoholic drinks, at least occasionally: a national survey carried out in 2018 reported that 70% of adult Americans stated that they consumed at least one drink in the previous month [2]. An important aspect of alcohol consumption is binge drinking. This is commonly defined as consuming four drinks for women or five drinks for men in about 2 hours. The above national survey reported that 26% of adult Americans had engaged in binge drinking in the previous month [2]. Beer remained the largest single source of intake in the USA, although wine consumption steadily increased to about 30% of intake, especially in those aged over 60 years and women [3].

Possible Beneficial Health Effects Associated with Alcohol Consumption

A substantial body of epidemiological evidence has accumulated over the past several decades regarding the relationship between alcohol intake and health. A major analysis of this evidence was published in 2018 [4]. The focus of that study was on cardiovascular disease and total mortality. The authors combined the findings from 83 prospective cohort studies that included, in total, 787,000 subjects. These numbers dwarf previous studies. For that reason, the following discussion relies heavily on the findings reported in that study.

Many cohort studies have reported a clear negative association between moderate alcohol consumption and risk of coronary heart disease (CHD). These findings suggest that moderate consumption – one or two drinks per day – reduces risk. Millions of people have been more than happy to accept these findings as they seem to justify drinking moderate amounts of alcohol. Alcohol may therefore be an exception to the rule: All the best things in life are illegal, immoral, or fattening.

This epidemiological story has generated heated debate in the medical literature which reflects the pitfalls that often arise when interpreting the findings of epidemiological studies. One aspect of the debate relates to the challenge created by "sick quitters." This refers to persons with a diagnosis of a condition related to CHD, such as hypertension or diabetes, who quit drinking alcohol. This causes a spurious artificial jump in the risk of CHD in nondrinkers and a lowering of the risk among drinkers. Other possible sources of error are that many people may choose to abstain from alcohol for reasons of religion, personal philosophy, or their state of health. The debate on this question has been ongoing with little sign of settlement. Because of these possible sources of error, we must be hesitant before making any firm conclusion that a moderate intake of alcohol does indeed offer a significant degree of protection against CHD.

Taking all this evidence together, what can we reasonably conclude? The lowest risk of CHD is seen at an alcohol intake of about one drink per day, but possibly less. This is also true for cardiovascular disease in general. There is no dispute that as alcohol intake climbs, so does the risk of cardiovascular disease, especially stroke and heart failure.

Research studies indicate that alcohol brings about an increase in the blood level of HDL-cholesterol [5]. If alcohol does indeed have some protective action against the risk of CHD, then this is likely to be an important mechanism by which this achieved.

For several aspects of poor health status, there is a J-shaped relationship between alcohol consumption and risk [6]. People who consume alcohol in moderation have a lower risk than that seen in nondrinkers, while risk increases sharply in heavier drinkers (more than four drinks per day). Here are some examples of this.

That excessive alcohol intake leads to poor erectile function is well known. As Shakespeare put it: "It provokes the desire, but takes away from the performance" (Macbeth, Act 2, Scene 3). But research findings have pointed to a modest beneficial effect of moderate alcohol consumption. In the case of erectile dysfunction, therefore, a J-shaped curve appears to be true in more ways than one.

The same serendipitous discovery has also been made for the cognitive decline that occurs with aging. It is well known, of course, that heavy drinking has a damaging effect on brain function. But

research has revealed that moderate drinkers actually have an enhanced cognitive ability or a slower rate of decline with aging [7, 8]. This effect is generally more pronounced in women. These benefits may even extend to the risk of dementia, mostly Alzheimer's disease. Similar findings have been reported for type 2 diabetes.

These findings suggest that a moderate intake of alcohol provides some protection against the health problems mentioned above. But the possible sources of error discussed with respect to CHD may be equally relevant here. For that reason, we must be cautious before jumping to bold conclusions.

Harmful Effects of Alcohol

Alcohol consumption has myriad effects on the body, many of which are damaging to health. Alcohol and its metabolites may also alter the efficacy, metabolism, and effect of nutrients as well as medications, and specific drug-nutrient interactions are reviewed in Chap. 26.

It is well established that abuse of alcohol, especially binge drinking, is associated with accidents, violence, and suicide. It is a factor in about one third of all traffic-related deaths in the USA. The most dramatic evidence of the dangers of binge drinking comes from Russia. Between 1984 and 1994, there was serious economic decline and great political turmoil in that country and a dramatic jump in mortality rates reflected by a decline in life expectancy of 4 years in men and 2 years in women. A major factor was apparently widespread alcohol abuse, particularly binge drinking, which led to large increases in deaths from accidents, homicide, and suicide, as well as heart disease and stroke.

For many persons, years of alcohol abuse eventually lead to chronic nutritional and health problems. Alcoholic beverages are relatively poor sources of nutrients, apart from some sugars and minerals, and in some cases, some amino acids. This is especially true for hard liquors. Heavy drinkers are at high risk of malnutrition, especially for folate and thiamin (Wernicke–Korsakoff syndrome). The end result following years of heavy drinking is fatty liver, alcoholic hepatitis, and, eventually, cirrhosis. The consumption of hard liquor is more strongly associated with alcoholism, cirrhosis, and accidental death than is the case with beer or wine.

Heavy consumption of alcohol is associated with an increased risk of several types of cancer. However, the relationship between alcohol intake and overall cancer incidence for light-to-moderate alcohol intake does not appear to be strong for men; however, breast cancer risk increases for women at levels as low as 5–15 g/day of alcohol [9]. An alcohol intake at the high end of moderation (two drinks per day in women, four in men) is associated with relative risks (RRs) for different types of cancer as follows: 1.8 for mouth and pharynx, 2.4 for esophagus, and 3.0 for liver [10]. Our best evidence is that lower intakes of alcohol produce proportionately smaller RRs. For all types of cancer combined a significant risk is seen starting at an alcohol intake of two drinks per day, with a RR of 1.22 at 4 drinks per day [11].

Colorectal cancer manifests a rather different pattern: there is a J-shaped relationship with this type of cancer [12]. The RR is 0.92 for an intake of up to two drinks per day, suggesting a minor degree of protection. But when intake exceeds three drinks per day, the RR climbs to 1.25.

The effects of alcohol consumption on body weight are unclear. Alcohol, of course, is a source of calories (7 kcal/g), and as mentioned earlier, most types of wine and beer also contain carbohydrates that add additional calories. A half-liter of wine contains about 350 kcal while three cans of beer supply about 250–450 kcal, clearly enough to tip the energy balance well into positive territory. However, intervention studies are inconclusive on the weight-alcohol interaction. For example, in one experiment, men consumed 35 g/day of alcohol (equivalent to a little less than three glasses of wine) for a period of 6 weeks, but this did not affect their weight [13]. Similar results were seen when overweight women consumed 25 g/day of alcohol, 5 days/week, for 10 weeks [14].

Several long-term cohort studies have been carried out to examine the relationship between alcohol intake and body weight. In the Health Professionals Follow-Up Study, a cohort study of 16,600 men aged 40 – 75, change in alcohol intake was not associated with change in waist circumference over 9 years of follow-up [15]. In the Women's Health Study, a cohort study of 19,200 women of normal BMI at baseline, alcohol intake displayed a clear negative association with risk of becoming overweight or obese over the following 13 years [16]. In sharp contrast, other cohort studies have reported a positive association between alcohol consumption and weight gain [17]. At present, therefore, it is far from clear whether alcohol intake poses a risk for weight gain.

Effect of Alcohol on Total Mortality

Alcoholic beverages have many different effects on health. The dose-response relationship seems to vary from one disorder to the next. This begs the question: What is the impact of different levels of alcohol intake on total mortality? Here, age is an important variable. For younger people, alcohol can cause much harm while doing very little to improve health. That is because the leading cause of death in Americans under age 40 is accidents, with homicide and suicide also being major causes, especially in men. They are all linked to excessive consumption of alcohol. The sole positive attribute of alcohol for people in this age group is providing enjoyment.

It is only among people older than about 50 or 60 where alcohol consumption in moderation may cause a reduction in mortality [18]. At that age, the possible health benefits, especially the prevention of heart disease, dominate the picture. As a result, it is among this age group that we see a J-shaped relationship between alcohol intake and risk of mortality. But, as with coronary heart disease (CHD), there is debate as to whether this protection is real or spurious [19].

The best evidence for the effect of alcohol on life expectancy comes from the study that was described earlier that pooled the findings from 83 prospective cohort studies and included 787,000 subjects. This study concluded that for persons aged between 40 and 50, life expectancy was longest when alcohol intake was under 100 g/week (between zero and one drink per day) [4]. As alcohol intake went up, life expectancy fell as follows:

- By 6 months at an intake of 100 – 200 g/week (between one and two drinks per day)
- By 1.8 years at 200 – 350 g/week (between two and 3.5 drinks per day)
- By almost 5 years at over 350 g/week (3.5 drinks per day)

These highly credible findings led the authors to conclude that current guidelines set limits on alcohol consumption that are too high.

Phytochemicals in Alcoholic Beverages

Many alcoholic beverages, especially red wine and dark beers, contain a variety of phytochemicals with biological activities that may interact with the health effects of alcohol. These phytochemicals mostly come from the raw plant foods from which the particular beverage is fermented. Red wine contains phenolic compounds such as resveratrol, tannins, and catechins. These substances have been associated with antioxidant protection, vasodilatation, inhibition of platelet aggregation, and improved plasma cholesterol profile. Beer, particularly darker ones, tends to have a higher polyphenolic content and greater antioxidant capacity relative to light beers. However, spirits, because of the distillation process, usually have a very low content of phytochemicals.

It has long been speculated that red wine may be especially potent for the prevention of CHD. This is based on the so-called French paradox. It was observed that French people have a surprisingly low

rate of CHD in comparison with some northern European countries, such as the UK [20]. This could not be easily explained by the "usual suspects" as France has high rates of both smoking and consumption of foods rich in saturated fat. It was reasoned that the explanation for the French paradox could be found in the popularity of red wine in that country.

But when we carefully examine the evidence as a whole, red wine does not appear to live up to the hype. Cohort studies indicate that all types of alcoholic beverages – wine, beer, and spirits – have a similar association with risk of CHD. It is true that some cohort studies have reported a lower risk of CHD in wine drinkers, but this is probably because wine drinkers often have a healthier lifestyle and a higher socioeconomic status (both factors are associated with a lower risk of CHD).

However, it is premature to completely dismiss the possible health benefits of red wine. The beverage contains phenolic compounds, such as catechin and resveratrol that may give red wine some beneficial properties.

As is the case with fruits and vegetables, current knowledge regarding the thousands of phytochemicals in alcoholic drinks prepared from various plant foods is still quite limited. While we can confidently state that a diet rich in foods that contain an abundance of phytochemicals is likely to be healthy and should be recommended, there is still a great deal to be learned about the disease-preventing action of specific substances.

Fetal Alcohol Exposure

Alcohol use during pregnancy can induce fetal alcohol syndrome (FAS). This irreversible condition encompasses symptoms that include prenatal and postnatal growth retardation, mental retardation, and the hallmark clinical sign of abnormal facial features. A subclinical form of FAS is known as fetal alcohol effects (FAE). Children with FAE may be short in stature or have only minor facial abnormalities, or develop learning disabilities, behavioral problems, as well as both cognitive and motor impairments.

It is estimated that 10.3% of US pregnancies were associated with prenatal alcohol exposure, and binge drinking occurred during 3.1% of pregnancies [21]. Because many pregnancies are unplanned, the fetus is often unknowingly exposed to dietary alcohol; the clinician should screen for patient alcohol consumption during prenatal visits. There is no known safe level of fetal alcohol exposure or maternal alcohol consumption during pregnancy, and abstinence should be promoted [22]. Because the use of chemical substances during pregnancy is often stigmatized in society, clinicians should also be aware that a pregnant woman may not openly wish to discuss their alcohol use habits [23].

Effect of COVID-19 Pandemic on Alcohol Consumption

The COVID-19 pandemic led to lockdowns and human distress in many countries. Stress and social isolation have always been factors associated with increased substance abuse and, more specifically, excessive alcohol consumption, and COVID-19 has led to a global increase in alcohol consumption [24]. Increased drinking in the USA has been reported by as much as 60% of people, with reasons for greater intake being associated with a sense of increased stress, increased availability, and boredom [25]. There was an especially steep jump in online sales of alcohol in the USA in the early period of the pandemic, isolation changed the reasons that people drink and the way they access alcohol [26]. Of special concern with respect to potential violence or potential fetal alcohol syndrome is the observation that 54% of those living with children 18 years of age or younger during the COVID-19 pandemic reported increased alcohol consumption [25]. The COVID-19 lockdown can also be expected to lead to a greater number of people with alcohol-use disorder relapsing away from abstinence,

possibly related to social isolation and to the fact that during the COVID-19 pandemic state-mandated social isolation requirements that made treatment or counseling difficult [27].

Alcohol: What Advice Should a Healthcare Professional Give?

Despite the potential health benefits of moderate drinking with respect to cardiovascular disease, medical experts should not recommend that nondrinkers commence light-to-moderate drinking. A major reason for this is that around 5–10% become alcohol abusers. However, if a person is already a light drinker and has no sign of an alcohol-related problem, there is little reason to advise them to stop. Our evidence informs us that the healthiest level of drinking is a maximum of one drink per day. The more common limit of one to two drinks per day may be a little too high, and during pregnancy abstinence is advised by the American Obstetrics Association and other healthcare organizations.

It is, of course, imperative that a person's past history be considered. For those with a history of alcoholism, the ability to "stop after just one drink" may not exist. Recommendations regarding alcohol consumption should remain in large part a personal decision of the patient based upon clinical realities.

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Dietary Fiber: All Fibers Are Not Alike

33

Kyle J. Sloan and Johnson W. McRorie Jr

Keywords

Dietary fiber · Insoluble fiber · Soluble fiber · Gel forming · Cholesterol · Glycemic control · Colorectal cancer

Key Points

- What is believed about the health benefits of a high-fiber diet is derived primarily from epidemiologic studies. These can establish statistical associations but lack the control necessary to establish causation.
- In contrast, causation can be established for isolated fibers (e.g., fiber supplements). The beneficial physiologic effects of specific isolated fibers can be established in randomized, well-controlled clinical studies.
- Not all fibers are alike. Some show beneficial effects in randomized controlled clinical studies, but most are not different from placebo.
- In the small bowel, beneficial effects include cholesterol lowering and improved glycemic control. Only gel-forming fibers (e.g., psyllium, β-glucan [e.g., oatmeal]) are clinically proven to provide both of these health benefits, and the beneficial effects are highly correlated with the viscosity of the gelling fiber.
- In the large bowel, not all fibers provide a laxative effect, and some can actually be constipating. Fermented fibers "disappear" from the gut lumen and are not different from placebo for a laxative effect. Only fibers that resist fermentation and remain intact throughout the large bowel can be present in stool and can provide a laxative effect. There are only two mechanisms by which fiber provides a laxative effect:
  - Poorly fermented coarse insoluble wheat bran mechanically irritates the gut mucosa, stimulating water and mucosal secretion which bulks/softens stool. By contrast, finely ground insoluble wheat bran and wheat dextrin add only to the dry mass of stool, a stool-hardening effect that can be constipating. Note that mechanical irritation of the gut mucosa caused by coarse insoluble fiber particles is not recommended for patients with irritable bowel syndrome.
  - Non-fermented soluble/gel-forming psyllium retains its high water-holding capacity to resist dehydration throughout the large bowel, providing a dichotomous stool-normalizing effect:

K. J. Sloan (✉) · J. W. McRorie Jr
Procter & Gamble and Personal Healthcare, Mason, OH, USA
e-mail: sloan.kj@pg.com; mcrorie.jw@pg.com

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Table 33.1 Clinical efficacy supported by placebo-controlled, reproducible clinical data

	Wheat bran	Wheat dextrin	Inulin	Methylcellulose	Calcium polycarbophil	Partially hydrolyzed guar gum (PHGG)	Psyllium
Example brands	All Bran®	Benefiber®	Fiber Choice®	Citrucel®	FiberCon®	NutriSource®	Metamucil®
Natural/ synthetic, fermentation	Natural, poorly fermented	Synthetic, fermented	Natural, fermented	Semi-synthetic, non-fermented	Synthetic, non-fermented	Hydrolyzed, fermented	Natural, non-fermented
Source	Wheat	Wheat	Chicory	Wood pulp	Synthesized	Guar bean	Plantago plant
Glycemic Control	–	–	–	–	–	–	+
Cholesterol Lowering	–	–	–	–	–	–	+
Satiety/weight loss	–	–	–	–	–	+/–[e]	+
Chronic constipation	+/–[b]	–[d]	–	–	–	–	+[f]
Diarrhea	–	–	–	–	–	–	+
IBS[a]	–[c]	–	–	–	–	–	+

[a]*IBS*: Irritable bowel syndrome
[b]Coarse wheat bran has a modest stool softening/laxative effect. Fine wheat bran has a stool-hardening effect and can be constipating
[c]The mechanical irritation of the gut mucosa by coarse wheat bran can exacerbate IBS symptoms, and is not recommended
[d]Wheat dextrin can have a stool-hardening, constipating effect
[e]Satiety/weight loss is a viscosity (gel-dependent) phenomenon. If PHGG is non-viscous, it would not have an effect
[f]Psyllium is 3.4-times more effective that wheat bran for increasing stool output in constipation [18]

softens hard stool in constipation (superior to docusate), firms loose/liquid stool in diarrhea, and normalizes stool form in irritable bowel syndrome.

- Conclusions: While it is reasonable to recommend a diet rich in fruits, vegetables, and whole grains, it has not been established that dietary fiber is the direct cause of the observed health effects. Fiber supplements may appear to be a convenient and concentrated source of fiber, but most isolated fibers have no clinical evidence of a health benefit. Therefore, a generic recommendation to "increase fiber intake" is akin to a recommendation to "increase pill intake" without regard to therapeutic benefit or adverse effects. Fiber recommendations should be based on reproducible clinical evidence of a meaningful health benefit (Table 33.1). For most fiber-related health benefits: *Fiber needs to gel to keep your patients well.*

Introduction

The Institute of Medicine (IOM) published a definition of total fiber that differentiated *dietary fiber* (nondigestible carbohydrates and lignin that are intrinsic and intact in plants) from *functional fiber* (isolated, nondigestible carbohydrates that have been shown to have beneficial physiological effects in humans) [1]. Much of what we believe about the health benefits of dietary fiber is derived from population-based (epidemiologic) studies. These are useful for establishing statistical associations between consumption of high-fiber diets and a reduced risk of disease (or, conversely, low-fiber diets and an increased risk of disease) but lack the control necessary to establish causation. It is therefore unclear to what degree an observed health benefit is attributable to dietary fiber versus how much may be attributable to a reduction in fat/calorie intake or other constituents of a high-fiber diet (e.g., micronutrients, phytochemicals). Even though causation cannot be established, the Adequate Intake for

fiber (14 g/1000 kcal) is based on epidemiologic data: the median fiber intake that was associated with the lowest risk of coronary heart disease [1]. Based on average calorie intake, this translates to a recommended dietary fiber intake of 25 g/day for adult women and 38 g/day for adult men. In contrast to these recommendations, average dietary fiber intake for US adults is only about 15 g/day.

Unlike "dietary fiber," isolated fibers can be directly assessed for beneficial physiological effects in randomized, well-controlled clinical studies. Note that, by definition, an isolated fiber must show clinical evidence of a health benefit to be considered a "functional fiber." The term "fiber supplement" may therefore be misleading to healthcare professionals in that the term implies that regular consumption will fill the "fiber gap" and provide the health benefits associated with a high-fiber diet. Most isolated fibers/fiber supplements do not meet the definition of a "functional fiber" because they have no clinical evidence of a health benefit and should not be recommended. This chapter provides an appreciation for the underlying mechanisms that drive specific beneficial physiologic effects and summarizes which fiber supplements have clinical evidence of a health benefit.

Physical Effects of Fiber in the Small Intestine

Type 2 Diabetes/Glycemic Control

Epidemiological evidence suggests that high consumption of cereal fiber is associated with a reduced risk of developing type 2 diabetes (relative risk, RR 0.77), but the evidence is less convincing for fruit fiber (RR 0.94) and vegetable fiber (RR 0.95) [2]. When isolated fibers are assessed in randomized well-controlled clinical studies, only soluble gel-forming fibers significantly improve glycemic control, and the effect is proportional to the viscosity of the gel-forming fiber [3]. Nonviscous soluble fibers (e.g., partially hydrolyzed guar gum [PHGG], inulin) have no effect on glycemic control. Chyme is normally low in viscosity and readily mixed with digestive enzymes for nutrient degradation. Introduction of a gel-forming fiber (e.g., psyllium, β-glucan) significantly increases the viscosity of chyme, which slows the mixing of digestive enzymes and slows nutrient degradation/absorption.

This delay in nutrient absorption can have a significant effect on long-term glycemic control. Multi-month clinical studies have demonstrated that consumption of a viscous, gel-forming fiber mixed with meals can lower fasting blood glucose, insulin, and HbA_{1c} in patients with the metabolic syndrome and patients being treated for type 2 diabetes mellitus (T2DM) [3]. A meta-analysis of 35 clinical studies showed that psyllium significantly improved both fasting blood glucose concentration (−37 mg/dL [−2.1 mmol/L]; $p < 0.001$) and HbA1c (−1.0; $p = 0.048$) in patients being treated for T2DM [4]. These improvements in glycemic control observed with psyllium are additive to the effects of a restricted diet and stable doses of prescription drugs (sulfonylurea and/or metformin). A gel-forming fiber will not directly cause hypoglycemia, but fasting blood glucose concentrations should be monitored when starting an effective fiber therapy in patients already taking prescription drugs to control blood glucose. The added benefit of a gel-forming fiber may decrease the required dose for prescription drugs, and this may lead to hypoglycemia.

Cardiovascular Disease/Cholesterol Lowering

When specific isolated fibers were assessed for lowering elevated serum cholesterol, the results were similar to those in glycemic control: only gel-forming soluble fibers lower elevated serum total and low-density lipoprotein (LDL) cholesterol, and the degree of cholesterol lowering was highly correlated with the viscosity of the gel-forming fiber [5]. This viscosity was actually a better predictor of cholesterol-lowering efficacy than the quantity of fiber consumed. The primary mechanism by which soluble gel-forming fibers lower serum cholesterol is by trapping and eliminating bile acids [6]. These substances are normally recovered via active uptake in the distal ileum and recycled, potentially

several times within a single meal. When bile acids are trapped and eliminated in a gel-forming fiber via stool, the reduction in the bile acid pool causes hepatocytes to express LDL receptors that facilitate clearance of LDL cholesterol from the blood to synthesize more bile acids (cholesterol is a component of bile). This clearance of LDL cholesterol effectively lowers serum LDL cholesterol and total cholesterol concentrations, without affecting high-density lipoprotein (HDL) cholesterol concentration [6].

Only viscous, gel-forming fibers (e.g., psyllium, high-molecular-weight β-glucan), consumed with meals to coincide with bile release, effectively lower elevated serum LDL and total cholesterol concentrations [6]. This was confirmed in a head-to-head clinical study comparing the cholesterol-lowering efficacy of psyllium, a natural gel-forming soluble fiber (3.4 g three times a day with meals) versus wheat dextrin, a synthetic nonviscous soluble product (3.5 g three times a day with meals) [7]. This 3-month study showed that gel-forming psyllium significantly ($p < 0.05$) lowered both LDL cholesterol (−17%) and total cholesterol (−11%), without affecting HDL cholesterol [7]. A recent meta-analysis of 28 studies ($n = 1924$) confirmed the importance of gel formation, showing that psyllium (mean dose 10.2 g/day) reduced LDL cholesterol by 13 mg/dL [8]. The authors concluded: "Psyllium fiber effectively improves conventional and alternative lipid markers, potentially delaying the process of atherosclerosis-associated CVD [cardiovascular disease] risk in those with or without hypercholesterolemia." [8]. Note that only two fibers, both gel forming (psyllium and β-glucan), are FDA approved to claim a reduced risk of CVD by lowering serum cholesterol [9]. It is also important to note that the cholesterol-lowering benefit of psyllium is additive to the action of statin drugs. A recent meta-analysis showed a clinically and statistically significant ($p = 0.001$) cholesterol-lowering advantage for psyllium plus statin combination treatment over a statin alone. Adding psyllium resulted in reductions in LDL cholesterol equivalent to doubling the statin dose. The authors concluded that the data support that psyllium fiber taken before meals adds to the efficacy of statins, providing an easy-to-implement dietary intervention for those who cannot tolerate side effects associated with higher-dose statins [10].

In summary, cholesterol-lowering efficacy is highly correlated with the viscosity of the hydrated fiber, and only gel-forming fibers, such as psyllium and β-glucan, can effectively lower elevated serum cholesterol. Since the adequate intake recommendations for fiber are based on a reduced risk of CVD, it is reasonable to assert that only those fibers that are FDA approved to claim a reduced risk of CVD (i.e., psyllium and β-glucan) should be recommended to bridge the "fiber gap" in dietary fiber intake.

Satiety/Weight Loss

Besides improved glycemic control and cholesterol lowering, there are other viscosity/gel-dependent phenomena, most notably satiety and weight loss. There is a hierarchy of data: increased satiety (decreased hunger) is a feeling that *may be* predictive of decreased energy intake; decreased energy intake *may be* predictive of short-term weight loss; and short-term weight loss *may be* predictive of long-term weight loss/maintenance. Natural viscous/gel-forming fibers, such as psyllium, show efficacy in satiety [11]. In contrast, nonviscous fibers, for example, synthetic wheat dextrin, have no effect on satiety and are used as a placebo [12]. Further, studies that only assess satiety may be misleading in that some fibers (e.g., FOS) may show a subjective increase in the sensation of satiety (possibly due to fermentation/adverse effects) but in the same study fail to show a reduction in energy intake [13]. Since satiety is lower in the hierarchy of evidence than energy intake, the lack of effect on energy intake means that the satiety effect is not predictive of decreased energy intake and must be disregarded. If there are no contradictory higher-order data, then lower-order data (e.g., satiety) should be considered valid. Viscous/gel-forming fibers, such as psyllium, have a significant effect on satiety/

hunger [11], energy intake (−19%) [14], and weight loss [14–16], showing that each step on the hierarchy of data is predictive of efficacy in the next.

A relatively new semisynthetic version of carboxymethylcellulose has been FDA cleared as a medical device to treat obesity. PLENITY™ (Gelesis100) is a prescription capsule that forms a gel and increases viscosity in the stomach and small intestine (degraded by bacteria in the large intestine). In a pivotal study, 6 out of 10 adults treated with PLENITY were responders, losing on average 10% of their weight (22 pounds, 10 kg) and 3.5 inches (9 cm) from their waists within 6 months [17].

Large Bowel Effects

Constipation/Diarrhea/Irritable Bowel Syndrome (IBS)

Constipation can be defined as infrequent elimination (e.g., <3 bowel movements per week) of small/hard difficult to pass stools that require straining [3]. It is a misconception that consuming the recommended levels of dietary fiber will reduce the risk of constipation. As discussed previously, the adequate intake guidelines for dietary fiber are based on reducing the risk of CVD, not reducing the risk of constipation. Note that "dietary fiber" does not differentiate between specific fiber characteristics, and not all fiber types provide a laxative effect (some can be constipating). For fiber to soften stool and significantly increase stool output, it must resist fermentation so as to remain intact and be present throughout the large bowel. By this means, the fiber in the stool can increase stool water content, which is the primary mechanism for both a stool-softening effect and increased stool bulk [3]. There are two mechanisms by which a fiber can significantly increase stool water content and stool bulk: (1) poorly fermented coarse insoluble fiber particles (e.g., coarse wheat bran) mechanically irritate the gut mucosa, stimulating water and mucous secretion (fine/smooth wheat bran particles only add to the dry mass of stool, a stool-hardening effect that can be constipating), and (2) non-fermented viscous/gel-forming psyllium retains its water-holding capacity throughout the large bowel to resist dehydration [18]. Both mechanisms increase stool water content (softer stool) and stool output, resulting in bulky/soft stools that are easy to pass.

The texture of stool is highly correlated with the percentage of water content: hard stool is ≤72%, normal/formed stool is ≈74%, and soft/formed stool is ≈76% [18]. Note that only a 2% change in stool water content is needed to significantly alter stool form. An effective fiber, such as psyllium, increases stool water content, resulting in a significant stool-softening effect and increased stool bulk, both of which make stools easier to pass without straining. For over three decades, wheat bran has been incorrectly touted as the "gold-standard" fiber for regularity. A recent comprehensive review and meta-analysis showed that psyllium was 3.4 times more effective than wheat bran for increasing stool output in constipated patients [18]. Both psyllium and *coarse* wheat bran increase stool water content which is a stool-softening effect. In contrast, finely ground wheat bran added only to the dry mass of stool and decreased stool water content, a stool-hardening effect that can be constipating [18]. Note that wheat bran product labels do not provide information on whether the bran is coarsely or finely ground, so there is no way to predict whether the product will provide a laxative effect or be constipating. Wheat dextrin, a synthetic soluble nonviscous "fiber," also causes a *decrease* in stool water content and as a result a stool-hardening effect that can be constipating. Taken together, most fibers have no effect on laxation, and some can be constipating. Psyllium has been proven to be the gold-standard fiber for regularity [18]. Further, gel-forming psyllium also provides a stool-normalizing effect: the high water-holding capacity of the gel softens hard stool in constipation (superior to docusate) [19] and firms loose/liquid stool in diarrhea [3, 5], making psyllium an effective fiber choice for normalizing stool form in irritable bowel syndrome [5].

Colorectal Cancer

The theory that low fiber consumption is associated with an increased risk of colorectal cancer, and that a high-fiber diet and high stool output may be protective, is supported by epidemiologic evidence. In a study that assessed fiber intake, stool output, and cancer risk in 20 populations across 12 countries, there was a very wide range in average stool output (72 to 470 g/day) [20]. The study found a significant correlation between fiber intake and mean daily stool weight ($r = 0.84$) and a significant inverse correlation between stool weight and colon cancer risk ($r = -0.78$). The occurrence of colorectal cancer varies ≈25-fold across different regions of the world, and Westernized populations tend to have the lowest stool weights (e.g., 80 − 120 g/day) and the highest colon cancer risk. Faster transit through the large bowel, which would potentially limit exposure to carcinogens, may also play a role in a reduced risk of colon cancer. Stool weight and transit time are related: low stool weights (e.g., 50 g/day) are seen with slow colonic transit (e.g., ≥100 hours), while higher stool weights (e.g., 150 g/day) are associated with faster colonic transit (e.g., 40 hours) [20]. A correlation between faster colonic transit and a reduced risk of colon cancer was not assessed in the cited study due to the limited data on transit time across regions, but it is reasonable to assert that transit time may play an important role in reducing the risk of colon cancer [20].

It is important to be aware that these data do not control for other dietary factors that may influence risk, such as other risk-reducing constituents of a high-fiber diet (e.g., phytochemicals) or risk-increasing components like red meat and processed meat. It is noteworthy that the number of new colorectal cancer cases tends to increase in countries that experience rapid economic growth and adopt a Western lifestyle. A prospective population-based study examined the association between colorectal cancer incidence, constipation, non-fiber laxative use, and fiber laxative use in over 75,000 patients [21]. The study showed a significant increase in risk with *non-fiber* laxative use and a decreased risk in developing colorectal cancer with *fiber*-laxative use [21]. Taken together, epidemiologic data suggest that a diet that is rich in fruits, vegetables, and whole grains, low in red and processed meats, and supplemented with an isolated fiber that has been shown to be effective for increasing stool output in chronic constipation (e.g., psyllium) may decrease the risk of developing colorectal cancer.

How to Avoid Fiber-Induced Gastrointestinal Symptoms and Enhance Compliance

Consumption of fermentable fibers can cause significant increases in flatulence, stomach rumbling/borborygmus, bloating, and discomfort in a dose-responsive manner; these effects can significantly limit the tolerable dose [6]. Even non-fermented fibers, such as psyllium, can be associated with sensations of bloating and discomfort if the fiber is effective for softening stool/increasing stool bulk, and the patient is constipated when fiber consumption is initiated [6]. If the stool is of similar formed consistency in the distal large bowel, there is minimal deformation of the stool with peristalsis, so there is no significant bowel wall distention. In normal individuals, the propulsion of formed stool is not typically perceived unless it causes rectal filling, stimulating an urge to defecate. Effective fiber therapy (e.g., psyllium) can create a bolus of soft stool. If a high-amplitude propagating contraction propels the bolus of soft stool against more distal hard stool, the readily deformable soft stool can "balloon out," causing acute bowel wall distention. This distention is similar to that observed with colorectal balloon inflation in studies assessing the pain threshold of patients with IBS. Bowel wall distention stimulates mechanoreceptors, generating sensations that are proportional to the degree and rate of distention: gas/bloating, discomfort, pain, and cramping pain. The term "cramping pain" is actually a misnomer in that it is caused by normal peristalsis resulting in acute bowel wall distention,

not by spastic contraction [6]. The risk of fiber-induced discomfort can be minimized by gradually initiating and increasing the dose to reach an effective fiber therapy (e.g., one dose per day week 1, two doses per day week 2, etc.), which may improve long-term compliance. Constipated patients may also benefit from the elimination of hard stool (e.g., osmotic laxative) before initiating an effective fiber therapy [3, 6].

Conclusion

Based on epidemiologic data, it is reasonable to recommend a diet rich in fruits, vegetables, and whole grains. Most Americans consume only about half of the recommended intake for dietary fiber, potentially increasing the risk of CVD. To mitigate this risk, only those fiber supplements that have FDA approval to claim a reduced risk of CVD by lowering serum cholesterol (i.e., psyllium, β-glucan) should be recommended to fill the "fiber gap." Similarly, only gel-forming fibers (e.g., psyllium, β-glucan) should be recommended for improved glycemic control and satiety/weight loss. While prebiotics (e.g., inulin) are an emerging area of science with significant effects on the microbiome, they are nonviscous, readily fermented soluble fibers and have no significant effect on cholesterol lowering, improved glycemic control, weight loss, or regularity. It is therefore important to recognize which physical characteristics of isolated fibers drive specific health benefits and to look for supplements with reproducible clinical evidence of a meaningful physiologic effect (Table 33.1). Not all fibers are alike. Most beneficial physiologic effects are exerted only by gel-forming fibers, and efficacy is proportional to the viscosity of the gel. In other words, "fiber needs to gel to keep your patients well".

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The Essential Vitamins: From A to K

34

Karen M. Davison

Keywords

Vitamins · Supplements

Key Points

- The vitamins discussed in this chapter are considered as essential organic compounds required for normal physiological function.
- Vitamins may be classified according to their solubility in fat or water, or by common functions.
- Suboptimal or excess vitamin intakes can lead to inadequacy/deficiency or toxicity, respectively; the latter usually occurs due to excesses from supplement sources, particularly the fat-soluble types.
- Vitamins function synergistically and are best derived from food. Supplementation may be indicated for at-risk subpopulations.

Introduction

Vitamins are a group of organic essential compounds required for normal physiological function. They are required in minute amounts (i.e., μg or mg). They are not synthesized endogenously and therefore must be obtained from the diet. In a few cases, vitamins may also be obtained from the human gut microbiota. Vitamins are commonly classified based on their solubilities in fat or water. The fat-soluble vitamins (A, D, E, and K) are absorbed passively, must be transported with lipid, tend to be stored in the liver and in body fat, and may be excreted with the feces. The water-soluble vitamins (C and the eight B vitamins) are absorbed by passive or active mechanisms, transported by carriers, are not stored in appreciable amounts in the body, and are excreted in the urine.

Vitamins are essential for growth, development, reproduction, and maintenance of health. Healthy individuals consuming more than 75% of the Recommended Dietary Allowance (RDA) but less than the Tolerable Upper Intake Level (UL) of the *Dietary Reference Intakes* (see Chap. 39 for more details) minimize their risk of vitamin deficit or excess. Health professionals caring for special population groups should, where possible, adjust these nutrient-based recommendations to the special needs imposed by factors such as life stage, disease conditions, race/ethnicity, and/or environmental

K. M. Davison (✉)
Nutrition Informatics Lab, Kwantlen Polytechnic University, Richmond, BC, Canada
e-mail: Karen.Davison@kpu.ca

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situations. Table 34.1 provides an overview of the vitamins according to requirements, reliable food sources, solubility, stability, body systems they support, functions, as well as deficiency and toxicity symptoms.

Table 34.1 Vitamins: requirements, food sources, stability, associated body systems, functions, deficiency, and toxicity symptoms [8]

Vitamin and adult requirements[a]	Reliable food sources	Solubility and stability	Associated body systems, functions, deficiency/toxicity symptoms
Vitamin A RDA: M: 900 μg RAE[b] F: 700 μg RAE[b] Provitamins: β-carotene (and related substances)	*Vitamin A (preformed retinol)*: fortified milk and margarine, milk fat, egg yolk, liver *Carotenoid precursors*: yellow, orange, and dark green leafy vegetables; deep-orange fruits (cantaloupe, apricots, peaches)	Fat soluble Stable in the presence of light, heat, and usual cooking methods Destroyed by oxidation, drying, very high temperature, ultraviolet light	*Systems*: Genitourinary, immune, integumentary, nervous, respiratory *Functions*: Vision; growth and maintenance of epithelial tissues; maintain mucous membranes; reproduction (sperm formation and women's fertility); bone and tooth formation; immunity; hormone synthesis; antioxidant (in the form of β-carotene only); gene regulation *Deficiency*: Night blindness, rough skin, susceptibility to infection, impaired growth, immunity, and reproductive dysfunction *Toxicity*: Blurred vision, irritability, loss of appetite, ↑ activity of bone-dismantling cells causing ↓ bone density & bone/joint pain, skin disorders, liver disease, birth defects β-carotene: harmless yellowing of skin
Thiamin (vitamin B_1) RDA: M: 1.2 mg F: 1.1 mg	Meat, pork, organ meat, fish, poultry, legumes, whole grain and enriched breads, cereals and grain products, nuts, potatoes	Water soluble Unstable in presence of heat, alkali, or oxygen. Heat stable in acid solution	*Systems*: Cardiovascular, digestive, muscular, nervous, respiratory *Functions*: Helps enzymes release energy from carbohydrate; essential for growth, normal appetite, digestion, and healthy nerves *Deficiency*: Beriberi: edema, heartrate irregularity, mental confusion, muscle weakness, apathy, impaired growth, shortness of breath *Toxicity*: None reported
Riboflavin (vitamin B_2) RDA: M: 1.3 mg F: 1.1 mg	Milk and dairy-based foods, leafy green vegetables, organ meats, meat, whole grain or enriched breads, eggs, yeast, mushrooms	Water soluble Stable in the presence of heat, oxygen, and acid. Unstable in the presence of light or alkali	*Systems*: Integumentary, muscular, nervous, respiratory, sensory *Functions*: Helps release energy from carbohydrate, fat, and protein; also promotes healthy skin and normal vision *Deficiency*: Eye problems, cheilosis (fissuring of the lips) and angular stomatitis (cracks in skin at corners of the mouth), dermatitis, swollen magenta tongue, hypersensitivity to light, peripheral neuropathy. Prevalence of inherited riboflavin malabsorption and utilization is 10%–15%. *Toxicity*: None reported

Table 34.1 (continued)

Vitamin and adult requirements[a]	Reliable food sources	Solubility and stability	Associated body systems, functions, deficiency/toxicity symptoms
Niacin (vitamin B_3) RDA: M: 16 mg NE[c] F: 14 mg NE[c] UL: 35 mg	Meat, eggs, poultry, fish, milk, whole grain and enriched breads, cereals and grain products, nuts, legumes, peanuts	Water soluble Stable in the presence of heat, light, oxidation, acid, and alkali	*Systems*: Genitourinary, integumentary, muscular, nervous *Functions*: Helps enzymes release energy from energy nutrients; promotes health of skin, nerves, and digestive system *Deficiency*: Muscle weakness, anorexia, indigestion, altered gait, memory loss, and skin eruptions. Pellagra characterized as dermatitis, dementia, and diarrhea ("three Ds") *Toxicity*: Flushing, nausea, headaches, cramps, ulcer irritation, heartburn, abnormal liver function, rapid heartbeat reported with doses above 500 mg/day. Risks are greater with time-release forms of supplements. Megavitamin use should be monitored by a medical doctor
Pantothenic acid (vitamin B_5) AI: 5 mg	All plant and animal foods. Eggs, kidney, liver, salmon, and yeast best sources. Possibly synthesized by intestinal bacteria	Water soluble Unstable in the presence of acid, alkali, heat, and certain salts	*Systems*: Endocrine, genitourinary, muscular, nervous *Functions*: Essential for energy production from major nutrients and synthesis reactions *Deficiency*: Impaired lipid synthesis and energy production; paresthesia in feet, numbness/burning sensations in extremities, depression, insomnia, and weakness *Toxicity*: No adverse effects reported
Vitamin B_6 (pyridoxine, pyridoxal, pyridoxamine) RDA: M: 1.3–1.7 mg F: 1.3–1.5 mg UL: 100 mg/day	Meat, poultry, fish, shellfish, legumes, fruits, soy products, cereal bran and germ, milk, egg yolk, oatmeal, legumes, potatoes	Water soluble Stable in the presence of heat, light, and oxidation	*Systems*: Genitourinary, immune, integumentary, muscular, nervous *Functions*: Protein and fat metabolism; formation of antibodies and red blood cells; helps convert tryptophan to niacin *Deficiency*: Dermatologic and neurologic changes; nervous disorders, skin rash, cheilosis, glossitis, stomatitis, muscle weakness, anemia, convulsions, kidney stones, impaired immunity *Toxicity*: Sensory and motor neuropathy; depression, fatigue, irritability, headaches, numbness, damage to nerves, difficulty walking
Folate (folic acid) (vitamin B_9) RDA: 400 µg UL: 1000 µg	Green leafy vegetables, liver, legumes, seeds, citrus fruits, melons, enriched breads and grain products, yeast	Water soluble Stable in the presence of sunlight when in solution. Unstable in the presence of heat in acid	*Systems*: Cardiovascular, gastrointestinal, muscular, nervous *Functions*: Essential for synthesis of DNA, RNA, and maturation of red blood cells; protein metabolism; new cell division *Deficiency*: Impairs synthesis of DNA and RNA; megaloblastic, macrocytic anemia; heartburn, diarrhea, smooth red tongue, depression, poor growth, neural tube defects; increased risk of heart disease, stroke, and certain cancers *Toxicity*: Diarrhea, insomnia, irritability; may mask vitamin B_{12} deficiency

(continued)

Table 34.1 (continued)

Vitamin and adult requirements[a]	Reliable food sources	Solubility and stability	Associated body systems, functions, deficiency/toxicity symptoms
Vitamin B_{12} RDA: 2.4 μg	Animal products: meat, fish, poultry, shellfish, milk, cheese, eggs; fortified cereals. Vegans require supplement	Water soluble Slowly destroyed by acid, alkali, light, and oxidation	*Systems*: Cardiovascular, muscular, nervous *Functions*: Helps maintain nerve cells; red blood cell formation; synthesis of DNA and RNA. Involved with folate metabolism; related to growth *Deficiency*: Impairs cell division especially in bone marrow, intestinal mucosa; arrests synthesis of DNA. Symptoms include anemia, smooth red tongue, fatigue, and nerve degeneration progressing to paralysis. May occur due to inadequate production and secretion of intrinsic factor *Toxicity*: None reported
Vitamin C RDA: M: 90 mg F: 75 mg UL: 2000 mg	Citrus fruits, brassica vegetables (Brussels sprouts, cauliflower, broccoli), tomatoes, potatoes, bell peppers, strawberries, guava, pineapple, kiwi (fresh fruits and vegetables are best sources)	Water soluble Unstable in the presence of heat, alkali, and oxidation, except in acids. Destroyed by storage	*Systems*: Integumentary, immune, muscular, nervous, respiratory, skeletal *Functions*: Antioxidant; restores vitamin E to active form; wound healing (synthesizes collagen); maintains bone and teeth, strengthens blood vessel walls; resistance to infection; helps body absorb nonheme iron *Deficiency*: Scurvy, anemia, depression, infections, bleeding gums, loose teeth, pinpoint hemorrhages, muscle degeneration, rough skin, bone fragility, poor wound healing, hysteria *Toxicity*: Toxicity is possible but very rare even at 2 g/day
Vitamin D RDA: 5 μg 51–70 years: 10 μg >70 years: 15 μg UL: 50 μg	Self-synthesis in presence of sunlight; fortified milk, fortified margarine, egg yolk, liver, fish	Fat soluble Stable in the presence of heat and oxidation	*Systems*: Cardiovascular, endocrine, integumentary, immune, nervous, skeletal *Functions*: A prohormone; calcium and phosphorus metabolism (bone and tooth formation); aids body's absorption of calcium *Deficiency*: Rickets in children; osteomalacia in adults; abnormal growth, joint pain, soft bones *Toxicity*: Deposits of calcium in soft tissues (kidneys, liver, heart), mental retardation, abnormal bone growth
Vitamin E RDA: 15 mg UL: 1000 mg	Wheat germ, vegetable oils, green leafy vegetables, whole grain products, liver, egg yolks, nuts, seeds	Fat soluble Stable in the presence of heat and acids. Destroyed by rancid fats, alkali, oxygen, lead, iron salts, and UV irradiation	*Systems*: Cardiovascular, immune, nervous, respiratory *Functions*: Strong antioxidant (protects fat-soluble vitamins and polyunsaturated fats); stabilizes cell membranes; protects red blood cells from hemolysis; epithelial tissue maintenance; prostaglandin synthesis *Deficiency*: Weakness, breakage of red blood cells, anemia, hemorrhaging *Toxicity*: May increase bleeding (blood clotting time)

Table 34.1 (continued)

Vitamin and adult requirements[a]	Reliable food sources	Solubility and stability	Associated body systems, functions, deficiency/toxicity symptoms
Vitamin K RDA M: 120 µg F: 90 µg	Liver, soybean and other vegetable oils, green leafy and cabbage-type vegetables, wheat bran. Synthesized by intestinal tract bacteria	Fat soluble Resistant to heat, oxygen, and moisture. Destroyed by alkali and UV light	*Systems*: Cardiovascular, endocrine, immune, nervous, skeletal *Functions*: Synthesis of proteins for blood clotting and bone mineralization *Deficiency*: Hemorrhage, ↓ calcium in bones *Toxicity*: Interferes with anticlotting medication; synthetic forms may cause jaundice

[a]Requirements are based on the Institute of Medicine Dietary Reference Intakes: Recommended Dietary Allowance (*RDA*), Adequate Intakes (*AI*), and Tolerable Upper Intake Level (*UL*) [8]
[b]*RAE*: Retinol activity equivalents
[c]*NE*: Niacin equivalent used to describe the contribution to dietary intake of all the forms of niacin that are available to the body. Thus, 60 mg of tryptophan are considered to be 1 mg NE

The Vitamins: From A to K

Vitamin A and β-Carotene

Preformed vitamin A (retinoids) refers to three compounds (retinol, retinal or retinaldehyde, and retinoic acid) that are only found in animal products and exhibit metabolic activity. Carotenoids are a related group of substances that are found in plants. Some carotenoids, such as β-carotene, can be converted to vitamin A activity. These are referred to as provitamin A. Plants also contain other carotenoids, such lutein and lycopene. Carotenoids often act as antioxidants [1]. Normal digestive processes free vitamin A and carotenoids from food, which is a more efficient process from animal than from plant sources.

Vitamin A functions at two levels in the body: the first is in the visual cycle in the retina of the eye; the second is in all body tissues where its functions include cell differentiation, surface function (e.g., cell recognition), growth and development, bone function, immune function, reproduction (e.g., sperm production and fetal development), and gene expression. Vitamin A is particularly important for immune system function as it maintains mucosal surfaces of the respiratory, gastrointestinal, and genitourinary tracts and is involved in the differentiation of immune system cells.

Deficiency symptoms of vitamin A include altered embryo development, reduced sperm production, impaired immunity, and bone formation. Other deficiency symptoms include keratinization of the mucous membranes that line the respiratory tract, alimentary canal, urinary tract, skin, and eye epithelium. Persistent large doses of vitamin A (>100 times the required amount) can exceed the liver's storage capacity and lead to joint pain, dryness of the skin, and hair loss. Large doses of retinoids in pregnancy can lead to fetal malformation. Daily intakes of as much as 30 mg of β-carotene have no side effects except for skin yellowing. Vitamin A supplementation in populations with low vitamin A status reduces both the incidence and mortality of infectious diseases [2]; however, excess intakes can suppress immune function [3]. Retinoids are often present in skin creams used as a treatment for acne and other skin conditions.

The B Vitamins

The B vitamins act as coenzymes that help in the metabolism of carbohydrate, protein, and fat. The B vitamins are grouped together as they are all water soluble and have interrelated, cellular coenzyme functions.

Thiamin

Thiamin is an essential cofactor in carbohydrate, fatty acid, and amino acid metabolism. It participates in the synthesis of various amino acid precursors of neurotransmitters and other bioactive compounds essential for brain function [4]. A severe deficiency, called beriberi, causes extreme mental confusion, muscular wasting, edema (wet beriberi), peripheral neuropathy, rapid and/or irregular heartbeat, enlargement of the heart, paralysis, and heart failure. Deficiency can occur in those who, on a long-term basis, consume excess alcohol or take diuretics. Affected individuals can develop Wernicke-Korsakoff syndrome where the signs vary from mild confusion to coma. High doses of thiamin appear to have minimal toxic effects.

Riboflavin

Riboflavin is an essential cofactor in the metabolism of lipids, drugs, and foreign substances, cell signaling, and protein folding [5]. Because riboflavin has a fundamental role in metabolism, a deficiency tends to be evident first in tissues that have rapid cellular turnover such as the skin and epithelium. Riboflavin deficiency tends to occur in combination with deficiencies of other water-soluble vitamins. Factors which contribute to riboflavin deficiency include diminished intestinal transport, aldosterone and thyroid hormone insufficiency, interactions with tricyclic antidepressants and tetracyclic antibiotics, and alcohol abuse [5]. Repeated intake of pharmacologic doses (>100 mg) has the potential to react with light and leads to adverse cellular effects, particularly to lens proteins and the retina [5].

Niacin

Niacin is the general term for nicotinamide and nicotinic acid. Coenzymes that contain niacin are central in the metabolism of carbohydrates, fatty acids, amino acids, regulating gene expression, as well as mediating neuronal development and survival [6]. Dietary tryptophan, an amino acid, can be converted to niacin, although the efficiency of conversion is low.

Pellagra, which results from niacin deficiency, is characterized by the "three Ds": dermatitis, dementia, and diarrhea. Pellagra is common in people who are malnourished, abuse alcohol, or who have conditions such as anorexia nervosa, AIDS, cancer, and malabsorptive disorders, such as Crohn's disease. In some clinical cardiovascular guidelines, pharmacologic doses of niacin (10 to 15 times the RDA) have been used to treat hyperlipidemia [7]. Side effects of this level of supplementation include nausea, flushing of the skin, rash, fatigue, and liver damage.

Pantothenic Acid

Pantothenic acid has critical roles in energy production from the major nutrients and synthesis reactions. The vitamin is metabolized into two major coenzymes: coenzyme A (CoA) and acyl carrier protein (ACP); both are essential in fatty acid synthesis. CoA contributes to the structure and function of brain cells, neurotransmitter synthesis, and the production of steroid hormones [5]. Deficiency is rare but has been observed among severely malnourished individuals. Massive doses (e.g., 10 g/day) have produced only mild intestinal discomfort and diarrhea.

Vitamin B_6

Vitamin B_6 refers to the numerous derivatives that exhibit biologic activity of pyridoxine. The metabolically active form is pyridoxal phosphate (PLP). It is a coenzyme for numerous enzymes involved in the metabolism of amino acids, neurotransmitters, glycogen, sphingolipids of nerve cells, heme, and steroid hormones, and the conversion of tryptophan to niacin. Vitamin B_6 has direct effects on immune function, gene transcription and expression, and brain glucose regulation [5]. Vitamin B_6, like folate and vitamin B_{12}, is involved in lowering blood levels of homocysteine. High levels of homocysteine lead to inflammatory processes that contribute to the development of numerous pathological states including cardiovascular disease, dementia, and cognitive decline [5].

A person's requirement for vitamin B_6 is proportional to protein intake. A deficiency of vitamin B_6 appears as dermatologic and neurologic changes and symptoms such as weakness, irritability, insomnia, glossitis, stomatitis, and impaired immunity. Deficiency may be precipitated from the use of certain medications (e.g., nonsteroidal anti-inflammatory drugs and oral contraceptives), pregnancy, alcohol abuse, and some diseases such as autoimmune disorders. The vitamin has a low toxicity, although high doses (several grams daily) have produced sensory and motor neuropathy [8].

Folate

Folate is a term that applies to natural folates in food, and folic acid, the synthetic form used in supplements and fortified food (also called folacin). Folate is a coenzyme that is critical in the metabolism of DNA and RNA precursors and several amino acids, methylation reactions, and synthesis of red and white blood cells. An important interrelationship occurs between folate and vitamins B_6 and B_{12} as all three function to regenerate methionine from homocysteine and prevent a buildup of blood homocysteine levels.

Folate deficiency results in impaired synthesis of DNA and RNA, thus reducing cell division. This is most apparent in rapidly multiplying cells such as red blood cells, epithelial cells of the digestive tract, and those involved in embryo development. An adequate intake of folate reduces the risk of neural tube defects such as spina bifida. Because intake is often low, folic acid is added to flour and grain products sold in the USA and Canada. Women who are pregnant or who may become pregnant are often advised to boost their folate status with a multivitamin/mineral supplement that contains appropriate amounts of folic acid.

Folate deficiency can also cause macrocytic anemia and symptoms such as fatigue, diarrhea, irritability, forgetfulness, lack of appetite, and headache. Factors which contribute to folate deficiency include excess alcohol consumption, conditions such as cancer and malabsorption disorders (e.g., inflammatory bowel diseases and celiac disease), polypharmacy, and genetic diseases affecting its absorption or metabolism. Because high levels of blood folate can mask a vitamin B_{12} deficiency, total folate intake should not exceed 1 mg daily [8]. Concerns regarding the safety of excess folate intake are limited to the intake of synthetic folic acid.

Vitamin B_{12}

Vitamin B_{12} (cobalamin) is involved in the metabolism of amino acids and folate. It is essential for the normal metabolism of cells, especially those of the gastrointestinal tract, bone marrow, and nervous tissue. The vitamin also preserves DNA integrity and maintains the myelin sheaths that protect nerve fibers.

Vitamin B_{12} deficiency is uncommon in healthy individuals but can result in megaloblastic anemia that is characterized by large, immature red blood cells. Folate supplementation can alleviate the anemia, but other symptoms will progress. Vitamin B_{12} deficiency produces neurologic abnormalities, including irreversible paralysis of the nerves and muscles. A type of vitamin B_{12} deficiency, called pernicious anemia, can result from malabsorption related to inadequate production and secretion of

gastric intrinsic factor. This is common in the elderly due to changes in their gastrointestinal function. Neurological symptoms, including depression, cognitive decline, dementia, and autonomic dysfunction, are common across vitamin B_6, B_9, and B_{12} deficiencies [5].

Foods of animal origin are the only food sources of vitamin B_{12}. For that reason, strict vegetarians need to find alternative sources such as supplements or vitamin-fortified soy beverages or cereals. There are no adverse effects associated with large intakes of vitamin B_{12} from food or supplements in healthy people.

Vitamin C

Vitamin C (ascorbic acid and ascorbate) functions as an antioxidant. It is also involved in the synthesis of collagen in the skin, maintenance of connective tissue, and stabilization of collagen. It promotes resistance to infection through its involvement with the immune activity of leukocytes, inflammatory reaction processes, and mucous membrane integrity [9]. Vitamin C supplementation is often promoted as a means for preventing and treating the common cold and to support cardiometabolic health, but the evidence is inconclusive [9]. Vitamin C deficiency can result in scurvy.

Vitamin D

Vitamin D is essential in bone health by regulating calcium and phosphorus, a topic discussed at greater length in Chapter 11. Because the body can make vitamin D with the help of solar UVB, it is thought that people can meet their requirement via sun exposure, as well as from the diet. However, the most recent studies about exposure to very high natural sunlight exposure have led to uncertainty about how much vitamin D can be produced after sun exposure [10]. In addition, people with dark-colored skin may be able to synthesize more vitamin D from sun exposure than what was previously thought. Individuals who reside at latitudes further from the Equator than 40° north or south have less exposure to UVB radiation available for at least 5 months of the year. Women who are completely covered in clothing, as in the Middle East, often have low vitamin D levels. For these people, a diet containing ample amounts of vitamin D-rich foods or supplements is particularly important. Vitamin D also exhibits many nonskeletal effects, particularly on the immune, endocrine, and cardiovascular systems [10]. There has been considerable epidemiological research investigating associations between vitamin D and many chronic diseases such as cardiovascular disease, diabetes mellitus, and cancer; knowledge about the role of vitamin D in these conditions continues to evolve. It is known that serum 25(OH)D concentrations <50 nmol/L are likely to have adverse effects on health and that this affects one quarter of the world's population [10].

Vitamin D deficiency depresses calcium absorption which can lead to abnormal bone development. Children who fail to obtain enough vitamin D can develop the deficiency disease rickets (leg bowing); in adults, it is called osteomalacia. Long-term vitamin D insufficiency may also contribute to osteoporosis. Excess vitamin D induces abnormally high serum calcium levels and deposition in soft tissues resulting in bone loss, kidney stones, and calcification of organs such as the heart and kidneys.

Vitamin E

Naturally occurring vitamin E includes the tocopherols and the less biologically active compounds, the tocotrienols. The body prefers to use α-tocopherol.

Vitamin E is the most important lipid-soluble antioxidant in cells as it protects the body against the damaging effects of reactive oxygen species (free radicals) formed by the body or encountered in the

environment. Vitamin E is important in protecting the lungs as they are constantly exposed to free radicals formed as a result of exposure to oxygen. It also helps protect the central nervous system. Vitamin E protects polyunsaturated fatty acids and other fatty components of the cells and cell membranes from being oxidized. Vitamin E and related nutrients, such as vitamin C, were for a number of years thought to be important in preventing and treating conditions associated with oxidative stress, but evidence from clinical trials of supplements has been mostly negative. Vitamin E may also regulate cell signaling and gene expression [11]. Deficiency and toxicity of vitamin E are uncommon.

Vitamin K

Vitamin K is important for both blood clotting and bone mineralization. It may also have a role in the regulation of enzymes in the brain [12]. Naturally occurring vitamin K comprise the phylloquinone (vitamin K_1), which is the primary source of vitamin K, and a series of menaquinones broadly designated as vitamin K_2 that differ in source, absorption rates, bioavailability, and functions. Some vitamin K is synthesized by human intestinal microbiota. For that reason, vitamin K deficiency is a potential side effect of antibiotic treatment.

Vitamin K deficiency has been associated with lipid malabsorption, destruction of intestinal flora from chronic antibiotic therapy, liver disease, increased risk of hemorrhage, interactions with drugs that interfere with the activity of lipases, or are bile acid sequestrants. There has been no known toxicity associated with high doses of the vitamin. For individuals taking anticoagulants, the content of vitamin K in the diet must be kept relatively constant to prevent clot formation and subsequent stroke or heart attack [12].

Vitamins: How Much Do We Really Need?

As the science of nutrition progresses and we consider factors such as the *Dietary Reference Intakes (DRIs)*, the role of vitamins in the prevention of disease, and movements toward personalized medicine and nutrition, the answer to the question of how much of each vitamin we need is not straightforward.

Recommendations for Vitamin Intakes in the General Healthy Population

As noted in Chapter 39, the *DRI*s are a set of reference values determined from the best evidence available that are used to assess nutrient intakes of healthy people and for making dietary recommendations. The Recommended Daily Allowances (RDA) represent the average daily levels of intake sufficient to meet the nutrient requirements of nearly all healthy people. The Tolerable Upper Intake Levels (UL) represent the highest usual level of nutrient intake that pose no risk of adverse health effects. When intakes exceed the UL, especially for a prolonged period, the probability of an adverse effect increases.

Vitamins in the Prevention and Management of Communicable and Noncommunicable Diseases

The *DRI*s can help to determine the need for supplementation for individuals. Based on assessment of one's nutrient intakes, if levels are very low, deficiency symptoms may emerge. This can be confirmed by checking blood levels of nutrients where there may be a deficiency. If a deficiency is confirmed,

supplementation with the problem vitamins can replenish body stores and reverse deficiency symptoms. When individual intake levels are adequate (e.g., about 75% of the RDA or higher), supplements seldom have any effect. When intake is consistently above the UL, toxicity symptoms may appear.

Studies have demonstrated that several vitamins may have roles beyond those functions normally credited to them in the prevention of deficiency diseases; suboptimal levels may have important impacts on the development of chronic disease. For example, vitamin D is essential for healthy bones and is protective against bone diseases. But there is also evidence that vitamin D deficits can predispose individuals to cardiovascular disease and cancer (especially colon cancer) [13], and communicable diseases such as SARS coronavirus [14]. Knowledge about the multifunctional roles associated with vitamin K has been growing with evidence showing its involvement in a wide range of biological functions related to low-grade inflammation that can potentially lead to chronic diseases such as cardiovascular diseases, chronic kidney disease, osteoarthritis, rheumatoid arthritis, osteoporosis, cancer, and dementia [12].

Given that dietary intake measurement at a population level indicates that there are widespread intake deficits for sizeable sections of the population, the question is often asked: Should vitamin supplements be recommended? Most nutrition experts would indicate that supplementation is not needed if one is consuming a reasonably healthy diet that enables synergistic interactions of nutrients and other compounds within and among the foods consumed. The pros and cons of taking dietary supplements, such as vitamin D and multivitamins, are further examined in Chapter 42.

Vitamins as Epigenetic Modifiers

Epigenetic changes include DNA, RNA, and histone modifications along with expression of noncoding RNAs. These can play an important role in disease pathogenesis [15]. Studies suggest that vitamins A, C, D, and the B vitamins, such as niacin, and pantothenic acid, can regulate both physiological and pathological processes through their impacts on the epigenome. However, much is still unknown about the vitamin-mediated epigenetic regulation related to disease pathogenesis.

Nutrigenomics, which investigates how nutrients and bioactive compounds present in food affect human health through epigenetic modifications [16], may enable customization of an individual's dietary intake at a given life stage to prevent or delay deterioration of health [17, 18]. Much of our past knowledge about vitamin requirements has stemmed from population studies that have not accounted for genetic differences. However, many investigations have emerged that show that versions of a gene can make individuals respond differently to specific components of foods, such as vitamins. For example, variations in the methylenetetrahydrofolate reductase (*MTHFR*) gene determine the way individuals utilize dietary folate [19]. In the future, the testing of biomarkers and genomic markers, as well as gene-based personalized nutrition approaches, may improve our ability to provide definitive individualized recommendations for vitamin intakes.

Summary

The discovery of vitamins dates back to the early 1900s. The 13 known vitamins have myriad roles in the body; new roles for old vitamins are still being discovered. For example, research in recent years has shown that vitamin D has actions that go well beyond calcium balance and bone health. Because of their many vital functions in the body, an adequate intake of vitamins is essential for good health.

The general public has been provided a great deal of misinformation regarding the importance of vitamins. They have often been credited with great healing abilities. Many times, the recommended dose has been based on the principle: "If some is good, more is better." But that is seldom the case.

Vitamins most certainly do have potent therapeutic value, but this is almost entirely confined to situations where a person has a deficiency in which case a supplement of the vitamin will reverse the deficiency symptoms.

COVID-19 Addendum

The COVID-19 pandemic has led to a search for ways to enhance the body's resistance to the virus that causes the infection. The potential of some vitamins has been investigated. Some suggestive evidence has appeared indicating that vitamin C may be of modest value [20]. However, vitamin D has attracted most attention, but the findings are inconclusive. One review concluded that vitamin D deficiency has a significant association with risk of COVID-19 [14], while another review reported that the findings are inconsistent [21]. Other evidence indicates that vitamin D supplements are of little protective value against the virus [22].

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Suggested Further Readings

Office of Dietary Supplements. National Institutes of Health (NIH). This site provides information on vitamins (and minerals), the safe use of supplements, and the research available on the treatment of health problems and disease with various supplements. http://ods.od.nih.gov

US Department of Agriculture's Food and Nutrition Information Center. This site provides information on food composition and topics related to vitamins and minerals. https://fnic.nal.usda.gov

Essential Minerals: Nutritional Requirements, Dietary Sources, and Deficiencies

35

Elad Tako

Keywords

Minerals · Electrolytes · Dietary supplements

Key Points

- Minerals are inorganic substances required by the body in small amounts for a variety of different functions.
- Minerals are classified as macro-, micro-, or ultra-trace according to the amounts that are present in the body and amounts required from the diet to maintain health.
- Minerals are involved in the formation of bones and teeth; they are essential constituents of body fluids and tissues; they are components of enzyme systems; and they are involved in normal nerve function.
- The body requires different amounts of each mineral; people have different requirements according to their age, sex, physiological state (e.g., pregnancy, anemia), and sometimes their state of health.
- Mineral bioavailability is affected by body needs, interactions with other nutrients, inhibitors such as phytates, polyphenols, and oxalates, and enhancers such as ascorbic acid.
- Deficiencies of certain minerals are global health concerns; in some cases, ingestion of large doses leads to accumulation in the body and can be fatal.

Introduction

There are 16 essential minerals: calcium, phosphorus, potassium, sulfur, sodium, chloride, magnesium, iron, zinc, copper, manganese, iodine, selenium, molybdenum, chromium, and fluoride. Minerals play important roles in maintaining blood pressure, fluid and electrolyte balance, and bone health; making new cells; delivering oxygen to cells; and contributing to normal muscle and nerve functioning. Minerals are widely distributed in foods, with specific minerals being found in certain foods. By eating a variety of nutrient-dense foods from the five food groups, people consume a mineral-rich diet. Minerals form only a minor amount of the typical human diet but are essential for

E. Tako (✉)
Department of Food Science, Cornell University, Ithaca, NY, USA
e-mail: et79@cornell.edu

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normal health and function. Macrominerals are defined as minerals that are required by adults in amounts greater than 100 mg/day or make up less than one percent of total body weight. Microminerals (or trace minerals) are usually defined as minerals that are required in amounts less than 100 mg/day by adults or make up less than 0.01% of total body weight.

Recommended intakes for trace elements are expressed as Recommended Dietary Allowances (RDA) or Adequate Intake (see Chap. 39). This amount will satisfy the needs of practically all the population; in other words, it is usually not necessary to exceed the RDA.

The upper limit is the quantity of the nutrient considered to cause no adverse effects in healthy individuals. These parameters have been estimated for each trace mineral. Table 35.1 provides an overview of the minerals according to their functions, food sources, recommended levels of intake to support health, deficiency and toxicity symptoms, as well as population groups that may be at risk of deficiency.

The Macrominerals

The main macrominerals are electrolytes, substances that dissociate in water into positively and negatively charged ions (cations and anions). The extracellular electrolytes are sodium and calcium; the intracellular electrolytes are potassium, magnesium, and phosphate.

Calcium

It is involved in a large number of vital functions [1]. In addition to its importance to bone health, there is a relationship between calcium intake and preeclampsia/eclampsia during pregnancy [2]. Calcium-rich foods are dairy products, especially hard cheese that can provide 1 g of calcium per 100 g, whereas milk and yogurt can provide between 100 and 180 mg per 100 g. In the United States, 72% of calcium comes from dairy products [3]. Fortified foods, such as cereals and juices, can become additional important sources of calcium. Supplements are also a dietary source of calcium for some populations.

In 2010, the Institute of Medicine (IOM) set the dietary intake upper limit for pregnant women at 3000 mg/day for those aged 14–18 years and 2500 for older pregnant women [3]. Since 2013, WHO has recommended that all pregnant women from areas of low dietary calcium intake receive calcium supplementation from 1500 to 2000 mg/day from 20 weeks gestation, as evidence from randomized control trials has shown a reduced risk of preeclampsia [4].

Phosphorus

This is an essential mineral required for cell structure, signaling, energy transfer, and other important functions. In the United States, the average intake of phosphorus for men is 1655 mg/day and 1190 mg/day for women, with intake decreasing with increasing age [5]. The main sources of phosphorus include dairy, meat, grain, and fish; inorganic phosphorus-based additives used by food manufacturers may contribute up to 10–30% of total phosphorus intake [6]. Because phosphorus is widespread in food, including processed foods and soft drinks, dietary inadequacy is uncommon. Deficiency tends to only occur in people who are taking phosphate-binding drugs or among older adults due to general poor food intake.

Table 35.1 Minerals: reliable food sources, stability, associated body systems, functions, deficiency, and toxicity symptoms [26]

Minerals and adult requirements[a]	Reliable food sources	Associated body systems, functions, deficiency/toxicity symptoms	Probability of deficiency
Macrominerals			
Calcium AI: 1000 mg/day >50 years: 1200 mg/day UL: 2500 mg/day	Milk and milk products, small fish (with bones), tofu, certain green vegetables, legumes, fortified foods	*Systems*: Circulatory, endocrine, immune, muscular, nervous, skeletal *Functions*: Bone and tooth, nerve transmission, muscle contraction, blood clotting, pressure regulation, hormone secretion *Deficiency*: Stunted growth, bone loss *Toxicity*: Elevated blood calcium, kidney stones	Bones serve as homeostatic mechanism; long-term deficiency leads to osteoporosis later in life *At risk*: Postmenopausal women; elderly people; individuals who consume a vegan diet, are lactose intolerant, or have kidney disease
Magnesium RDA: M (19–30 years): 400 mg/day; (>31 years): 420 mg/day F (19–30 years): 310 mg/day; (>31 years): 320 mg/day UL: 350 mg/day from nonfood sources	Dark greens, whole grains, nuts, seeds, legumes, seafoods, cocoa	*Systems*: Circulatory, endocrine, immune, muscular, nervous, skeletal *Functions*: Bone structure, ATP stabilization, enzyme activity, nerve and muscle function *Deficiency*: Nausea, weakness, muscle pain, confusion, depressed pancreatic secretion, growth failure *Toxicity*: Excess intakes has caused low blood pressure, lack of coordination, coma, and death	Conditional deficiencies are common with surgery, alcoholism, malabsorption, loss of body fluids, and certain hormonal and renal diseases *At risk*: Individuals with alcoholism, kidney, or gastrointestinal disease
Phosphorus (major mineral) RDA: 700 mg/day UL: 4000 mg/day	Meat, poultry, fish, dairy products, soft drinks, processed foods	*Systems*: Circulatory, endocrine, immune, nervous, skeletal *Functions*: Structure of bones and teeth, membranes, ATP, and DNA; acid-base balance *Deficiency*: Bone loss, weakness *Toxicity*: Cause calcium excretion and deposits in soft tissues	Inadequacy is unlikely if protein and calcium intake are adequate *At risk*: Premature infants; those with alcoholism; elderly

(continued)

Table 35.1 (continued)

Minerals and adult requirements[a]	Reliable food sources	Associated body systems, functions, deficiency/toxicity symptoms	Probability of deficiency
Potassium AI: 4700 mg/day	All whole foods: meats, milk, fruits, vegetables, grains, legumes	*Systems*: Circulatory, endocrine, muscular, nervous, skeletal *Functions*: Protein synthesis, fluid balance, nerve transmission, and muscle contraction *Deficiency*: Muscle weakness, paralysis, confusion; can cause death; accompanies dehydration. Mildly low intake is associated with raised blood pressure *Toxicity*: Causes muscular weakness; triggers vomiting; high doses of supplements or IV administration causes irregular heartbeat	Rare in healthy individuals *At risk*: People consuming low-quality diets high in processed foods; people with medical conditions such as kidney disease, diabetic ketoacidosis, extreme dehydration, vomiting, and diarrhea; people who take certain diuretics (thiazides) or misuse laxatives
Sodium AI (19–50 years): 1500 mg/day UL: 2300 mg/day	Salt, soy sauce; processed foods such as cured, canned, pickled, and many packaged foods	*Systems*: Circulatory, endocrine, immune, nervous, skeletal *Functions*: Fluid and acid-base balance; nerve impulse transmission. Dietary salt (chloride) necessary for proper digestion, fluid balance *Deficiency*: Muscle cramps, mental apathy, loss of appetite *Toxicity/high intake*: High blood pressure	Extremely rare *At risk*: Active people who drink large volumes of water and fail to replace sodium; people consuming a severely sodium restricted diet
Chloride AI: 750–900 mg/day	Table salt or sea salt as sodium chloride; seaweed, rye, tomatoes, lettuce, celery, and olives	*Systems*: Negatively charged ion of the blood *Functions*: Maintain electrical neutrality across the stomach membrane *Deficiency*: Rare, results in a condition known as alkalosis, in which the blood becomes overly alkaline *Toxicity*: Fluid retention and high blood pressure	
Microminerals			
Fluoride AI: M: 4 mg/day F: 3 mg/day UL: 10 mg/day	Fluoridated water (1 ppm), tea, coffee, rice, soybeans, seafood	*Systems*: Skeletal *Functions*: Formation of bones and teeth; resistance to tooth decay *Deficiency*: Susceptibility to tooth decay *Toxicity*: Fluorosis (discoloration of teeth), kidney damage, bone abnormalities	Occurs in areas where fluoride content in water is low (<1 ppm) *At risk*: Populations in areas with un-fluoridated water; those who drink mainly bottled water (deionized, purified, demineralized, or distilled water may contain no or only trace amounts of fluoride)

Table 35.1 (continued)

Minerals and adult requirements[a]	Reliable food sources	Associated body systems, functions, deficiency/toxicity symptoms	Probability of deficiency
Iron RDA: M: 8 mg/day F (19–50 years): 18 mg/day; (>50 years): 8 mg/day UL: 45 mg/day	Red meats, fish, poultry, shellfish, eggs, legumes, dried fruits, molasses, whole, enriched, or fortified grains	*Systems*: Circulatory, endocrine, immune, muscular, nervous *Functions*: Part of hemoglobin and myoglobin; electron carriers in electron transport chain; immune function *Deficiency*: Iron deficiency anemia – small, pale red blood cells, low hemoglobin, weakness, pallor, headaches, reduced immunity, inability to concentrate, cold intolerance *Toxicity*: GI upset, iron overload, infections, liver damage, acidosis, shock	Common in at-risk groups. Deficiency may be associated with unusual blood loss, parasites, or malabsorption *At risk*: Infants and preschool children; adolescents; women of childbearing age; pregnant women; athletes; vegetarians
Zinc RDA: M: 11 mg/day F: 8 mg/day UL: 40 mg/day	Meats, seafood, poultry, whole grains, legumes, wheat brain, eggs	*Systems*: Immune, integumentary, muscular, nervous, reproductive *Functions*: Regulates protein synthesis; functions in growth, development, wound healing, immunity, and antioxidant protection, vitamin A transport, fetal development *Deficiency*: Poor growth and development, skin rashes, decreased immune function, loss of taste, poor wound healing *Toxicity*: Decreased copper absorption, depressed immune function, kidney failure	Extent of inadequacy unknown. Conditional deficiency can occur with systemic childhood illness and individuals who or are nutritionally depleted or have experienced severe stress such as surgery *At risk*: Vegetarians; low-income children; elderly
Ultra-Trace Minerals			
Copper RDA: 900 µg/day UL: 10 mg/day	Organ meats, seafood, nuts, seeds, whole grains, cocoa	*Systems*: Immune, muscular, nervous *Functions*: Part of proteins needed for iron absorption, lipid metabolism, collagen synthesis, nerve and immune function, and antioxidant protection *Deficiency*: Anemia, poor growth, bone abnormalities *Toxicity*: Vomiting, diarrhea	No evidence *At risk*: Those who over-supplement with zinc; Menkes disease is a genetic disorder resulting in copper deficiency

(continued)

Table 35.1 (continued)

Minerals and adult requirements[a]	Reliable food sources	Associated body systems, functions, deficiency/toxicity symptoms	Probability of deficiency
Chromium AI: M (19–50 years): 35 μg/day F (19–50 years): 25 μg/day UL: no UL	Brewer's yeast, meats, nuts, whole grains, mushrooms	*Systems*: Endocrine *Functions*: Associated with glucose metabolism; enhances insulin action *Deficiency*: Abnormal glucose metabolism; high blood glucose *Toxicity*: Can occur with occupational exposure; causes damage to skin and kidneys	Found in those with severe malnutrition and may be a factor in diabetes development in older adults *At risk*: Malnourished children
Iodine RDA: 150 μg/day UL: 1100 μg/day	Iodized salt, seafood, bread	*Systems*: Endocrine *Functions*: Synthesis of thyroid hormones *Deficiency*: Goiter, cretinism, intellectual disability, growth and developmental abnormalities *Toxicity*: Enlarged thyroid; depressed thyroid activity	Iodization of table salt recommended, especially in areas where food is low in iodine *At risk*: Populations in areas with low-iodine soil and iodized salt is not used
Selenium RDA: 55 μg/day UL: 400 μg/day	Grains, organ meats, milk, seafood, eggs; vegetables – depending on selenium in soil	*Systems*: Endocrine, integumentary *Functions*: Fat metabolism, spares vitamin E, antioxidant as part of glutathione peroxidase; synthesis of thyroid hormones *Deficiency*: Muscle pain, weakness, Keshan disease *Toxicity*: Vomiting, diarrhea, hair and nail changes	Has occurred in patients receiving long-term TPN without selenium supplementation *At risk*: Populations in areas with low selenium in soil

[a]Requirements are based on the Institute of Medicine Dietary Reference Intakes: Recommended Dietary Allowance (*RDA*), Adequate Intakes (*AI*), and Tolerable Upper Intake Level (*UL*) [26]

Magnesium

This essential mineral represents the fourth most abundant mineral in the body. Nuts, seeds, legumes, whole-grain cereals, leafy vegetables, and drinking water are important dietary sources; consumption of a diet plentiful in these foods enables the dietary intake to reach the RDA of 420 mg/day for adult men and 320 mg/day for adult women [7]. Dietary surveys in the United States have shown that the RDA of magnesium is unmet in a large proportion of the population, probably as a result of following Western dietary patterns [7].

Sodium

This is essential for fluid balance and cellular homeostasis. The amount of sodium needed in the daily diet to maintain homeostasis in adults is exceedingly low (<500 mg) compared to the average intake of most Americans (>3200 mg) [8]. Studies suggest that elevated dietary sodium expands the extracellular volume and increases cardiac output, which increases blood pressure if there is no compensatory decline in peripheral resistance [9].

Potassium

This is one the four major shortfall nutrients in the American diet according to the 2010 Dietary Guidelines for American's Advisory Committee [10]. The average potassium intake of Americans (2590 mg/day) is just over half of the requirement. Adequate dietary potassium is important for heart and bone health and reduces the risk of stroke and coronary heart disease.

Chloride

This mineral represents 70% of the body's total negative ion content. An adult human body contains, on average, approximately 115 g of chloride, making up about 0.15% of total body weight [11]. The suggested amount of chloride intake ranges from 750 to 900 mg/day, based on the fact that total obligatory loss of chloride in the average person is close to 530 mg/day.

Microminerals

Fluoride

Fluoride enters the body with food and products containing fluoride [12]. Fluoride is found in all-natural waters. Seawater contains 1.2–1.5 ppm of fluoride. Freshwater concentrations are usually lower ranging from 0.01 to 0.3 ppm. Higher concentrations of fluoride in water can be present near hot springs of volcanic origin [13]. It is also often present in toothpaste and fluoridated water and helps prevent tooth decay.

Iron

For many years, nutritional interest in iron focused on its role in hemoglobin formation and oxygen transport. Nowadays, although low iron intake and/or bioavailability are responsible for most cases of anemia in industrialized countries, they account for only about half of the anemia in developing countries where infectious and inflammatory diseases (especially malaria), blood loss from parasitic infections, and other nutrient deficiencies (vitamin A, riboflavin, folic acid, and vitamin B_{12}) are also important causes [14].

The World Health Organization estimates that approximately one-third of worldwide infant deaths, and one-half in developing countries, can be attributed to malnutrition, specifically to iron deficiency, as it is the most common nutritional deficiency worldwide and a major cause of infant mortality. Diets with chronically poor iron bioavailability, which result in a high prevalence of Fe deficiency and anemia, increase the risk of all-cause child mortality and may also lead to many pathophysiological consequences including stunted growth, low birth weight, and delayed mental development and motor functioning.

Dietary iron occurs in two forms: heme and nonheme [15]. The primary sources of heme iron are hemoglobin and myoglobin from consumption of meat, poultry, and fish, whereas nonheme iron is obtained from cereals, pulses, legumes, fruit, and vegetables [15]. Heme iron is highly bioavailable (15–35%), and dietary factors have little effect on its absorption, whereas nonheme iron absorption is much lower (2–20%) and strongly influenced by the presence of other food components [15].

Ascorbate and citrate increase iron uptake in part by acting as weak chelators to help to solubilize the metal in the duodenum [16]. Iron is readily transferred from these compounds into the cells of the

mucosal lining. Ascorbic acid is the only absorption enhancer in vegetarian diets, and iron absorption from vegetarian and vegan meals can be best optimized by the inclusion of ascorbic acid-containing vegetables. The enhancing effect of meat, fish, or poultry on iron absorption from vegetarian meals has been shown, and 30 g muscle tissue is considered equivalent to 25 mg ascorbic acid [16].

Phytate (myo-inositol hexakisphosphate) is the main inhibitor of iron absorption in plant-based diets [15]. Common food sources include whole-grain breads, cereals, and legumes. The negative effect of phytate on iron absorption has been shown to be dose dependent and starts at very low concentrations of 2–10 mg/meal [16].

Polyphenols occur in various amounts in plant foods and beverages, such as vegetables, fruit, some cereals and legumes, tea, coffee, and wine. The inhibiting effect of polyphenols on iron absorption has been shown with black tea and to a lesser extent with herbal teas [17]. In cereals and legumes, polyphenols add to the inhibitory effect of phytate, as was shown in a study that compared high and low polyphenol sorghum [15].

Calcium has been shown to have negative effects on nonheme and heme iron absorption, which makes it different from other inhibitors that affect nonheme iron absorption only [18].

During early infancy, iron requirements are met by the little iron contained in human milk. The need for iron rises markedly 4–6 months after birth and amounts to about 0.7–0.9 mg/day during the remaining part of the first year. Between 1 and 6 years of age, the body iron content is again doubled [19]. Iron requirements are also very high in adolescents, particularly during the growth spurt.

The highest probability of suffering iron deficiency is found in those parts of the population that have inadequate access to foods rich in absorbable iron during stages of high iron demand. These groups correspond to children, adolescents, and women of reproductive age, in particular during pregnancy [19].

Excess iron is also a problem. Iron overload is usually due to hereditary hemochromatosis. Frequent transfusions or long-term ingestion of large amounts of iron can lead to abnormal accumulation of iron in the liver, saturation of the tissue apoferritin, and the development of hemosiderin.

Zinc

This is an essential micronutrient that contributes to the proper functioning of over 300 enzymes and multiple biochemical and structural processes in the body.

Zinc deficiency affects ~17% of the world's population (~1.3 billion people). Zinc inadequacy has been associated with poor growth, depressed immune function, increased vulnerability to and severity of infection, adverse outcomes of pregnancy, and neurobehavioral abnormalities. Deficiency of zinc is a major cause of early childhood morbidity and mortality. In the United States, about 12% (~40 million) of the general population and 40% (~18 million) of the elderly are at risk for zinc deficiency, due to inadequate dietary intake and less absorption of the nutrient.

A wide variety of foods contain zinc. Oysters contain more zinc per serving than any other food, but red meat and poultry provide the majority of zinc in the American diet. Other good food sources include beans, nuts, some types of seafood (such as crab and lobster), whole grains, fortified breakfast cereals, and dairy products.

Phytate, which was mentioned above, binds zinc and inhibits its absorption. For that reason, the bioavailability of zinc from grains and plant foods is lower than that from animal foods, although many grain- and plant-based foods are still good sources of zinc [20].

In North America, overt zinc deficiency is uncommon [20]. When zinc deficiency does occur, it is usually due to inadequate zinc intake or absorption, increased losses of zinc from the body, or increased requirements for zinc [21]. People at risk of zinc deficiency or inadequacy need to include good sources of zinc in their diets.

Ultra-Trace Minerals

Copper

The human body contains approximately 100 mg of this essential trace element. An overload of this metal easily leads to redox reactions, resulting in oxidative cell damage and cell death. However, copper toxicity as a result of dietary excess is generally not considered a widespread health concern, probably as a result of the homeostatic mechanisms controlling copper absorption and excretion [22].

Iodine

Iodine is a trace element that is naturally present in some foods, added to others, and available as a dietary supplement. Iodine is an essential component of the thyroid hormones thyroxine (T4) and triiodothyronine (T3). The earth's soils contain varying amounts of iodine, which in turn affects the iodine content of crops. In some regions of the world, iodine-deficient soils are common, increasing the risk of iodine deficiency among people who consume foods primarily from those areas. Salt iodization programs, which many countries have implemented, have dramatically reduced the prevalence of iodine deficiency worldwide [23]. Iodine deficiency causes goiter, a condition estimated to affect 200 million people worldwide. Other conditions such as mental retardation may also develop due to iodine deficiency. About 2 billion people living in less-developed nations remain at risk for moderate iodine deficiency which may not show an obvious goiter. Sources of iodine are seaweed as one of the best food sources, but it is highly variable in its content [23]. Other good sources include seafood, dairy products (partly due to the use of iodine feed supplements and iodophor sanitizing agents in the dairy industry), grain products, and eggs. Dairy products, especially milk, and grain products are the major contributors of iodine to the American diet.

Selenium

This trace element is naturally present in many foods, added to others, and available as a dietary supplement. Brazil nuts, seafoods, and organ meats are the richest food sources of selenium. Other sources are muscle meats, cereals and other grains, and dairy products. The major food sources of selenium in the American diet are breads, grains, meat, poultry, fish, and eggs [24].

Chromium

This mineral is required in trace amounts, although its mechanisms of action in the body and the amounts needed for optimal health are not well defined. It was identified as the active ingredient in the so-called glucose tolerance factor in 1959 [25]. Chromium also appears to be directly involved in carbohydrate, fat, and protein metabolism, but more research is needed to determine the full range of its roles in the body. Chromium is widely distributed in the food supply, but most foods provide only small amounts (<2 μg per serving). Meat and whole-grain products, some fruits, vegetables, and spices are relatively good sources. In contrast, foods high in simple sugars (like sucrose and fructose) are low in chromium [25].

Other Trace Elements

Manganese, sulfur, and molybdenum are essential for humans. There is evidence that vanadium, boron, arsenic, nickel, and silicon may also be essential. These elements may be necessary in extremely small amounts but can be toxic in excess.

Essential Minerals: Supplements

Select groups within the population may have an increased likelihood for requiring supplementation. For example, dietary intake inadequacies have often been reported among the elderly, those of lower socioeconomic status and those on diets restricted in energy or fat. In addition, physiologic states, such as pregnancy and lactation, increase requirements for calcium and iron. Further, chronic illness may result in increased requirements for certain nutrients; for example, those with malabsorptive disorders may need general supplementation, and those with osteoporosis may need bone-related nutrients. Finally, lifestyle choices may increase nutrient needs such as increased iron requirements in iron-deficient athletes. Populations at risk of deficiency for each of the minerals discussed in this chapter are indicated in Table 35.1.

In general, multivitamin-mineral supplements are sufficient to meet the needs of those with increased mineral requirements; however, these must be carefully selected as some types contain iron and others do not. While women may have heightened need for calcium and iron at some life stages, vitamin and mineral supplements formulated for women usually supply sufficient amounts. Some multivitamin-mineral supplements may have low calcium content and a separate calcium supplement may be needed. Calcium absorption is optimal when taken in amounts of no more than 500 mg at a time. Recent evidence suggests that the use of calcium supplements has some harmful side effects, the most notable being a 20–40% increased risk of myocardial infarction. Because of this the benefit of calcium supplements in reducing the risk of fractures is outweighed by its potential harm to other body systems.

More iron is needed during pregnancy; prenatal vitamins provide for these increased needs. For women who have reached menopause or have had a hysterectomy, it is advised to switch to a supplement that reduces or eliminates iron. For men, iron supplementation is not recommended as it can lead to iron overload; some men carry the genetic defect. Multivitamin and mineral formulations promoted for men typically include selenium which may protect against certain types of cancer. Most minerals have a narrow range of safety, and therefore it is not advised to take supplements that contain a single mineral.

Summary

The body requires different amounts of each mineral because each mineral has a different set of functions. Requirements vary according to age, sex, and physiological state (e.g., pregnancy). They may also be influenced by state of health. Recommended intakes are expressed as Recommended Dietary Allowances (RDA) or Adequate Intake.

The bioavailability of a mineral (i.e., how readily it can be absorbed and used by the body) may be influenced by a variety of factors. Bioavailability depends on the chemical form of the mineral, other substances present in the diet, and (for nutrients such as iron) the individual person's needs as determined by how much of the nutrient is already stored in the body. This is because the body has sensitive mechanisms for preventing storage of nutrients that can be damaging in excess (as is the case with iron). For example, the bioavailability of iron from plant sources (nonheme iron) is relatively poor compared with iron from meat (heme iron), but absorption is increased when vitamin C is consumed

during the same meal because the vitamin C converts it to a more bioavailable chemical form. Some dietary constituents reduce bioavailability. Phytate, found in products made from wholegrain cereals, can bind and hence reduce the absorption of calcium, iron, and zinc. Iodine absorption may be hindered by nitrates. Similarly, oxalate present in spinach and rhubarb binds any calcium present, making it unavailable for absorption. Also, an excess of one mineral may hinder the absorption of another by competing for the same transport systems in the gut, for example, excess iron reduces zinc absorption. This generally only becomes a problem when zinc intakes are already marginal. Unlike some vitamins, minerals are fairly stable in normal food processing and storage conditions.

COVID-19 Addendum

The COVID-19 pandemic has sparked enormous interest in the potential for improved nutrition to enhance resistance to infection by the virus and to reduce the severity of the disease. A limited amount of research has looked at some minerals. In particular, zinc and selenium have attracted interest. While some reports suggest that each of these minerals may possibly be of value, the evidence has been described as "observational and weak" [27].

According to epidemiological data, most deaths from COVID-19 are concentrated in the elderly with common comorbidities such as hypertension, diabetes, or obesity [28–30]. In general, this group of individuals has a higher prevalence of zinc deficiency, given that aging is associated with a progressive decline in zinc status in the body due to several factors, including reduced food intake, decreased nutrient absorption efficiency, and the use of medications. Similarly, obese individuals or those with chronic kidney disease often exhibit zinc deficiency [31].

Increasing zinc deficiency and particularly reductions in intracellular zinc levels in immune cells are associated with greater difficulty in mobilizing rare zinc reserves in the body of elderly individuals and, consequently, with the progressive dysregulation of immune responses, resulting in higher susceptibility to infectious diseases. In general, elderly individuals with chronic diseases or who are hospitalized have even lower levels of minerals than do healthy elderly individuals, which may be responsible for the high incidence of infections and age-related degenerative pathologies [31].

During an infection, an organism can mobilize zinc reserves for priority functions, such as those associated with the immune system, leading to a decrease in zinc levels and, possibly, to the lack of zinc to other less essential functions, such as the maintenance of smell and taste, senses often affected in patients with COVID-19. This notion agrees with the triage theory cited above [30, 31].

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Nutrition and the Gut Microbiome

36

Charles B. Chen, Chetan Mandelia, and Gail A. M. Cresci

Keywords

Gut microbiome · Gut dysbiosis · Early-life colonization · Prebiotics · Probiotics · Fermented foods

Key Points

- The gut microbiome plays an important role in supporting health.
- Diet is a main environmental factor which influences the structure and stability of the gut microbiome.
- Many chronic diseases are associated with gut dysbiosis.
- In addition to altering dietary composition, dietary supplementation with prebiotics, probiotics, and consumption of fermented foods are current nutrition-based strategies utilized to reprogram the gut microbiome.

Introduction

Coevolving with their host, the trillions of microbes habituating within the human gut are vital for maintaining overall health (Fig. 36.1). A healthy gut microbiome is involved with normal gastrointestinal (GI) tract functions including digestion, absorption, immune function, and pathogen exclusion. Beneficial gut microbes also synthesize vital compounds for the host such as vitamins, enzymes, and short-chain fatty acids (SCFAs), the fermentation by-products of indigestible dietary polysaccharides. Many studies have sought to investigate the effect of dietary practices, medications, and diseases on the development and organization of the microbiome. This has led to the use of certain compounds,

C. B. Chen
Department of Pediatric Gastroenterology, University of Missouri Women's and Children's Hospital, Columbia, MO, USA

C. Mandelia
Division of Pediatric Gastroenterology, East Carolina University Brody School of Medicine, Greenville, NC, USA

G. A. M. Cresci (✉)
Department of Pediatric Gastroenterology, Cleveland Clinic Children's Hospital, Cleveland, OH, USA

Department of Inflammation & Immunity, Lerner Research Institute, Cleveland Clinic, Cleveland, OH, USA

Center for Human Nutrition, Digestive Disease and Surgery Institute, Cleveland Clinic, Cleveland, OH, USA
e-mail: crescig@ccf.org

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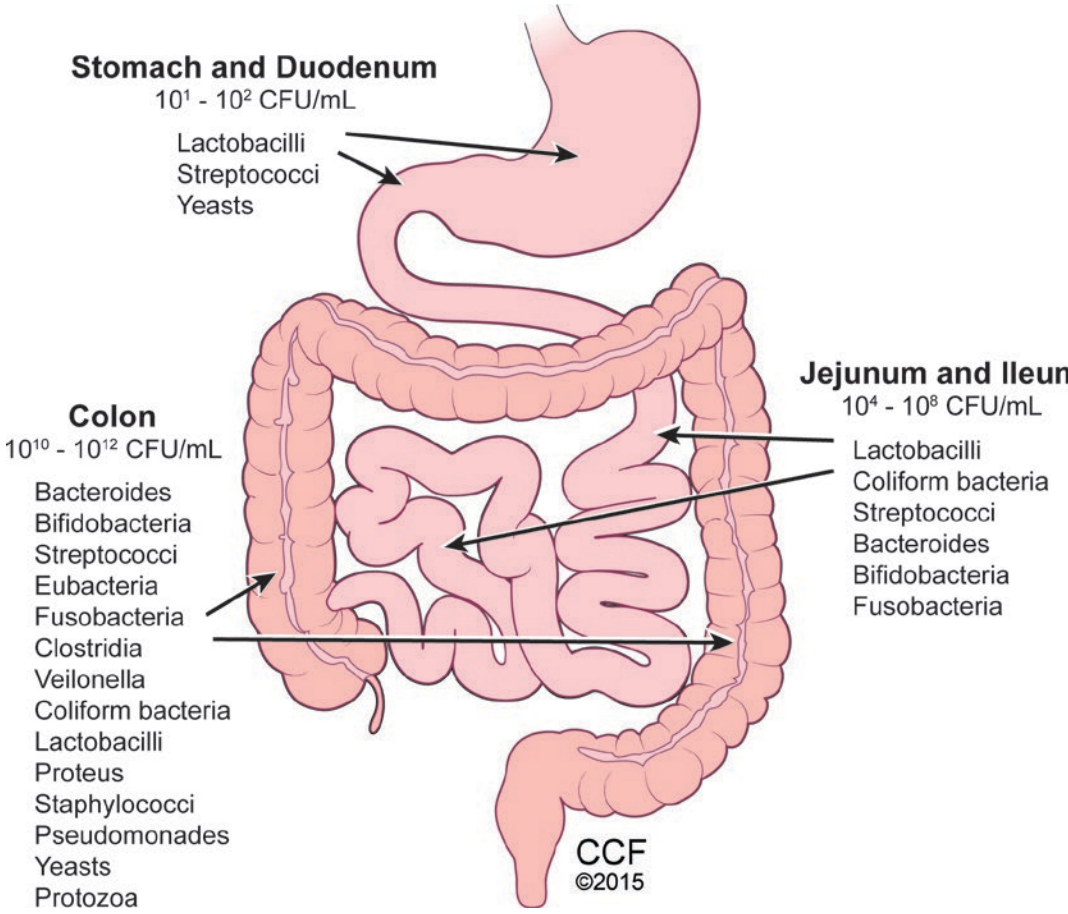

Fig. 36.1 Gut microbes colonizing the human intestinal tract. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2015–2020. All Rights Reserved)

such as probiotics, to alter the microbiome in order to confer benefits to the individual. Clinically observed are less diverse gut microbial profiles associated with chronic diseases ranging from metabolic disease (e.g., obesity, type 2 diabetes mellitus) to gastrointestinal disorders (e.g., inflammatory bowel disease, irritable bowel syndrome) and colorectal cancer. Gaining a better understanding of the crosstalk between the microbiota and the host allows physicians and researchers more opportunities to manipulate this interaction. Conversely, understanding the role of the microbiota in specific disease states may uncover targets for both pharmacologic and non-pharmacologic therapy**.**

Early Colonization of the Gastrointestinal Tract

Early-life microbial colonization of the gastrointestinal tract is critical in establishing the microbiome later in life. Initially, an aerobic environment, within the first few days of life the neonatal intestinal tract, is quickly colonized with anaerobic bacteria (e.g., *Clostridia* and *Bifidobacteria*), with *Bifidobacteria* being the most significant bacteria in the infant microbiome [1]. Early microorganisms also have important roles in providing specific substrates and a favorable environment for future microbe colonization.

Steward et al. proposed the gut microbiota undergoes three distinct stages of change within the first 2–3 years of life, progressing from a developmental phase at 3–14 months, to a transitional phase at 15–30 months, and finally to a stable phase at 31 months [2]. Gut microbial composition is relatively stable in adults due to multiple protective factors; however, these protective barriers are not as robust in the immature gastrointestinal tract of newborns [3]. By 3 years of age, the complexity of the microbiota resembles that of the adult. Multiple antenatal and postnatal factors help to determine the organisms that comprise the microbiome, as well as timing of their colonization. Figure 36.2 summarizes the influential role that maternal diet, medication use, mode of birth, and the feeding method after birth play in this process [4].

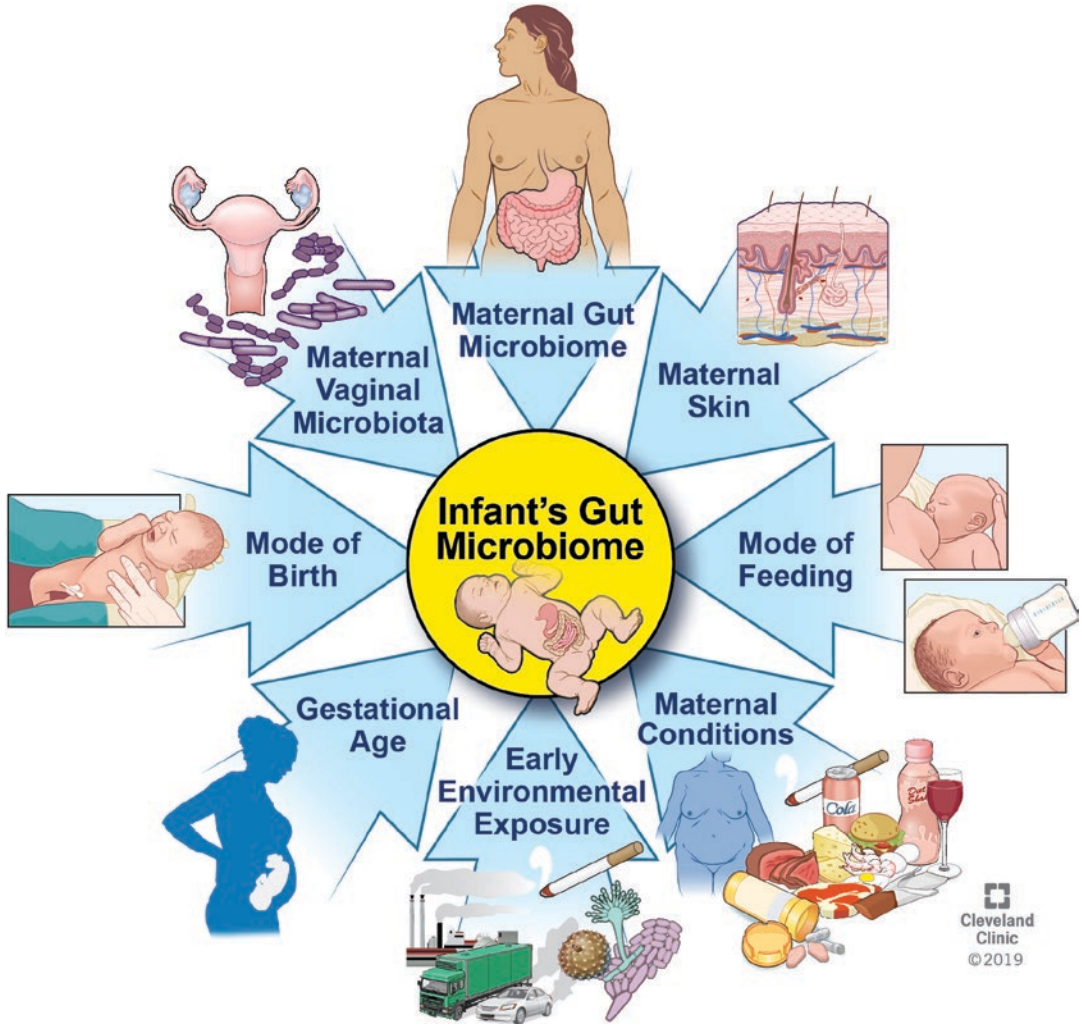

Fig. 36.2 Known factors influencing the development of the infant microbiota. Several factors play a role in shaping of the bacterial seeding in infants early in life. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2015–2020. All Rights Reserved)

Infant Delivery Mode

While colonization does take place in utero, the first significant colonization occurs with the infant mode of delivery [4]. Delivery through the birth canal exposes infants to maternal microbes composed of an array of aerobic and anaerobic bacteria [1]. Common organisms seen in vaginally delivered newborns include *Bifidobacteria* and *Bacteroides* [5]. In contrast, external exposures such as the hospital environment are more significant determinants of the microbiome in infants born by Cesarean section (C-section) [4]. For example, C-section infants have a higher population of *Clostridioides difficile*, a hospital-acquired pathogen. Overall, C-section infants have less diverse microbiomes and delayed colonization compared to those born by vaginal delivery [6].

Infant Feeding

Mode of feeding is the next major factor influencing early colonization, and many studies have investigated the impact of breastfeeding compared to formula feeding [4]. A large meta-analysis by Ho et al. of 684 infants showed that non-exclusively breastfed infants had greater intestinal microbial diversity with large populations of *Firmicutes* and *Bacteroidetes* in the first 6 months of life compared to exclusively breastfed infants [7]. Decreased microbiome diversity has been associated with increased risk of certain conditions such as infantile colic [1]. Greater populations of anaerobes have been found in formula-fed infants compared to more aerobic bacteria in breastfed infants. *Bifidobacteria* is one of the most well-represented species in breastfed infants and is thought to enhance resistance to pathogens and improve gut integrity [2]. Breastmilk also contains antibacterial proteins including lactoferrin and lysozyme which can inhibit growth of pathogenic microbes [1, 4]; the importance of breastmilk is also discussed in Chap. 3.

As human milk contains microbes and prebiotics which help colonize and shape the neonatal gut microbiome [4], evidence finds that even a small amount of formula exposure shifts the microbiome to a pattern consistent with formula-fed infants. In some cases, the addition of prebiotics and probiotics to infant formula has shown efficacy in changing the microbiome back to a breast-fed pattern [8]. With the introduction of more complex diets, the differences between the two types of microbiomes decrease [4]. Changes in fermentation and nutrient utilization occur with cessation of breast or formula-feeding and introduction of solids foods, and this process leads to the maturation of the gut microbiome [3]. As more is being learned about the gut microbiome, families may inquire into specific dietary modifications or feeding practices to prevent dysbiosis in infants. It is important to understand that decisions regarding infant feeding practices must take multiple other variables into account, such as other underlying medical conditions and the patient's growth.

Antibiotics

Infant and maternal exposure to medications, especially antibiotics, also plays a role in the maturation and composition of intestinal microbes [4]. Taipenen et al. performed a prospective clinical study on 149 neonates and found multiple differences in the microbiome of infants with exposure to perinatal antibiotics (either prophylactic antibiotics in the infant or intrapartum antibiotics in the mother) compared to those who did not receive antibiotics. There were increased populations of *Bacteroidetes*, decreased populations of *Firmicutes*, and a decreased presence of antimicrobial resistance genes in the antibiotic-free group [9]. The differences between the two groups continued to persist for at least 6 months after birth and were not ameliorated by the addition of *Lactobacillus reuteri* probiotics.

Maternal Diet

Maternal diet also has been shown to pass microbes to the infant through vertical transmission [4]. Lundgren et al. sequenced 16S rRNA from stool samples of 145 infants and reported that maternal fruit consumption intake was associated with a high abundance of *Streptococcus* and *Clostridium* in infants of vaginal deliveries. Maternal dairy intake was associated with higher levels of *Clostridium* in infants born by C-section, and seafood intake was associated with a higher abundance of *Streptococcus* [10]. The impact of maternal diet likely also depends on the mode of delivery, as opposing changes in microbial growth have been observed in vaginal compared to C-section deliveries even while consuming the same foods.

Other Factors

Other factors associated with microbial change include the social environment, especially household exposures [2, 11]. Lane et al. showed that the presence of siblings is associated with increased *Lactobacillus* abundance in the fecal microbiome. However, there were no significant associations between the composition of the household in terms of number of siblings or family members and the diversity of the microbiome [11]. Interestingly, the presence of animals in the household, especially furry pets, have been associated with microbiota maturation [2].

Many studies have explored the impact of the early microbiome on the immune system as well as chronic disease later in life. There is evidence suggesting that a limited microbial exposure early in life is associated with increased risk of atopic disorders [6]. Dysregulation of the microbiome is thought to alter the epithelial barrier in patients with atopic dermatitis. Many infections in the neonatal period, such as pneumonia, are associated with a decrease in microbiota diversity [6]. Studies on prebiotics and probiotics have shown that the microbiome can also affect immune function, although the exact effects of those supplements have not been well characterized.

Although many studies are performed in healthy infants, the microbiome in chronically ill infants may be quite different due to a variety of factors including antibiotics, parenteral nutrition, and mechanical ventilation. Critically ill patients have less diverse microbiomes with a higher proportion of pathogenic bacteria such as *Clostridium* and *Shigella* [6]. Certain organisms are thought to modulate gut permeability and systemic immune responses, which may lead to bacterial translocation and promote sepsis in high-risk infants. Because the clinical implications of microbiota alterations are not fully understood, further research is needed to better understand these mechanisms as well as the impact on long-term health.

Factors Influencing the Gut Microbiome

While the gut microbiome is established by 2–3 years of age, various factors contribute to its ongoing alteration. Host genetics modulate the microbiome through intrinsic mechanisms such as mucus, antimicrobial peptides, immunoglobulins, and microRNA. Although there is a heritable component, environmental factors such as diet and medications have been shown to play a larger role in determining gut microbial diversity [12] (Fig. 36.3).

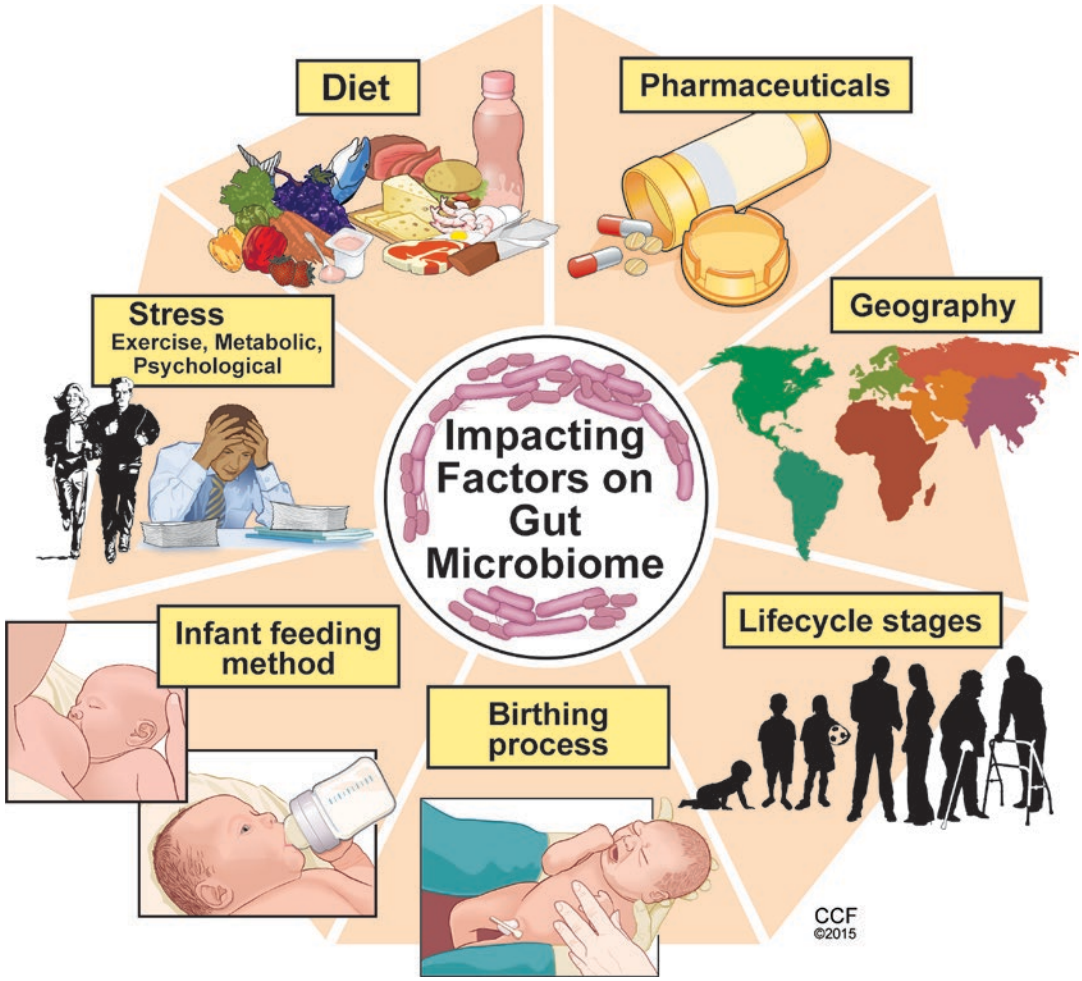

Fig. 36.3 Factors affecting the gut microbiome diversity. (Reprinted with permission, Cleveland Clinic Center for Medical Art & Photography © 2015–2020. All Rights Reserved)

Diet

What we eat has a direct effect on our gut microbiome, and a complex and varied diet is associated with increased gut microbial diversity. Diets high in fruits, vegetables, and fibers provide a higher load of indigestible polysaccharides, which can be fermented into SCFAs by the gut microbes in the distal gut. Major SCFAs produced by gut bacteria include acetate, propionate, and butyrate, and these have been associated with a variety of physiological effects including appetite regulation, gluconeogenesis, gut oxygen homeostasis, and apoptosis of colon cancer cells [13]. Higher production of SCFAs in subjects consuming a vegan or vegetarian diet has been shown to lower stool pH and suppress the growth of harmful gram-negative Enterobacteria, such as *E. coli* [14].

Several studies have evaluated the role of diet and geography on microbial diversity [14]. Yatsunenko et al. compared the fecal bacteriological profiles of healthy children and adults from Venezuela, rural Malawi, and US metropolitan areas [15]. While all populations showed increased bacterial diversity with age, the US population showed the least diversity. Enzymes involved in

degradation of amino acids and simple sugars were overrepresented in the US fecal microbiome reflecting consumption of a Western diet (high sugar, high protein, high fat, low fiber), whereas Malawian and Amerindian fecal microbiome had an overrepresentation of alpha-amylase reflecting their corn-rich resistant starch diet.

In a study by De Filippo et al., the gut microbiota of rural African children who were breast-fed until 2 years of age and then consumed a predominantly vegetarian diet rich in starch, plant polysaccharides, and fiber was compared with Italian children who were predominantly formula-fed and then consumed a typical Western diet high in animal protein, sugar, starch, and fat [16]. There were significant differences in the proportion of the four most populated bacterial phyla, with *Actinobacteria* and *Bacteroidetes* more prevalent in African children while *Firmicutes* and *Proteobacteria* were more abundant in European children. Bacteria that use indigestible plant polysaccharides to produce SCFAs and have a protective role against gut inflammation were found exclusively in the African children who also had four times higher butyrate and propionate levels.

One of the best-studied diets in gastrointestinal disorders is the low FODMAP diet which restricts short-chain fermentable carbohydrates and has been shown to be an effective treatment for irritable bowel syndrome (IBS), a topic also discussed in Chap. 19 by Liu, Hurt, and Camilleri. A low-FODMAP diet alters the gut microbiota by reducing the amount of indigestible substrates, such as fructans and galacto-oligosaccharides, which subsequently become available for colonic fermentation. Studies looking at the effects of a low-FODMAP diet on stool microbiota in patients with IBS have found significant alterations in the abundance of different species with reduced concentration of *Bifidobacterium*. The clinical relevance of these changes and their downstream effects are not yet fully understood, but there is evidence that a low-FODMAP diet leads to decreased colonic gas production, and responsiveness of IBS patients to this diet can be predicted by fecal bacterial profiles [17, 18].

Food additives, such as emulsifiers and artificial sweeteners (e.g., sucralose, aspartame, and saccharin), have been shown to have negative effects on the gut microbiota. While a gluten-free diet has beneficial effects on the microbiome of patients with Celiac disease, healthy people on a gluten-free diet have a lower abundance of beneficial microbial species [13].

Medications

The drug-microbiome-host interactions are complex, and several classes of medications such as proton pump inhibitors (PPIs), NSAIDs, antipsychotics, antibiotics, antidiabetics, and chemotherapeutics have been shown to have significant effects on the composition of the gut microbiome [19]. Prolonged use of PPIs suppresses normal gastric flora and decreases diversity of commensal microbes and overgrowth of pathogens. PPIs have been linked to the development of small intestinal bacterial overgrowth (SIBO) although data is conflicting. Long-term PPI use has been shown to be associated with increased risk of development of *C. difficile*-associated diarrhea [20].

Antibiotics, targeting pathogenic as well as commensal microbial communities, can lead to dysbiosis and growth of unwanted microbes such as *C. difficile*. Through biliary excretion, intravenous antibiotics also negatively affect the gut microbiome. Deceased microbial diversity is seen after antibiotic treatment, and even though most of the microbiota returns to pretreatment levels, some members are lost from the community indefinitely [14]. Low doses of antibiotics are widely used in livestock farming, and studies have shown an obesogenic effect of such antibiotic exposure through food on humans. There is a growing body of evidence that exposure to antibiotics in childhood is associated with increased risk of diseases including obesity, types 1 and 2 diabetes, inflammatory bowel disease, celiac disease, allergies, and asthma [4, 14].

Stress

Stress – physiological, pathological, or emotional – can lead to alterations in gut microbiome through release of neurochemical mediators by the host. Physiological stress, such as high-intensity exercise, has been positively correlated with enhanced microbial diversity, while patients with critical illnesses, such as systemic inflammatory response syndrome (SIRS), have significantly unfavorable alterations [14]. Redistribution of splanchnic circulation in critically ill patients causes intestinal hypoperfusion and gut ischemia which plays an important role in promoting infectious complications and multi-organ dysfunction syndrome. Alterations in the gut microbiome occur within hours of a metabolic insult and do not revert back to the pattern seen in healthy controls [14]. Attempts to modify the gut microbiome to improve clinical outcomes in critically patients have been studied, and it appears that probiotic supplementation improves outcomes, but further research is needed before general recommendations can be made [14].

Nutritional Modulation of the Gut Microbiome

Overview

Probiotics, prebiotics, and fermented foods all play a role in modulating the gut microbiome in a variety of ways. These effects can result in gut microbial compositional and functional changes which can lead to therapeutic effects including resolution of clinical symptoms or remission of disease. While numerous studies have proposed the use of certain probiotics, prebiotics, and fermented foods, their clinical utility for many conditions is not well defined, and their mechanism of action needs to be better elucidated.

Probiotics

Probiotics are live nonpathogenic microorganisms that can produce beneficial effects when introduced in adequate amounts into a host [14]. These are generally bacteria or yeast and may consist of one or multiple strains. Well-known probiotics include *Lactobacillus*, *Bifidobacterium*, and *Saccharomyces* species. Probiotics may affect the gut microbiome in multiple ways, and their effects are strain specific. Certain strains have been demonstrated to be antagonistic against pathogens by yielding by-products that inhibit the growth of other microorganisms (e.g., bacteriocins, antimicrobial peptides) or competing for the same substrates; enhancing the integrity of the intestinal barrier and thereby decreasing bacterial translocation; and also modulating cytokine release and affecting the metabolic activity of the microbiome [14]. *Lactobacillus reuteri*, for example, releases an antimicrobial compound called reuterin which directly kills pathogenic microbes [14].

While there is a surprising lack of agreement regarding the efficacy of probiotics in the treatment of many diseases, probiotics are frequently used as an adjuvant therapy. The effectiveness depends on the strain of the probiotic, its targeted mode of action, as well as the disease manifestation. In particular, probiotics have been used in various GI conditions including IBS, necrotizing enterocolitis, inflammatory bowel disease, small intestinal bacterial overgrowth, and antibiotic-associated diarrhea, as well as non-GI-related conditions such as critical illness, eczema, and vaginal candidiasis [14].

Prebiotics

Prebiotics stimulate the growth of specific microorganisms (e.g., *Lactobacillus*, *Bifidobacterium*) that subsequently confer a benefit to the host. Prebiotics are typically nonsynthetic or synthetic indigestible polysaccharides (e.g., inulin, fructo- or galacto-oligosaccharide) that are fermented by the host commensal gut microbes [4, 14]. Fermentation of prebiotics can lead to a variety of biochemical effects such as decreasing the intestinal pH which leads to a less favorable environment for pathogen survival [14]. Prebiotic fermentation yields the SCFAs, acetate, propionate, and butyrate. The interaction of SCFAs with receptors expressed in the intestinal mucosa and on immune cells can positively alter immune and inflammatory responses [14]. Additionally, butyrate is the primary fuel source for the colonocyte and is known to support intestinal epithelial barrier integrity, regulate water and electrolyte absorption, mediate immune and inflammatory responses, and as a histone deacetylase inhibitor, butyrate affects gene expression [14]. SCFAs can also enter circulation and affect distant organ systems.

Fermented Foods

Fermented foods are an important component of the human diet, and their consumption may contribute to gut microbial composition. Food fermentation is centuries old and used as a means to preserve foods; however, in the past few decades, fermented foods are becoming more popular for health purposes. Commonly fermented foods include yogurt, kefir, kombucha, kimchi, kefir, and sauerkraut. Fermentation of carbohydrates involves the enzymatic action of various microbes (e.g., bacteria, yeasts, molds) and yields various organic acids (e.g., alcohol, glucuronic acid), metabolites, and gases [21]. Resultant metabolites (e.g., vitamins, polyols) may confer multiple benefits such as the production of antimicrobial molecules that may lengthen preservation of foods and help with pathogen elimination. While the microbes found naturally in fermented foods are not probiotics, fermented foods may also have added probiotics (e.g., yogurt, kefir). Adding probiotics to fermented foods provides a food source for the probiotic assisting in probiotic viability, and the food matrix of the fermented food may provide a buffering effect which protects the probiotic from the upper GI tract acidic environment. Through the fermentation process, food ingredients that may not be tolerated (e.g., lactose) are digested by microbes during the fermentation process making the fermented food now tolerated, such as fermenting milk into yogurt or kefir [22].

Demonstrating clinical efficacy of fermented foods on alleviating health conditions is challenging due to multiple confounding factors, such as inconsistency with batch-to-batch metabolic by-products released in the food. Nonetheless, evidence is emerging regarding health benefits of fermented foods, such as the beneficial effects of kefir consumption in eliminating *Helicobacter pylori* infections [22].

Nutritional-Targeted Gut Microbiome Reprogramming and Chronic Diseases

Investigations into the role of ingesting probiotics, prebiotics, and fermented foods on altering gut microbial composition and subsequent disease processes are ongoing. There is evidence that probiotics including *Lactobacillus* and *Bifidobacterium may be effective in decreasing obesity. Lactobacillus rhamnosus GG* administered to mothers 4 weeks prior to expected delivery and to infants within the first 6 months of life was shown to improve appropriate growth at 1 and 4 years of age [4]. *Prebiotics have been shown to* improve glucose and lipid metabolism, and modulation of the intestinal microbiome affects entero-endocrine cells that results in changes in energy homeostasis and food intake [14]. Fermented foods such as yogurt and kimchi may also decrease obesity.

Evidence supports that manipulation of the microbiome in inflammatory bowel disease plays a role in the disease course. The probiotic supplement VSL #3® contains eight probiotic strains and in a number of clinical trials involving patients with ulcerative colitis (UC) and pouchitis, it has been shown to be effective in maintaining remission [23]. However, the data is less promising in patients with Crohn's disease. Prebiotics have been tested mostly in animal and in vitro studies, and there is clinical evidence that inulin supplementation can reduce inflammation in both UC and pouchitis [24]. In IBS, VSL #3® along with other *Lactobacillus* species-containing probiotics have been found to improve clinical symptoms and have been successful in treating abdominal pain-related functional gastrointestinal disorder [23]. The evidence for prebiotics is less clear, and they are not well studied in pediatric patients.

Probiotics have been shown to be most efficacious in reducing the incidence of antibiotic-associated diarrhea and treatment of acute infectious diarrhea. In particular, *Lactobacillus GG* and *Saccharomyces boulardii* have been widely tested with multiple studies showing their efficacy in decreasing the duration of antibiotic-induced diarrhea and stool frequency [14, 25]. While the clinical improvements may be modest, the safety of probiotics has made it a popular adjunct therapy to more conventional medications in the management of diarrhea.

Summary

Over the past decade, growing evidence has emerged that supports the important role of the gut microbiome in maintaining gut homeostasis and overall health. Changes in the microbiome can also play a significant role in altering or exacerbating certain disease processes, such as inflammatory bowel disease and irritable bowel syndrome. We are beginning to learn more about how early-life colonization is important for later-in-life chronic disease development. Our appreciation is also growing regarding environmental factors which impact the gut microbiome and contribute to pathology.

While many studies have been published on the impact of particular medications, probiotics, prebiotics, and foods on the gut microbiome, their overall efficacy has not been well characterized. Further research is needed to better investigate the mechanism by which these compounds affect the microbiome composition and function. While probiotics and prebiotics are becoming increasingly popular as adjunctive therapies, more studies are needed to examine their long-term effects and safety. Appropriate choice of the probiotic strain, dosage, and timing of delivery should also be determined for the condition of interest. The impact of diet on the microbiome also should not be underestimated as the gut microbiome composition is enhanced with a diet rich in fermentable fibers (e.g., fresh fruits and vegetables, resistant starches), and certain fermented foods may impact multiple disease processes.

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Part VII

Influencing Dietary Health Decisions

How to Create Nutritional Behavior Change

37

Katherine M. Appleton and Emmy van den Heuvel

Keywords

Eating behavior · Food choice · Behavior change · Behavior change techniques

Key Points

- Eating behavior is important for and affects health.
- Eating behavior and food choice are determined by many factors.
- Behavior change interventions typically consider the many factors that affect eating behavior.
- Behavior change techniques target specific factors that encourage or discourage behavior change.
- Behavior change techniques are effective in creating nutritional behavior change.

The Importance of Behavior in Nutrition

Behavior is important for and affects health. Unhealthy nutrition habits (behaviors) are recognized as major risk factors for chronic disease morbidity and mortality [1]. Understanding how nutrition influences physiology is fundamental to nutrition science, but this knowledge will have little impact on health if we do not know how to also address eating behavior, that is, how to encourage people to eat certain foods and avoid others. Human food choice is not biologically programmed to meet exact nutritional requirements; we can gain most nutrients from different food sources. Nutritional health is a product of eating behavior and food choices.

Many people do not eat according to nutritional recommendations [2, 3]. Healthy eating campaigns typically focus on education or providing information on nutritional requirements and health consequences, but these campaigns have achieved only limited success at reducing disease incidence and burden [1]. Health promotion messages may improve a person's knowledge, attitudes, and intentions toward healthy eating. However, these campaigns typically ignore a myriad of other factors that influence eating and that could facilitate or hinder behavior change. The failure of a patient to

K. M. Appleton (✉)
Research Centre for Behaviour Change, Bournemouth University, Poole, UK
e-mail: k.appleton@bournemouth.ac.uk

E. van den Heuvel
Research Centre for Behaviour Change, Bournemouth University, Poole, UK

Laboratory of Behavioural Gastronomy, Maastricht University, Maastricht, Netherlands

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implement recommended dietary changes can be discouraging to both the patient and the clinician. Believing that people should take more responsibility for their health and can change to a healthy lifestyle without help can be seen as simplistic or even unrealistic [1]. This chapter discusses how to improve healthy dietary behavior changes.

Eating Behavior and Food Choice

Eating behavior has many different determinants, and the salience of these determinants and their influence on food choices will depend on the individual and the situation. Nutritional knowledge is positively correlated with healthy food intake [4]. Understanding the health consequences of a change in diet is important in order to both increase awareness of the need for change and to create the intention to change a behavior [5]. Healthy eating behavior can therefore be based on rational decision-making.

However, for many everyday food choices, an intention to eat healthily is in competition with desires, habits, impulses, and social pressures [6]. Eating behavior and food choices are not only based on rational consideration but also on less rational, automatic determinants, such as preferences, habits, emotions, and social or environmental cues [6]. Hedonic appeal (whether a person likes a food) has a strong influence on food intake independent of hunger [7]. Indeed, hedonic reasons can have a greater impact on eating than health-based reasons even for healthy foods [8, 9]. Many eating behaviors are habitual; for example, a person may habitually consume a cookie with their morning coffee [10]. Determinants of food choice also include emotions and mood, where some people are likely to eat different amounts and different types of foods when they experience different emotions [11]. Eating behavior can be impulsive, where immediate rewards (e.g., sensory appeal or relief from depressed mood) tend to be preferred over longer-term rewards (e.g., healthy aging or weight control) [12]. Additionally, eating behavior is complicated by the abundance of food in the environment, and overabundance can promote excessive food intake [13]. These influences mean that food choice can be unplanned, mindless, or even irrational [6]. Understanding how these rational and irrational influences determine eating behavior is helpful in providing an understanding of the everyday barriers and facilitators that may hinder or encourage people to adjust their eating behavior.

Behavior Change and Behavior Change Techniques

The best dietary prescriptions based on evidence-based practice can still result in continued unhealthy eating and frustration for clinician and patient when there is no dietary compliance on the part of the patient. If eating behavior and food choice stem from a range of determinants, including knowledge, it stands to reason that interventions intended to change eating behavior and encourage healthy food choices need to involve more than knowledge provision. Thus, behavior change interventions will be more effective if they also consider factors like social influences, the physical environment, and motivation [1].

Behavior change techniques (BCTs) are defined as "observable, replicable, and irreducible component[s] of an intervention designed to alter or redirect causal processes that regulate behavior" [14]. BCTs are evidence-based determinants of specific behaviors or evidence-based strategies to change behavior. BCTs have long been recognized as helpful in promoting changes in behavior, but, until recently, there was little consensus on definitions and terminology.

In 2008, Michie and colleagues began defining BCTs and developing BCT taxonomies after systematically reviewing the published research [14–16]. The most recent BCT taxonomy (v1) [14] consists of 93 different BCTs used for general behavior change, classified into 16 different categories: goals and planning; feedback and monitoring; social support; shaping knowledge; natural

consequences; comparison of behavior; associations; repetition and substitution; comparison of outcomes; reward and threat; regulation; antecedents; identity; scheduled consequences; self-belief; and covert learning [14]. The CALO-RE taxonomy consists of 40 BCTs and is specifically focused on healthy eating and physical activity behavior [15]. BCTs relate both to behaviors, such as healthy eating and weight loss, and to intended outcomes, such as a weight-loss goal or improved vitality, and can be applied separately or in combination, on an individual basis or as part of a large group intervention. Some of the BCTs that are most commonly used to change nutritional behavior are summarized, with examples, in Table 37.1.

Table 37.1 Overview of the most commonly used BCTs in interventions focused on healthy eating [20–22]

BCT	Definition/description	Examples
Instruction on how to perform a behavior	Advise or agree on how to perform the behavior	Suggest healthy shopping practices by making and adhering to a shopping list Take cooking classes to help increase vegetable consumption Avoid tempting high-energy snacks by supplying your own healthy options Eat the fruit first, then the chocolate cookie
Information about health consequences/consequences of behavior in general[a]	Provide information (e.g., written, verbal) about health consequences of performing the behavior	Provide information about diet-related health conditions Include information on added risks, such as poor mental health and low well-being Provide information on disability and/or mortality rates related to obesity Provide information on the health benefits of eating more vegetables
Action planning	Prompt detailed planning of the performance of the behavior (must include at least one of frequency, duration, intensity, or context)	Plan healthy evening meals for the whole week to avoid the need for takeaways Decide on the number of drinks you will have in advance of meeting friends Plan where in the day you will add some fruit (at least one occasion) Decide to avoid sugary snacks at work
Goal setting (behavior)	Set or agree on a goal defined in terms of the behavior to be achieved	Aim to eat five portions of fruit and vegetables per day Aim to eat one more portion of fruit or vegetables each day Swap full-sugar beverages for low-sugar versions Replace high-fat desserts with fruit options
Goal setting (outcome)	Set or agree on a goal defined in terms of a positive outcome of the behavior	Aim to lose 1 lb. a week for the next month Aim to lose 2 inches around your waist before your holiday Aim to fit into a smaller dress size Aim for noticeably clearer skin

(continued)

Table 37.1 (continued)

BCT	Definition/description	Examples
Feedback on behavior/on performance[a]	Monitor and provide informative or evaluative feedback on performance of the behavior	Record and review daily intake of sugary food items Consider the value of this consumption Record and review your vegetables consumed Record and review your alcohol consumption
Social support (unspecified)	Advise on, arrange, or provide social support (e.g., from friends, relatives, colleagues, "buddies," or staff)	Describe your goal to your partner and ask for his/her support Identify friends who will support your target behavior, explain your aims, and ask for their support Find a "buddy" with a similar goal and support each other Consider counseling or therapy from a professional, if this may be useful
Social comparison	Draw attention to others' performance to allow comparison with the person's own performance	Provide information on national averages for fruit and vegetable consumption Provide information on personal fat intake, and the fat intake in similar gender and/or age groups Consider previous consumption at a more desirable weight Ask for details about the eating patterns of a friend/family member with a healthy lifestyle and look for differences

[a]Some BCTs have different labels but similar definitions in the different taxonomies

The Selection of Behavior Change Techniques

There are a number of available BCTs. This begs the question: How do I know which BCT will work best for me or my patient?

It is important to recognize that all behavior is individual, and there is no "one size fits all." Ideally, BCTs are selected from the range available through careful consideration of the facilitators for and barriers toward the desired behavior. These facilitators and barriers can be gained at the individual level through direct contact with the patient. It may be possible for a patient to identify their own facilitators or barriers to nutritional change, or these may need teasing out or become apparent during a consultation. Once ascertained, these facilitators and barriers can be used directly to suggest some BCTs. For example, one individual may struggle to eat healthily because they do not know which foods are healthy, they do not have many healthy foods available, and they are unwilling to try new foods. This individual may benefit from BCTs associated with shaping knowledge, goals and planning, reward and threat, and covert learning. For another individual, healthy eating might depend more on the consumption patterns of their partner and their confidence in their own abilities to make changes. This individual might benefit from BCTs associated particularly with social support, identity, and self-belief.

Different BCTs will be more or less attractive to different individuals, or in different situations; thus, practitioners working on an individual basis tend to offer a number of potentially useful BCTs to their patient and ask the patient to choose and implement those that they feel are most appropriate for them.

Alternatively, facilitators and barriers can be applied to psychological theory, and the theory then used to suggest BCTs. For larger groups and larger interventions, psychological theories are often used, to include the Theory of Planned Behavior [5], Social Cognitive Theory [17], the Transtheoretical Model [18], and, more recently, the COM-B Model [19]. On a group basis, interventions tend to be developed based on the most salient barriers and facilitators identified from multiple opinions from several individuals. Interventions tend to be developed, therefore, so as to involve a range of BCTs with the hope of covering a variety of potential issues. It is unusual, consequently, for all aspects of an intervention to impact any one individual. Instead, it is more likely that specific BCTs will impact specific individuals, possibly in specific situations, at specific time points, etc.

The Effectiveness of Behavior Change Techniques

By definition, all BCTs are effective to some degree, for some individuals, in some situations, and so on. Several systematic reviews and meta-analyses have attempted to identify the BCTs with the greatest impact on nutritional outcomes [20–24]. These reviews have focused solely on nutritional outcomes in young adults [20], all adults [21], and retired adults [22] or consider combined interventions targeting nutritional behaviors and physical activity [23, 24]. The BCTs that were considered most effective in the reviews that focus solely on nutritional outcomes [20–22] are given in Table 37.2.

Table 37.2 Overview of the most effective BCTs in interventions focused on healthy eating [20–22]

BCT	Definition/description	Examples
Habit formation	Prompt rehearsal and repetition of the behavior in the same context repeatedly so that the context elicits the behavior	Make it a habit to consume a piece of fruit with morning coffee in place of a cookie so that after a few weeks reaching for fruit becomes automatic Make it a habit to alternate alcohol and soft drinks when out in the evening Make it a habit to supply a healthy salad lunch instead of buying a less healthy one Make it a habit to eat a healthy snack late afternoon to avoid getting hungry and eating a larger evening meal
Salience of consequences	Methods specifically designed to emphasize the consequences of performing the behavior with the aim of making them more memorable	Highlight clear skin following increased daily water intake Notice increased afternoon energy and performance with the reduced consumption of large lunch meals Notice reduced hangovers with the consumption of less alcohol Look at pictures of health consequences of a diet high in saturated fat to highlight the dangers of continuing similar eating habits (like the pictures of diseased lungs on cigarette packets)
Generalization of target behavior	Advice to perform the target behavior, which is already performed in a particular situation, in another situation	Try reducing sugar in coffee now that you can do this in tea Try low-fat desserts now that you know these swaps can work for beverages Try avoiding cookies at home now that you have achieved this at work Try new types of vegetables as you have been able to try new dishes consisting of foods that you already know

(continued)

Table 37.2 (continued)

BCT	Definition/description	Examples
Reduce negative emotions	Advise on ways of reducing negative emotions to facilitate performance of the behavior	Suggest alternatives to chocolate that may also improve mood, such as phoning a friend or taking a bath Focus on liked fruit as opposed to disliked vegetables Set up rewards or positive experiences in association with increased salad intake Advise on stress management skills to reduce anxiety in case anxiety induces overeating
Verbal persuasion about capability	Tell the person that they can successfully perform the target behavior, arguing against self-doubt, asserting that they can and will succeed	Provide advice to increase confidence Suggest memories of other achievements Provide reminders of previous successes Suggest counseling or therapy from a professional, if this may be helpful
Information about antecedents	Provide information about antecedents (e.g., environmental situations, emotions) that reliably predict performance of the behavior	Notice unhealthy takeaway consumption following a few drinks after work Highlight a pattern of reaching for chocolate after conversations with certain friends Notice increased fruit or healthy food consumption following visits to the local park Notice unhealthy food shopping when going to the supermarket when you are hungry
Barrier identification/ Problem-solving[a]	Prompts to think about factors influencing the behavior including potential barriers, and identify the ways of overcoming barriers and/or increasing facilitators	Identify why fruit and vegetables are not sufficiently consumed, and how these barriers can be overcome Ascertain why cookies are consumed with coffee and how this habit can be changed Identify why one drink always leads to several Keep a record of situations in which you tend to buy fast food and think about how these situations can be avoided
Planning social support or social change/Social support (practical)[a]	Prompts to plan how to elicit social support from other people to help him/her achieve their target behavior/outcome	Describe your goal to your partner, and ask him/her to help by eating the same meals Identify friends who share your goals to eat healthier and make plans to work together Join a weight-loss support group and attend regular meetings Consider counseling or therapy from a professional, if this may be useful
Use of follow-up prompts	Follow-up components are gradually reduced in intensity, duration, and frequency over time	Identify support that can be lessened to improve confidence and reduce reliance Switch face-to-face counseling sessions to telephone- or online-based support Switch weekly counseling to every 2 or 4 weeks Agree to a follow-up email 1 month and 6 months after the appointment so your clinician can ask about your progress
Goal setting (outcome)	Set or agree on a goal defined in terms of a positive outcome of the target behavior	Aim to lose 1 lb. a week for the next month Aim to lose 2 in around your waist before your holiday Aim to fit into a smaller dress size Aim for noticeably clearer skin

[a]Some BCTs have different labels but similar definitions in the different taxonomies

In these reviews, "effective" was defined as having a significant impact on intervention effect size in statistical analyses, or inclusion of the BCT in over 80% of effective interventions.

The Value of Behavior Change Techniques

The value of BCTs for changing behavior is clearly demonstrated in the literature. It may, however, take some work to identify the barriers and facilitators to creating behavior change. Clinicians and patients may need to try a few potential solutions before finding one that is successful; thus, the use of BCTs can be time-consuming and costly. Furthermore, the barriers and facilitators to a behavior can change throughout the process of behavior change; thus, reidentification, reselection, and reassessment may be necessary and may be necessary repeatedly.

BCTs are currently offering a welcome promise for behavior change for a number of health behaviors, including nutritional and eating behavior. By targeting individual-specific barriers and facilitators, BCTs enable a focused, problem-solving, and supportive approach intended to identify problems and find solutions. As with any problem, the solution may not be easy or straightforward, but the range of BCTs available provides plenty of opportunities for success. We look forward to future developments and the collection of considerable future work attesting their value.

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Suggested Further Readings

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Nutritional Status: An Overview of Methods for Assessment

38

Catherine M. Champagne

Keywords

Nutrition assessment · Dietary assessment methods · Body composition · Adolescents · Elderly Healthy eating · Physical examination · Laboratory tests for nutritional status

Key Points

- Dietary intake and consumption patterns are challenging areas to evaluate accurately.
- Body mass index (BMI), body composition, and routine laboratory testing supplement the information obtained from dietary history and provide further insight into the individual's biological state.
- Poor diets are observed at various ages, particularly in adolescents and the elderly, often for very different reasons due to the aging process or other conditions.
- Characterizing a poor diet is equally difficult, since the food supply is vast with thousands of choices in the marketplace.

Introduction

A wide spectrum of nutritional assessment tools is available that can aid in determining the health of an individual. This critical assessment process typically includes in-depth evaluation of both subjective data and objective evaluations of an individual's food and nutrient intake, components of lifestyle, and medical history. Such an assessment provides an overview of nutritional status; it focuses on nutrient intake analysis of the diet, which is then compared with blood tests and physical examination.

With comprehensive data on diet and biological parameters, the physician or other healthcare professional can more accurately assess a person's nutritional status. Decisions can then be made on an appropriate plan of action to either maintain current health status or refer to counseling or other interventions that would enable the individual to reach a more healthy state. Only with sufficient anthropometric, biochemical, clinical, and dietary information can a plan be drafted.

C. M. Champagne (✉)
Pennington Biomedical Research Center, Baton Rouge, LA, USA
e-mail: catherine.champagne@pbrc.edu

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Many years ago, one of the main objectives of assessing nutritional status was to improve nutritional status of malnourished individuals suffering from protein and micronutrient deficiencies, in addition to caloric deficiencies. Essential to determining nutritional status of the individual, we must consider nutritional needs of those who are suffering from undernutrition as well as overnutrition. With the advent of the new "obesity epidemic" in most states, we have to deal with energy-dense diets as a contributing factor, rather than nutrient dense diets which would enable individuals to consume adequate nutrition as opposed to high-calorie, nutrient-poor diets.

Associated with the epidemic of obesity is the increased health comorbidities for both men and women. The body mass index (BMI), defined as weight in kilograms divided by height in meters squared (kg/m^2), remains the initial criterion for assessing overweight and obesity. Overweight is commonly defined as a BMI greater than or equal to 25, and obesity is defined as a BMI greater than or equal to 30. Measurement of the waist circumference to gauge the degree of central adiposity is also recommended.

Obesity is associated with the presence of chronic disease risk factors, including cardiovascular disease, some cancers, type 2 diabetes, hypertension, and many others, such that The Obesity Society in a 2018 Position Statement classified obesity as a disease [1]. A report by Flegal et al. [2] indicated that individuals who were underweight or had obesity were associated with excess mortality compared to individuals of normal weight but that those individuals who were overweight (BMI 25–29.9) had reduced mortality – these analyses were found after adjusting for sex, smoking status, race, and consumption of alcohol.

Principles of Nutritional Assessment

There are a number of instruments and questionnaires that can help to identify potential areas of concern regarding caloric intake and perhaps a lack of essential nutrients for health.

Food Frequency Questionnaires: Diet History Questionnaires

Currently, there are very extensive validated diet history questionnaires available from the National Cancer Institute (NCI) that are very efficient for the identification of dietary components and help in the identification of nutritional status, particularly malnutrition, in conjunction with biochemical measurements. The Diet History Questionnaire (DHQ) was originally developed in 2001 (DHQ 1) with the most recent version (DHQ III) in 2018. The DHQ III was based on NHANES 24-hour dietary recall data covering years 2007 through 2014. Paper forms are not available, but researchers can create an account for studies by contacting the NCI at the following URL to set up a study: https://epi.grants.cancer.gov/dhq3/history.html [3].

NCI's Epidemiology and Genomics Research Program has shorter dietary questionnaires in the public domain for clinicians and investigators that are focused on targeted intakes (e.g., fruits, vegetables). These screening tools can be used to determine percentage of energy from fat, fiber, added sugars, whole grains, calcium, dairy products, and red and processed meats are also available from NCI. These short dietary assessment instruments, along with the scoring procedures, may be found at the following URL: https://epi.grants.cancer.gov/diet/screeners/ [4].

A food frequency questionnaire – often referred to simply as FFQ – is one means of establishing what usual intakes are, and, depending on the care taken by the patient in filling out this information and how carefully it is reviewed with them, valuable insight on his or her usual diet can be gleaned. In actuality, the DHQ is an FFQ, but other investigators, such as Walter Willett, have developed FFQs for their own studies (https://snaped.fns.usda.gov/library/materials/harvard-willett-food-frequency-questionnaire) [5].

Diet and Lifestyle History

An example of a basic nutrition and lifestyle history is included in Box 38.1. Sample questions can be used depending on the information desired. Questions are asked about the previous day's food intake, specific foods, lifestyle, and behaviors. These can be helpful in providing information that may be predictive of successful weight management and disease risk but likely will involve more time than the physician has for the visit. Some investigators have weighed in on the need to perform a lifestyle history as an essential component of the medical history [6].

Box 38.1 Sample Questions for Basic Nutrition and Lifestyle History

I would like to know everything you ate and drank yesterday.
When did you first have something to eat or drink, and what did you have? _____.
When was the next time you ate or drank something? _____
Do you avoid any foods for any reason (religious, cultural, likes/dislikes, food sensitivity or allergy)?
Yes __ No ___ Which ones? _____.
How often do you eat away from home? _____.
Do you drink alcoholic beverages? Yes ___ No ___ How often? _____.
How much? _____.
Do you take any vitamin, mineral, or other supplements? Yes _____ No _____.
What kind? _____ How much? _____.
Do you exercise? Yes ___ No ___ What kind? _____ How often?_____.
Do you smoke cigarettes? Yes _____ No ____.
How many hours do you sleep in a typical night? _____.
Has your weight changed in the past 5 years? Yes ___ No ___ How? _____.
Are you trying to lose (or gain) weight? Yes ___ No ___ How? _____ Why? _____.
What personal support do you have in your life? _____.
Are you on a special diet? Yes ____ No ____ What kind? _____ Why? _____.
Do you have problems with planning and preparing meals for yourself or your family?

Assessing Current Dietary Intake

Several options exist for collecting current dietary intake and eating patterns. The 24-h recall is a simple method that can be very helpful, especially if those foods are representative of usual intake. The methodology promoted in this type of assessment is best described as a multiple pass method, which is the current method used for reporting foods consumed in the *What We Eat in America* Survey [7]. Using this procedure, one obtains a quick listing of foods from the individual, probes for foods commonly forgotten (condiments, common foods added to other foods, etc.), and collects the time and information about the eating occasion, which may further prompt the individual's memory. A more detailed cycle follows, and the description, portion size, and additions to foods are collected; probes for omitted foods are used for what may be consumed between main meals (e.g., snacks). The final step in the process is a question that asks whether anything else has come to the individual's memory, even in very small amounts. This methodology is used in the National Health and Nutrition Examination Survey (NHANES) to track what Americans are eating and eventually to inform public policy [8].

The 24-h recall may be helpful in targeting behaviors linked to obesity and disease risk. Information on intakes of fat, sugar, and unhealthy food options (fast-food restaurants and foods high in sugars or high-fructose corn syrup) may enable the physician or healthcare professional to counsel the patient more effectively. However, due to limitations of time in a primary care setting, this recall is most efficiently collected by a registered dietitian nutritionist (RDN) who most likely will be tasked with counseling the patient.

A less attractive, though more burdensome option, is to have the patient keep a record or diary of foods consumed over a specified period of time. This would mean an additional return visit with the patient in a week or two following the initial visit or having the subject maintain a longer record and return it to the physician's office without an additional visit. This allows the dietitian to review it and discuss the information with the healthcare professional. A number of problems with dietary intake information have been observed: the patient may not accurately report foods consumed or portion sizes due to inaccurate recall; they may choose to modify intakes knowing that the dietitian and/or physician will review the diary, or they may intentionally fail to disclose everything they consume for fear of judgment or other concerns, especially simple forgetfulness if they do not record foods eaten soon after consumption.

Underreporting of Dietary Intake

It is important to realize that the underreporting of food eaten is one of the major sources of error [9]. Men and women with obesity underreport more than normal weight individuals, but both underreport. This has been routinely observed in surveys of the US population, despite improvements in measurement protocols [10]. Misreporting of energy intake has been observed among Latin American populations [11], in the elderly, those with low-socioeconomic status and rural populations [12], in Middle Eastern countries [13], in developing nations [14], and even in people with significant disease conditions [15]. Therefore, underreporting is an expectation, rather than a rare occurrence. Subar et al. [16] point out, however, that despite the error associated with self-reported dietary data, dietary guidance and public health policy are informed by this data.

Physical Examination

As part of measuring the patient's vital signs, the healthcare professional needs to measure height and weight, which are needed for calculation of BMI, as well as waist circumference (Table 38.1). For practical information on BMI and the treatment of overweight and obesity in adults, clinicians should refer to the guidelines of the National Heart, Lung, and Blood Institute (http://www.nhlbi.nih.gov/

Table 38.1 Classification of overweight and obesity by BMI, waist circumference+, and associated disease risks

			Disease risk[a] relative to normal weight and waist circumference+	
	BMI (kg/m^2)	Obesity class	Men 102 cm (40 in) or less Women 88 cm (35 in) or less	Men >102 cm (40 in) Women >88 cm (35 in)
Overweight	25.0–29.9		Increased	High
Obesity	30.0–34.9	I	High	Very high
	35.0–39.9	II	Very high	Very high
Extreme obesity	40.0 +	III	Extremely high	Extremely high

[a]Disease risk for type 2 diabetes, hypertension, and CVD

+ Increased waist circumference also can be a marker for increased risk, even in persons of normal weight

Reprinted from NIH/National Heart, Lung, and Blood Institute. https://www.nhlbi.nih.gov/health/educational/lose_wt/BMI/bmi_dis.htm [21]

files/docs/guidelines/prctgd_c.pdf) [17] and those released in 2013 by The Obesity Society, the American Heart Association, and the American College of Cardiology [18]. Guidelines are also available for children and adolescents from the Endocrine Society (https://www.endocrine.org) [19] and for adults from the American Association of Clinical Endocrinologists (https://www.aace.com) [20].

The BMI has a curvilinear relation to the risks related to excess weight and provides one of the "vital signs" needed to assess any patient. A BMI between 18.5 and 25 is considered normal for most Americans. The BMI is divided into five-unit intervals that are used to define overweight and various levels of obesity (Table 38.1).

The BMI must be interpreted in an ethnically sensitive context because the amount of body fat for a given BMI differs among ethnic groups. For Asians, a BMI cutoff point for observed risks varies from 22 to 25 and for high risk it varies from 26 to 31, even though a normal BMI is considered to be <23. For African Americans and probably for Hispanics and descendants of Polynesians, a BMI of 27 is probably equivalent to a BMI of 25 in Caucasians. Once the BMI has been determined, assessment should include central fat distribution measured as waist circumference, along with appropriate laboratory and clinical measures. The rate of weight gain (greater than 1 kg [2.2 lb]/yr. is high) and the level of physical activity are additional criteria for determining the risk for a given BMI.

Fat located in the abdominal and visceral fat depots carries a higher risk for diseases associated with obesity than does extra fat on the hips and thighs [hence, the so-called apple versus pear fat distribution]. The challenge for clinicians is the estimation of fat distribution, with considerations as to accuracy, time, and cost. Several studies have suggested that waist circumference provides a reasonable surrogate for the more precise measurements provided by computed tomography or magnetic resonance imaging. As shown in Table 38.1, waist circumference greater than 88 cm (35 in) in women or 102 cm (40 in) in men signifies elevated risk. A very large international trial, the International Day for the Evaluation of Abdominal Obesity (IDEA) study, noted that waist circumference was a stronger predictor of cardiovascular disease (CVD) outcomes than BMI. First results of this large international study in 168,000 primary care patients in 63 countries reported that waist circumference was associated with CVD, independently of the relationship that BMI has with CVD risk, regardless of age or geography [22].

Waist circumference is a measurement that is relatively easy to determine using a tape measure and locating the important strategic points to take the reading. Since waist circumferences of >102 cm (>40 in) for men and of >88 cm (>35 in) for women are the defining levels of risk factors for diagnosis of the metabolic syndrome, this is valuable information to collect on a routine office visit with a physician [23].

A steady weight gain exceeding 1.0 kg (2.2 lb) per year over a number of years and a sedentary lifestyle are additional hints that an individual may have a future risk of heart disease, diabetes, or hypertension. There is also the option of measuring body fat which can be valuable in some populations, such as athletes, who may have a high BMI but relatively low body fat.

Body Composition Analyses

Dual X-ray absorptiometry (DXA) has replaced underwater weighing as the gold standard for determining body fat and lean body mass. The advantages of DXA are safety, ease of use, and accuracy with the use of appropriate standards. The disadvantages are generally high cost and need for regular cross-standardization of the instrument, as well as the weight limits of the table (e.g., for assessment of people with severe obesity) [23]. However, iDXA (GE Lunar) scans can provide closely comparable data to whole-body analysis with a half-body analysis in subjects with obesity [24]; in addition, iDXA is a good alternative to the more complicated and time-consuming magnetic resonance imaging (MRI) [25].

Bioelectric impedance analysis (BIA) has also been used to determine body composition, and, with proper training and careful placement of electrodes, very reproducible measurements can be obtained. Compared to DXA, BIA is relatively low cost, easy to use, and measures body water, which is then used to estimate body fat [23].

In children, Lazzer and colleagues [26] found that DXA and BIA were not interchangeable for the assessment of percent fat mass in children and adolescents with severe obesity; they offered a new predictive equation for estimation of body composition for use in such subjects. Researchers at the Children's Nutrition Research Center in Houston [27] have claimed that DXA has not achieved the reliability in children to be considered the "gold standard" for body composition assessment in pediatric studies. Nichols and colleagues [28] concluded that the relatively low cost and minimal time required for training makes the BIA a useful and appropriate technique for the assessment of body composition in adolescent girls.

Völgyi and colleagues [29] found that BIA methods systematically produced lower values for fat mass than did DXA, further suggesting that the difference depends on gender and body weight, which should be important considerations when identifying people with excess fat mass. DXA was found to be a reliable tool in assessing skeletal muscle mass in older women [30]. Others have suggested that BIA underestimates total and truncal fatness compared to DXA and, furthermore, that the discrepancies increase with degree of adiposity, an indication that accurate BIA measures are negatively affected by level of obesity [31]. BIA estimates of fatness are weakly correlated with obesity-related risk factors in women with abdominal obesity [32].

Laboratory Tests

Routine blood testing is necessary for the evaluation of nutrient status. Anemia is one of the most frequently detected abnormalities in women of postmenopausal age. Protein status based on a low albumin can also be assessed in both sexes. Routine laboratory testing should include lipid profiles to enable the physician or healthcare professional to diagnose the potential risk for CVD among both male and female patients. Laboratory examinations also are important to assess whether the patient has the metabolic syndrome. These laboratory examinations should include measurements of fasting plasma glucose, triglyceride, and HDL-C levels. The clinic visit should also include the measurement of blood pressure. Assessment of levels of HbA1c enables the clinician to determine what average blood glucose levels have been over a more extended period of time, the higher the HbA1c, the greater risk of developing diabetes-related complications. HbA1c will indicate whether the patient has prediabetes and can be referred to an appropriate lifestyle intervention.

Special Concerns by Age

Individuals can become overweight at any age, but obesity is more common at certain ages. Previously, it was suggested that 75–80% of individuals will become overweight at some time in their life. Between 20% and 25% of individuals will become overweight before age 20 yr., and 50% will do so after age 20. One third of overweight adults became overweight before age 20.

People can therefore be divided into four subgroups: (1) individuals who will never become overweight, although this group can be identified only in retrospect; (2) individuals with pre-overweight or pre-obesity who have a BMI of less than 25; (3) "preclinically overweight" individuals who become overweight without clinically significant problems at the time of evaluation, the "healthy obese"; and (4) individuals considered "clinically overweight or obese" with problems clearly related to having obesity.

Adolescents

Adolescence is a unique period in life during which there is intensive physical, psychosocial, and cognitive development. Nutritional needs are greatest during this period, when adolescents gain up to 50% of their adult weight, more than 20% of their adult height, and 50% of their adult skeletal mass. Although young people from low socioeconomic backgrounds are at greatest risk for poor dietary patterns, many adolescents rely on high-fat, high-fructose (sugar or high fructose corn syrup (HFCS)) foods for much of their intake or skip meals as a method of weight control. The diets of adolescents often lack adequate intakes of fruits and vegetables, in addition to vitamins A and C, folate, calcium, iron, and fiber.

Because most bone deposition occurs during adolescence, adequate intake of calcium and vitamin D intake is important. Many teenagers consume less than the adequate intake (AI) for calcium (1300 mg/day). It is important to recognize that adolescents who drink more soft drinks consume less milk and thus get less calcium. Dairy products, calcium-enriched orange juice, and calcium supplements can help to overcome this problem. Lower vitamin D levels are more likely to be seen in northern climates due to the lessened exposure to sun which activates vitamin D in the skin. Iron deficiency as a result of growth, menses, and poor diet is also common in adolescent girls.

Elderly

Elderly individuals often have poor dietary intakes, which may be due to inadequate finances to purchase nutritious food, ill-fitting dental appliances, or the inability or lack of desire to prepare healthful foods. Older people often find changes in intakes due to declines in smell and taste. In addition, sweet, easy-to-eat foods rich in refined carbohydrates (breads, cereals, sweet rolls) may be favored over more healthful items.

Inadequate intakes of fruits and vegetables may lead to a lack vitamins A and C, folate, and potassium. Inadequate consumption of protein-rich foods may result in poor vitamin B_{12} status, which may exacerbate the decline of vitamin B_{12} absorption which occurs with aging. Calcium intakes may be poor, often due to low intakes of dairy foods, which may be secondary to lactose intolerance, and reduced consumption of leafy green vegetables. Many elderly people spend a considerable amount of time indoors, often resulting in inadequate vitamin D. Although clinical zinc deficiencies are uncommon, older individuals often have marginal zinc levels because of low intake of protein-rich foods.

Reduced physical activity and a decrease in metabolic rate with aging require that older individuals choose foods that are high in nutrient density (e.g., fruits and vegetables) and low in energy density (e.g., dietary fats). A multivitamin/mineral supplement can provide nutritional insurance to older patients, especially if there are concerns about appropriate meal planning and/or problems consuming certain types of foods.

Food Access and/or Food Security

People who are food insecure are often faced with diminished access to healthy foods (high nutrient dense, low energy dense). They are faced with barriers such as availability of healthy food choices in rural areas of America, in addition to their potential to access those foods that are healthier due to a number of reasons (e.g., lack of transportation). These issues are common in rural areas of the United States as was reported years ago [33, 34]. Even to this day, these issues seem to persist as one listens to the popular media reports.

Other Areas of Concern

Key to women and, in particular people who adhere to a vegetarian diet, is iron deficiency. Obviously in all women, it is necessary to evaluate iron status and address the problem if the diagnosis is anemia.

Dietary fiber is an issue in practically all American diets, since the reported intake of dietary fiber falls short of the recommended adequate intake (AI) which is 30–38 grams/day for men and 21–25 grams per day for women [35, 36]. Focusing on increasing fruit and vegetable intake and reducing refined carbohydrates is a simple and easy way to increase fiber intake and should be a standard message disseminated by healthcare professionals.

Emerging evidence on the beneficial effects of vitamin D and *n*-3 fatty acids can also be a take-home message to the patient population. Because these are common dietary concerns, iron, calcium, fiber, vitamin D, and *n*-3 fatty acids should be considered in most conversations between the healthcare professional and the patient.

Healthy Eating Index

In assessing the adequacy of the patient diet, it may be helpful to utilize a tool such as the Healthy Eating Index or HEI [37]. The HEI-2015 is a standardized tool that can be used to monitor the quality of the diet, examine diet and health-related outcomes, and determine the effectiveness of nutrition, interventions, and potentially could be adapted for use in the primary care office. Scores are given for 13 dietary components that reflect the different food groups and key recommendations in the *2015–2020 Dietary Guidelines for Americans* (https://www.hhs.gov/fitness/eat-healthy/dietary-guidelines-for-americans/index.html) [38]. The standards for scores are expressed on a 1000-kcal basis with the maximum score of 100. Nine components receive high scores based on adequacy, while four components of concern (i.e., refined grains, sodium, added sugars, and saturated fats) receive high scores based on lower consumption (https://www.fns.usda.gov/resource/healthy-eating-index-hei) [39]. To evaluate dietary intake, an individual needs to complete a 24-h recall, food frequency, or food record; however, this will involve more time than might be available in a primary care clinic. Data from NHANES indicates that the total HEI-2015 score for Americans was 59 out of 100. If individuals strive to consume a diet that aligns with the Dietary Guidelines recommendations, then perhaps the risk of developing diet-related chronic diseases can be reduced. Referral by the physician to a registered dietitian nutritionist would be a step toward making this happen, especially with limitations of time in the primary care setting.

Conclusion

The healthcare professional plays a crucial role in assessing the nutritional status of the patient. Using the instruments available to evaluate dietary intake along with appropriate biological testing and physical evaluation, the healthcare professional will receive insight to assess both diet and environmental factors affecting the health status of the patient. The evaluation of weight status is, by far, the most pressing of diagnoses to aid in the prevention of obesity. Counseling during the visit could help an individual experiencing increasing levels of overweight begin a program to lose weight, especially if this occurs at an early age. Routine office visits present opportunities to encourage consumption of nutrient dense diets and manage weight to prevent obesity. Research continues to elucidate the pathologic process of obesity. However, because of the increase in obesity in the United States, the increase in type 2 diabetes (especially in children), and the limited effectiveness of seemingly the best treatments, a focus on prevention remains the best way to avoid the morbidity and mortality associated

with obesity. The healthcare provider needs to recognize that dietary behavior is modified by economic factors – the cost of food. Unfortunately, as long as cheap, energy-dense, nutrient-poor, and palatable foods are available and continue to be advertised by multimedia sources, obesity will be difficult to prevent.

COVID-19 Addendum

Since the pandemic can now be viewed as a recent and unprecedented situation, Mehta [40] in a paper published in May 2020 noted that at that time that there was no published evidence related to the impact of nutritional status on COVID-19 severity. Mehta [40] reported three observations might be related to this and are related to older patients with multiple comorbid conditions: (1) malnutrition is likely common; (2) malnutrition will affect the clinical outcomes adversely; and (3) the adverse effects may be modifiable when patients are provided with nutrition support. A subsequent paper by Wei et al. [41] reported that patients with moderate to severe malnutrition exhibited greater mortality than those who were only normal to mildly malnourished. These investigators developed a score called CONUT (controlling nutritional status) in evaluating the level of malnutrition, reporting that this score independently predicted the prognosis of infected COVID-19 patients in an effort to enable physicians to better evaluate patients with a poor prognosis. Brugliera et al. [42] noted that risk of malnutrition relates to chronic conditions, e.g., diabetes, cardiovascular disease, chronic obstructive pulmonary disease, and others, resulting in reduction of food intake due to nausea, diarrhea, and loss of appetite. Also pointed out was the fact that prolonged immobilization leading to sarcopenia adds to the problem. Their paper points out six steps related to nutritional assessment and malnutrition screening to consider the following: anthropometric parameters, impedance and vector analysis, weight loss, hematological parameters, swallowing ability, and food intake assessment.

As a result of the COVID-19 pandemic, Bagni et al. [43] point out that the whole process of social distancing has affected the way in which anthropometric measures are taken, suggesting that remote assessment may be a useful strategy to nutritional surveillance. Telehealth options can provide a means of meeting with the patient, as well as providing nutritional care and attempting to minimize malnutrition and diet-related disease risk. Suggestions for conducting these remote telehealth visits are provided by the researchers, specifically focusing on remote anthropometric assessments, ability of the patient to engage in the visit, and other factors related to conducting a successful remote appointment.

In conclusion, now more than ever, it is essential to complete an assessment of nutritional status, which the COVID-19 pandemic has made very clear. We need to use trained professionals to do this and within sanitary conditions or by using appropriate strategies remotely. These strategies will help us step to the plate and be ready for future unknown pandemics should they arise.

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Dietary Reference Intakes: Cutting Through the Confusion

39

Maria Morgan-Bathke and Kelsey McLimans

Keywords

Dietary Reference Intakes · Recommended Dietary Allowances · Deficiency · Energy requirement

Key Points

- The Dietary Reference Intakes (DRIs) are a set of reference values for nutrients. They are used for assessing and planning diets for individuals and groups.
- The DRIs include values for the following:
  - Estimated Average Requirement (EAR).
  - Recommended Dietary Allowance (RDA).
  - Adequate Intake (AI).
  - Tolerable Upper Intake Level (UL).
- DRI tables also include Estimated Energy Requirement (EER).
- The purpose of the DRI is to provide an estimation of the nutrient intake that will meet the needs of most individuals and groups within a specific population.
- The Dietary Guidelines for Americans and MyPlate translate the DRI into recommendations and guides for food selection by consumers.

Introduction

Dietary Reference Intakes (DRIs) are reference values that provide estimates of nutrient needs for planning and assessing the diets of healthy people [1]. These reference values are based on data and scientific judgment. DRIs include the Recommended Dietary Allowance (RDA), Adequate Intake (AI), Tolerable Upper Intake Level (UL), and Estimated Average Requirement (EAR). The DRIs are meant to assist clinicians and the healthy public in planning and assessing dietary intake of healthy individuals.

M. Morgan-Bathke (✉) · K. McLimans
Department of Nutrition and Dietetics, Viterbo University, La Crosse, WI, USA
e-mail: memorganbathke@viterbo.edu; kemclimans@viterbo.edu

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The Dietary Reference Intakes

The DRIs are developed utilizing data. However, because the studies providing this data are sparse and may have limitations, scientific judgment is also involved in establishing the DRIs. The different sets of values are intended for close to all healthy individuals. Separate values are given for several different age and life stage groups.

Estimated Average Requirement

The EAR is the nutrient intake value that is estimated to meet the requirement of half of the healthy individuals in a group [1]. The EAR is commonly utilized to assess a healthy individual's dietary intake. For example, the EAR can be used to determine the possibility of inadequacy in a diet or the prevalence of inadequate intake within a group. However, it is important to note that in order to assess the true dietary status, it is necessary to obtain clinical, biochemical, and anthropometric data.

Recommended Dietary Allowance

The RDA is the average daily dietary intake necessary to meet the nutrient requirement for 97–98% of healthy individuals in a group [1]. It is most useful for planning dietary intake for individuals. It is important to note that RDA values vary based on age as outlined in Table 39.1.

The first edition of the RDAs was published in 1943. It has been revised at regular intervals since then [2]. However, with little data available for dietary needs of youth and children as well as needs be defined for broad ranges of gender and age, the RDA values are not universally agreed upon [3].

Adequate Intake

An Adequate Intake (AI) is reported as a goal intake when there is limited evidence to support EAR and RDA values [4]. AIs are often used for infancy and pregnancy as research is more difficult at these life stages. For infants, AIs are based on average intake of a particular nutrient for healthy breastfed infants [4]. Adult AIs are often based on more limited scientific studies [5].

Table 39.1 presents a simplified version of the values for RDA and AI.

Tolerable Upper Level Intake

The UL is the highest level of daily nutrient intake that is unlikely to pose risks or adverse health effects to a majority of healthy individuals within a group [6]. The main purpose of the UL is to inform the public of risks associated with excessive nutrient intake.

In 1998, the Institute of Medicine developed a risk assessment model specifically for nutrients to quantify the UL [6]. This dose-response assessment is built upon three toxicology concepts: no-observed-adverse-effect level, lowest-observed-adverse-effect level, and uncertainty factor.

Table 39.1 Dietary Reference Intakes (DRI) consist of four tables. Here we present actual values in a simplified form. The numbers given here are for Recommended Dietary Allowances (RDA) or Adequate Intakes (AI). These values indicate a target amount (quantity per day) for each nutrient, depending on age and sex

		Male	Female				
		>18 years	19–50 years	51–70 years	>70 years	Pregnancy	Lactation
Dietary fiber	g	38[a]	25	25	21	28	29
Protein	g	56	46	46	46	71	71
Thiamin	mg	1.2	1.1	1.1	1.1	1.4	1.4
Riboflavin	mg	1.3	1.1	1.1	1.1	1.4	1.6
Niacin	mg	16	14	14	14	18	17
Vitamin B_6	mg	1.3[b]	1.3	1.5	1.5	1.9	2.0
Folate	µg	400	400	400	400	600	500
Vitamin B_{12}	µg	2.4	2.4	2.4	2.4	2.6	2.8
Vitamin C	mg	90	75	75	75	85	120
Vitamin A	µg[c]	900	700	700	700	770	1300
Vitamin D	µg[d]	15[e]	15	15	20	15	15
Vitamin E	mg	15	15	15	15	15	19
Potassium	mg	4700	4700	4700	4700	4700	5100
Calcium	mg	1000[f]	1000	1200	1200	1000	1000
Magnesium	mg	420	310	320	320	355	315
Iron	mg	8	18	8	8	27	9
Zinc	mg	11	8	8	8	11	12
Iodine	µg	150	150	150	150	220	290
Selenium	µg	55	55	55	55	60	70
Copper	µg	900	900	900	900	1000	1300

[a]30 g at age >50
[b]1.7 mg at age >50
[c]1000 µg of vitamin A = 3300 IU
[d]15 µg of vitamin D = 600 IU
[e]15 µg at age 19–70; 20 µg at age >70
[f]1200 mg at age >50
The full tables include values for people aged from birth to 18 years; values for energy, fat, carbohydrate, water, and 11 other nutrients; and values for Tolerable Upper Intake Levels. For the full tables, go to the following website: National Academy of Sciences. Summary Tables Dietary Reference Intakes 2000. https://www.nal.usda.gov/sites/default/files/fnic_uploads//SummaryTables.pdf [6]

Estimated Energy Requirement

An important inclusion in DRI tables is Estimated Energy Requirement (EER). Unlike the nutrients, there is no RDA for energy. This is because of the multitude of factors that play into an individual's energy needs. Estimation equations for energy requirements for *healthy* individuals are available. These provide a guideline for the number of calories required to maintain weight. These equations take into account age, sex, weight, height, and level of physical activity. Available equations include infants and young children, both boys and girls 3–8 and 9–18 years of age, male and female adults, and pregnant and lactating women [4].

Indirect calorimetry is considered the gold standard for determining calorie requirements for an individual. This involves the measurement of oxygen use and collection of exhaled carbon dioxide [7]. However, indirect calorimetry is typically limited to special circumstances as it is labor intensive and more costly than using predictive equations.

Acceptable Macronutrient Distribution Ranges

After determining an individual's estimated energy requirements, one can utilize the Acceptable Macronutrient Distribution Ranges (AMDR) to determine a range of calories that should be allotted to the three macronutrients: carbohydrates, protein, and fat, including breakdowns for omega-3 and omega-6 fatty acids. While the RDAs and EARs are aimed at preventing deficiencies, the AMDRs have a goal of preventing chronic diseases [8]. Thus, if an individual consumes a macronutrient outside of their AMDR range, they would be at increased risk for developing chronic disease making it essential for practitioners to discuss dietary intake with patients.

One interesting point to make is that the protein recommendations differ between the DRIs and the World Health Organization population nutrient intake goals. The DRIs recommend that 10–30% of calories come from protein for individuals [4] (except for young children who should receive 5–20% of calories from protein), while WHO recommends a *mean* intake range of 10–15% for populations of total calories for protein for the prevention of chronic disease [9]. Thus, it would be more appropriate for clinicians to utilize the DRIs when assessing protein intake for individual patients. During examinations, clinicians should ask patients questions about typical protein food intake (including portion sizes) to not only ensure that enough protein is being consumed but also that protein is not being overconsumed. In particular, overconsumption of red meat (includes beef, pork, lamb) and processed meat is linked with increased mortality risk [10].

Limits and Uses of the DRI

Limits

As stated above, the DRIs apply only to healthy people [4]. Much different levels of nutrients may be required by individuals with diseases, especially malabsorptive or inflammatory diseases.

Limitations of the EER formulas include difficulties in obtaining an accurate estimation of physical activity level. It is also necessary to gather accurate height and weight data which may be difficult in some community settings. In addition, these equations are not appropriate for hospitalized patients or patients in disease states who may require significantly more calories.

There is often a conflict between AMDR percent protein intake and the EAR/RDA g/kg body weight estimation. However, studies have shown that in healthy individuals, the RDA method sets a minimum for protein consumption, and there is little evidence of harm from consuming above the RDA while still within the AMDR range [11]. Similarly, the RDA for carbohydrates is set as a minimum to prevent deficiency symptoms, whereas the AMDR is set for optimal carbohydrate intake [12].

General Guidelines for Diet Assessment of Individuals

In general, the RDAs should be utilized in determining if an individual is at risk for nutrient deficiencies. If an individual is consuming above the RDA value for a particular nutrient, he/she typically does not need to decrease his/her consumption unless it is above the UL.

In order to determine the adequacy of the diet, intake should be recorded over several days. Because the typical individual's diet varies widely from day to day, it is insufficient to draw conclusions about adequacy from a single day's diet record [4].

DRI and the Consumer

DRIs are used widely in research, and they serve as the basis for developing nutrition public policy. They are utilized to create dietary guidelines, food guides, tracking nutrition-related public health programs, and creating educational programs [13]. The DRIs form the scientific foundation for federal food programs, including nutrition labeling, requirements for school meals, and the design of supplemental food packages for the Women, Infants, and Children (WIC) program.

Because of the complexity of using the DRIs and the associated tables to formulate diet plans, the US Department of Health and Human Services and the US Department of Agriculture (USDA) developed the *Dietary Guidelines for Americans* [14]. This document provides recommendations to promote health and reduce the risk of chronic disease. It is updated every 5 years.

MyPlate is the food guide used in the USA. When people base their diet on MyPlate, they will consume nutrients at or above the DRI recommendations for nearly all nutrients [14]. Their diet will also be consistent with Dietary Guidelines. MyPlate is described in Chap. 40.

Summary

In summary, the DRIs are formulated for nutrients based on current scientific evidence. The various tables provide guidelines for the intake that healthy individuals should consume across the life span. However, clinical judgment is warranted to ensure that these guidelines are appropriate as the DRIs are based on statistical calculations of reference populations. Without scientific experimentation, it is not possible to determine an exact nutrient requirement for an individual. In addition, a single-day food record is not enough to conclude that a diet is nutritionally adequate. At a minimum, several measurements of dietary intake are required before conclusions can be drawn.

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New Concepts in Nutritional Science: Food Not Nutrients

40

Norman J. Temple

Keywords

Food synergy · MyPlate · DASH Eating Plan · Mediterranean diet

Key Points

- The effects of different foods on the body reflect the synergistic interactions between the many substances present in foods, including micronutrients, phytochemicals, fats, sugar, and dietary fiber.
- The relationship between diet and disease is best explained in terms of foods rather than single nutrients.
- These concepts are known as food synergy.
- The key features of a healthy diet are described.
- Healthy eating plans are also described, including *MyPlate* (the food guide used in the USA), the DASH Eating Plan, and the Mediterranean diet.

The Concept of Food Synergy

Biomedical science has always been reductionist. Investigators are in a never-ending search for the detailed mechanisms that lie at the heart of body functioning. This rationale for this is certainly intellectually appealing. It can also be justified on the grounds that a detailed understanding of disease mechanisms will enable healthcare professionals to more effectively enhance health and prevent and treat diseases. This grand strategy has certainly met with much success. Drug development, in particular, rests heavily on an intimate understanding of body functioning at the molecular level.

What applies to biomedical science in general specifically applies to nutrition science where the dominant strategy that has guided nutritional research for the past century has been reductionist. Generations of researchers have searched for the substance in food that are responsible for each disease and the mechanisms that explain this. The fruits of this enormous research effort have given us detailed knowledge of the nutrients in food and their role in the body. But it has become increasingly clear in recent years that this reductionist strategy is failing to deliver the truly important results: what

N. J. Temple (✉)
Centre for Science, Athabasca University, Athabasca, AB, Canada
e-mail: normant@athabascau.ca

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changes we must make to the diet, such as adding or removing particular substances in food, so as to improve health and effectively prevent and treat disease. When we peer down the tunnel, we see more darkness than light.

The explanation for this frustrating story has slowly emerged. Nutrition science has been focused on individual substances in food. But disease mechanisms are seldom so simple that they can be properly explained by the dietary intake of single substances. We shall now look at some examples. The evidence supporting the various statements below is contained in other chapters.

During the 1970s, most nutrition researchers became convinced that a relatively high intake of fat is an important cause of several common health problems including cancer, heart disease, and obesity. This led to national policies across many countries advising populations to cut their fat intake. Millions of people followed this advice such as by switching from full-fat milk to low-fat milk and from fat-rich meat to lean meat. But the findings from dozens of prospective cohort studies failed to find solid evidence that fat intake was indeed related to disease risk.

For 40 years, it was widely believed that a relatively high intake of saturated fat plays a major role in the causation of coronary heart disease (CHD). However, the evidence referred to in Chap. 12 shows that intake of saturated fat has a much weaker association with risk of CHD than does the intake of various foods such as fish, fruit, vegetables, and whole grains. These findings show that several types of food have a stronger relationship with risk of a major disease than does a single nutrient, namely, saturated fat.

Evidence regarding the possible value of supplements of micronutrients was briefly reviewed in Chap. 42. That evidence is directly relevant here. Thirty years ago, many nutrition experts asserted that a relatively high intake of vitamin C and beta-carotene is protective against a number of diseases including cancer and heart disease. The supporting evidence appeared solid. First, many observational studies had reported that people whose intake of these nutrients was high had a relatively low risk of cancer and heart disease. Second, research studies of disease mechanisms indicated that free radicals were produced in cells which then cause damage to cellular structures, an important step on the way to disease. Antioxidants, including vitamin C and beta-carotene, neutralize free radicals, and it seemed logical to conclude that an increased intake of these vitamins would help protect against cancer and heart disease. However, the research evidence that has appeared since the 1990s has almost completely refuted these claims.

There has been wide support for the view that large sections of the population would benefit from supplements of vitamin D, calcium, and multivitamins (i.e., a broad spectrum of vitamins and minerals). But as briefly reviewed in Chap. 42, research studies have, with few exceptions, failed to generate solid supporting evidence.

Each of these examples tells a similar story. Based on limited evidence, there was wide support for the hypothesis that particular nutrients play an important role in disease. With the first two cases (a relatively high intake of fat and of saturated fat), an excessive intake was believed to be a major cause of some diseases, whereas in the other cases, supplements of various micronutrients were believed to be protective against risk of particular diseases. But, as a fuller picture emerged, each hypothesis failed to live up to its initial bold claims.

When attention is turned away from single nutrients and toward foods, a different story emerges: an impressive weight of research evidence has revealed close association between the intake of particular types of food (i.e., food groups) and disease risk. As will be stated more fully below, findings from prospective cohort studies demonstrate that a diet plentiful in intake of fruits and vegetables and in whole grains (and its associated cereal fiber) has a protective association with various chronic diseases of lifestyle, while consumption of red meat and processed meat manifests the opposite association.

Taking the above evidence as a whole points to the conclusion that the relationship between diet and disease is, in most cases, best explained in terms of food rather than single nutrients [1, 2].

Researchers often go beyond food groups and look at dietary patterns. The most common way this is done is by dividing diets into two broad groups. A generally unhealthy diet is often referred to as a Western dietary pattern, while a generally healthy diet is often called a prudent diet. Not surprisingly, many cohort studies have demonstrated that folks who habitually eat a Western dietary pattern have a higher risk of assorted diseases than those who generally eat a prudent diet.

What explains this new concept? The most plausible explanation is that the effects of different foods on the body are a reflection of the synergistic interactions between the vast number of substances present in foods, including micronutrients, phytochemicals, fats, sugar, and dietary fiber. In some instances, there may be an excessive intake of a substance, while in other cases intake is suboptimal. All this makes perfect sense; the human body is incredibly complex and so are most disease mechanisms. It is therefore anything but surprising that a wide variety of different substances act in concert in disease etiology. This new concept is known as food synergy [3, 4]. From this, it follows that attempts to explain disease etiology in terms of the actions of single substances are, in most cases, doomed to failure.

Single Substances That Are Linked to Health Disorders

The concept of food synergy is of great value in helping to explain the relationship between dietary intake and the development of many diseases. But, nevertheless, we still have several cases where solid research evidence indicates that a single substance, usually a nutrient, is clearly related to various health risks. This may be the result of either excessive intake of a substance or, more often, of suboptimal intake. Here are some examples.

Iron Iron deficiency is a common problem, especially for women in their reproductive years, where it leads to anemia.

Sodium In the opposite direction, a high intake of sodium (salt) is clearly linked to hypertension.

The following three sets of substances are seldom problematic in a healthy diet. In other words, a healthy diet has an adequate content of folate and dietary fiber, while the sugar content is never excessive. However, they are included here as particular issues need to be highlighted.

Folate This is another micronutrient where intake is often inadequate. The reason for this is that large sections of the population eat an unhealthy diet with a low content of healthy foods, especially fruit and vegetables. A low intake of folate is a serious concern as it may lead to the development of neural tube defects, such as spina bifida, during pregnancy. In order to help prevent this problem, folic acid is now added to grain products in the USA and Canada, and this has much reduced the incidence of this condition.

Dietary Fiber Fiber-rich foods, such as fruit, vegetables, and whole grains, have a clear negative association with risk of several diseases, including CHD. However, it is usually impossible to state with any confidence how much of the credit belongs to fiber and how much to the many other substances, including phytochemicals, found in these foods. But for some conditions, we have solid evidence that fiber (or some specific types of fiber) is of particular value (Chap. 33).

Sugar A common nutritional problem is a high intake of sugar, especially in the form of sugar-sweetened beverages. Many research studies have documented an association between sugar intake and increased risk of CHD and obesity.

An Overview of the Diet

This section summarizes what we know about the relationship between different foods, the preservation of good health, and the prevention of disease. The detailed evidence is presented in other chapters.

Fruit and Vegetables

There is strong evidence from prospective cohort studies that fruits and vegetables are protective against cardiovascular disease (including CHD and stroke), type 2 diabetes, cancer, and all-cause mortality [5, 6]. The evidence is much less positive for potatoes. Boiled and baked potatoes appear to have fairly little effect on health. But potatoes may pose some health risk when eaten as French fries as they appear to increase the risk of type 2 diabetes and hypertension [7].

Fruit juices also present a confusing picture. They are often marketed as a convenient way to boost the intake of fruit. However, their concentration of simple sugars is similar to that of sugar-sweetened soft drinks. In addition, their ease of consumption and low satiety means they may contribute to excessive energy intake. A few prospective cohort studies have examined the association between fruit juices and CHD, stroke, and all-cause mortality, but findings have been inconsistent [5, 8]. Other evidence suggests that a moderate intake of fruit juices does not pose a health risk apart from an increased risk of tooth decay in children. Fruit juice appears to have essentially no effect on weight gain in children and adolescents [9, 10], though it may lead to a small degree of weight gain in adults [11]. There is also evidence of a slight increase in risk of type 2 diabetes with high intake of fruit juices [12]. A reasonable conclusion from this mixed evidence is that fruit juices may be included in the diet but that intake should not exceed one or two servings per day.

Whole Grains

Much like fruit and vegetables, diets with a generous amount of whole grains are associated with a reduced risk of cardiovascular disease, type 2 diabetes, and all-cause mortality [13]. There may also be a modestly lower risk of cancer.

Meat, Fish, Legumes, and Nuts

We now have strong evidence linking consumption of red meat with major chronic diseases. The impact of red meat on health is the mirror image to that of fruit, vegetables, and whole grains. Red meat is divided into two main groups: unprocessed red meat including beef, pork, lamb, and mutton; processed red meat including ham, sausages, bacon, frankfurters, salami, etc. Steps involved in the production of processed meat may include curing, smoking, and salting. As a result, processed meat contains assorted added chemicals. People whose diet has a relatively high content of red meat have an appreciably raised risk of cardiovascular disease, various types of cancer, and all-cause mortality [14]. Risks are higher for processed red meat than unprocessed. Chicken and other poultry pose far less risk of these diseases than does red meat.

Fish makes an excellent substitute for meat consumption. As documented in Chap. 12, a large amount of research evidence has clearly shown that fish, especially fatty fish, has a strong protective benefit against CHD. Fatty fish include sardines, mackerel, herring, pilchards, salmon, and tuna. Beans are also a healthy substitute for meat. Strong evidence has emerged revealing that nuts contribute to good health. In particular, cohort studies [15] and one randomized controlled trial [16] have demonstrated that nuts have a clear protective association with risk of cardiovascular disease.

Milk and Dairy Products

Milk is a nutritious food. However, the evidence is inconsistent regarding the effect of consuming milk and other dairy on the risk of chronic diseases of lifestyle [17, 18].

Food and the Environment

Quite apart from its harmful health effects, red meat is also damaging to the environment. In particular, its production plays an important role in the cutting down of forests, including the Amazon, and the generation of greenhouse gases [19, 20]. The production of chicken and dairy foods causes only about one third as much environmental damage. Antibiotics used in factory farms also present a potential problem as this may over time lead to issues related to bacterial resistance to antibiotic medications used in humans.

Dietary Supplements

The case that healthy people eating a healthy diet would benefit from dietary supplements is weak. Some of this evidence was briefly reviewed in Chap. 42 and was referred to earlier in this chapter. But a great many people do not eat a healthy diet, while many others have particular health challenges. For people who are in these groups, dietary supplements may sometimes be advisable. The supplements most likely to fall into this category include iron, folic acid (the supplement form of folate), and vitamin D.

Food Guides

As explained earlier, the secret to a healthy diet is a focus on foods rather than nutrients and other substances. Accordingly, there is little to be gained by being concerned with the intake of vitamin C, folate, potassium, magnesium, sugar, fat (both total amount and saturated fat), and dietary fiber. If the diet is healthy, then the intake of these substances, and of many others, will also be in the ideal range. The one substance that requires special attention is salt as many otherwise healthy foods have a high salt content.

Dozens of countries produce food guides with the goal of presenting easy-to-understand guidelines for constructing a healthy diet. Such food guides are usually produced by an agency of the national government. In addition, some nongovernmental organizations have produced food guides. Here we examine three food guides.

MyPlate

The US Department of Agriculture (USDA) produces the food guide used in the USA. The current version was launched in 2011. It is a simple pictorial design called MyPlate (http://www.choosemyplate.gov) (Fig. 40.1) [21]. It is also available in Spanish. The recommended diet is depicted as a plate with food sectors. More of the diet should come from fruit and vegetables than from grains. The food guide places little emphasis on how many servings should be eaten from each food group.

A controversial question is whether dietary advice, including the design of food guides, should separate fruits and vegetables into two food groups. The food guides used in many countries, such as

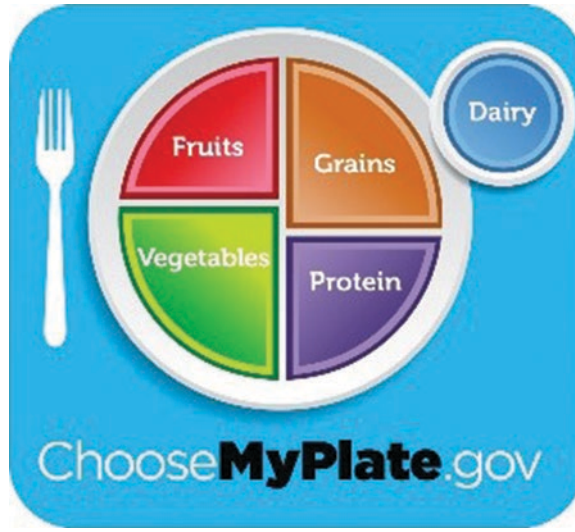

Fig. 40.1 MyPlate [21]. Reprinted from U. S. Department of Agriculture. Choose MyPlate https://www.choosemyplate.gov/

the USA, Germany, and Japan, do separate these foods into two groups, but many other food guides, such as those used in the UK, Canada, and China, combine these foods into one group. Taking the evidence as a whole, it makes most sense to combine fruit and vegetables into a single food group while stressing that people should eat a wide variety of these foods [22]. This design of food guides achieves the best of each world: a single food group is easier for the general population to remember and to follow, while the added advice encourages people to optimize their diet.

Based on the evidence outlined earlier, it makes most sense to include juices with fruit and vegetables. Advice should be added stating that intake of juices, especially fruit juices, be limited to no more than one or two servings per day. Potatoes are best included with other vegetables, but intake should be limited, especially of French fries.

DASH Eating Plan

This food guide grew out of the DASH trial (Dietary Approaches to Stop Hypertension). That intervention tested a diet that emphasizes fruit, vegetables, and low-fat dairy products while also providing a reduced intake of fat and saturated fat. The DASH diet succeeded in significantly lowering elevated blood pressure (see Chaps. 13 and 16).

The National Heart, Lung, and Blood Institute (NHLBI) then adapted the diet for the general population. This is known as the DASH Eating Plan (dashdiet.org) [23]. The diet has a generous content of fruit, vegetables, and whole grains and includes nuts, seeds, and beans. It is moderately high in low-fat dairy and seafood. It is reduced in meats, sweets, and sugar-sweetened beverages. Compared with MyPlate, the diet supplies more fiber but much less fat, saturated fat, and polyunsaturated fat.

Mediterranean Diet

This dietary plan has much in common with the previous diet. Interest in the Mediterranean diet started in the 1960s when it was realized that populations who live around the Mediterranean have much lower rates of cardiovascular disease than do populations from Northern Europe (who typically eat a Western diet).

The key features of the diet are as follows: high consumption of legumes, grains, fruit, vegetables, and nuts; low consumption of meat and meat products; low or moderate amounts of fish, milk, and dairy products; and liberal use of olive oil. Like the DASH Eating Plan, the Mediterranean diet has a low content of saturated fat; however, unlike that diet, it has a generous content of both fat and monounsaturated fat. As traditionally eaten, the diet typically includes low to moderate amounts of alcohol, especially of red wine consumed mainly at meals. The diet is described in more detail in Chap. 15.

Conclusion

Research studies into the relationship between diet and health over the past several decades have paid rich dividends. This large body of information enables us to design healthy diets, which, if consumed by the general population, would achieve major advances in public health. This information also gives healthcare professionals far greater capability to provide their clients with advice that can potentially prevent and treat a wide variety of diseases.

An important lesson that emerges from this research is that the relationship between diet and health is best explained by the concept of food synergy. In other words, healthcare professionals should emphasize healthy foods and dietary patterns, both those to consume and those to avoid, rather than single substances. However, in a few cases, advice focused on specific substances is justified, as is the case with iron, salt, and dietary fiber.

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Suggested Further Readings

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Food Labels and Sources of Nutrients: Sorting the Wheat from the Chaff

41

Karen M. Gibson and Norman J. Temple

Keywords

Nutrition facts label · Nutrition labeling · Daily values · Health claims

Key Points

- Food labels provide the information needed to guide the selection of foods that will help individuals meet nutrition and health goals.
- Recent changes in food label format necessitate reinterpretation of food label information.
- Health claims on food labels are tightly regulated by the FDA.
- This chapter explains how to best utilize the information contained in food labels.
- This chapter also provides information on (1) nutrient contributions of the food groups and of various foods and (2) food sources of select nutrients.

The Nutrition Facts Label

Food labels are important as they assist millions of people in making healthier food choices as demonstrated by a systematic review by Shangguan et al. [1]. But labels are only useful if one properly understands how to use them. Unfortunately, the ease of comprehension leaves much to be desired.

Regulations require that nutritionally important nutrients or food components found in a food must be listed on the nutrition facts label [2, 3]. A new design of the label was introduced in 2020. Figure 41.1 shows a typical example of both the old and new format of the nutrition facts label for the same food. The label focuses on nutrients that are associated with certain chronic diseases or with nutrient deficiencies. By law, the new version of the food label must contain the following information:

K. M. Gibson
Department of Nutrition and Dietetics, Viterbo University, La Crosse, WI, USA
e-mail: kmgibson@viterbo.edu

N. J. Temple (✉)
Centre for Science, Athabasca University, Athabasca, AB, Canada
e-mail: normant@athabascau.ca

T. Wilson et al. (eds.), *Nutrition Guide for Physicians and Related Healthcare Professions*, Nutrition and Health, https://doi.org/10.1007/978-3-030-82515-7_41

Nutrition Facts
Serving Size 2/3 cup (55g)
Servings Per Container About 8

Amount Per Serving

Calories 230	Calories from Fat 40
	% Daily Value*
Total Fat 8g	**12%**
Saturated Fat 1g	**5%**
Trans Fat 0g	
Cholesterol 0mg	**0%**
Sodium 160mg	**7%**
Total Carbohydrate 37g	**12%**
Dietary Fiber 4g	**16%**
Sugars 1g	
Protein 3g	
Vitamin A	10%
Vitamin C	8%
Calcium	20%
Iron	45%

* Percent Daily Values are based on a 2,000 calorie diet. Your daily value may be higher or lower depending on your calorie needs.

	Calories:	2,000	2,500
Total Fat	Less than	65g	80g
Sat Fat	Less than	20g	25g
Cholesterol	Less than	300mg	300mg
Sodium	Less than	2,400mg	2,400mg
Total Carbohydrate		300g	375g
Dietary Fiber		25g	30g

Nutrition Facts
8 servings per container
Serving size 2/3 cup (55g)

Amount per 2/3 cup
Calories **230**

% DV*	
12%	**Total Fat** 8g
5%	Saturated Fat 1g
	Trans Fat 0g
0%	**Cholesterol** 0mg
7%	**Sodium** 160mg
12%	**Total Carbs** 37g
14%	Dietary Fiber 4g
	Sugars 1g
	Added Sugars 0g
	Protein 3g
10%	**Vitamin D** 2mcg
20%	**Calcium** 260mg
45%	**Iron** 8mg
5%	**Potassium** 235mg

* Footnote on Daily Values (DV) and calories reference to be inserted here.

Fig. 41.1 Examples of old (*left*) and new (*right*) versions of nutrition facts label for the same food [4]. (Figure reprinted from FDA https://www.fda.gov/media/97999/download)

- List of ingredients arranged in descending order by weight (main ingredient first).
- Serving size (using a standardized serving size), plus the number of servings per container.
- Amount per serving of the following: total calories, fat, total fat, saturated fat, trans fat, cholesterol, sodium, total carbohydrate, dietary fiber, total sugar (including added sugar), protein, vitamin D, potassium, calcium, and iron. These quantities are also listed for the whole package for foods that are typically consumed in one sitting. However, if the food has a negligible amount of a particular food component, then it may be omitted from the label.
- The sugars listed on the label include naturally occurring sugars (like those in fruit and milk) as well as those added to a food or drink. The ingredient list states specifics on added sugars. If added sugars are listed as one of the first few ingredients, this is an indication that the food has a high content of sugar. Other names for added sugars include corn syrup, high-fructose corn syrup, fruit juice concentrate, maltose, dextrose, sucrose, honey, concentrated or organic cane juice, and maple syrup.

- Other information may be included, but this is optional unless the product is making a claim regarding that particular nutrient.

What are the key differences between the old and new labels? The new label reflects updated scientific information, including our greater understanding of the links between diet and chronic disease. It is also more realistic about how people eat today. Here are some of the changes:

1. In the new label, the number of calories, the serving size, and the number of servings per container are in larger, bolder type. These changes are of particular value for those people who are trying to count calories in order to help their weight control efforts.
2. The FDA is required to base serving sizes on what people actually eat and drink, so serving size requirements have been adjusted to reflect more recent consumption data. As a result, the nutrition information provided for each serving is more realistic. For packages that contain more than one serving, the label states the nutrition information per serving as well as per package.
3. Added sugars are now listed. The 2015–2020 Dietary Guidelines for Americans recommends that people consume less than 10% of calories per day from added sugars.
4. Changes have been made to the list of nutrients that must be included. Vitamin D and potassium are now included because Americans often fail to get the recommended amounts. By contrast, inclusion of vitamins A and C is no longer required because deficiencies of these vitamins are seldom seen today, but they can be listed by manufacturers voluntarily.
5. Daily values for nutrients like sodium, dietary fiber, and vitamin D have been updated and are used to calculate the % Daily Values (DVs) that are displayed on the label. The % DV helps people understand the nutrition information in the context of a daily diet. The footnote at the bottom of the label has been changed to better explain the meaning of the % DV. DV is further explained below.

Serving size is one of the most important items on a food label. This is stated in familiar units, such as cups or pieces, followed by the metric amount, such as the number of grams. In general, serving sizes are standardized to make it easier to compare similar foods. For example, the serving size for all ice creams is two-thirds of a cup and all soda beverages is 12 oz. The serving size indicated on a food label is intended to reflect the amount a typical person actually consumes on one occasion. But many people may consume significantly larger servings. Another source of possible confusion is that the serving sizes on food labels are not always the same as those of the USDA Food Guide or the diabetic exchange plan.

When looking at the serving size, consumers need to compare the size listed with the amount of the food that they will actually eat. In the sample label in the figure, for example, one serving of this food equals two-thirds of a cup. But if the consumer eats a larger amount, that obviously increases the calories and the quantity of other nutrients. The servings given to customers in restaurants are often considerably larger than the serving sizes used on food labels or food guides. This can result in people greatly underestimating their intake of food calories. [Note: In this chapter, we use the word calories for consistency with actual food labels. However, in the rest of this book, calories are abbreviated as kcal.]

Another feature of food labels is the use of Daily Values (DVs). DVs are shown on the sample label (bottom of Fig. 41.1). They reflect dietary recommendations for nutrients and dietary components that have important relationships with health. The DV indicates how much of a nutrient that should be obtained in the daily diet. The DVs cover several food components including cholesterol, sodium, potassium, calcium, iron, and dietary fiber as well as carbohydrate and fat. A % DV for protein is only listed if the food is meant for use by infants or children. Not all nutrients have a % DV listed. Reference DVs for trans fats have not been established. Amounts are shown based on a 2000 and a 2500 calorie diet. A 2000 calorie diet is considered about right for sedentary younger women, active older women, and sedentary older men. A 2500 calorie diet is considered about right for many men, teenage boys, and active younger women.

The DVs are based on the following daily allowances:

Total fat: Maximum of 65 grams
Saturated fat: Maximum of 20 grams
Carbohydrates: 300 grams
Fiber: 25 grams; 12.5 grams per 1000 calories
Cholesterol: Maximum of 300 mg
Sodium: Maximum of 2400 mg
Potassium: 3500 mg
Vitamin D: 5 μg (200 IU)

Food labels list the amount of a nutrient in a serving of the food as a percentage of its DV (Fig. 41.1). In other words, the DV for a nutrient represents the percentage contribution one serving of the food makes to the daily diet for that nutrient based on current recommendations for healthful diets. The * used after the heading "%Daily Value" refers to the footnote located at the bottom of the nutrition facts label. This reminds the consumer that the % DVs listed on the label are based on a 2000 calorie diet only. A lower DV is generally desirable for saturated fat, cholesterol, and sodium; a DV of 5% or less is a good indicator. A higher DV is generally desirable for dietary fiber, potassium, calcium, iron, and vitamin D, with 10% or more representing a good source, while a DV of 20% is considered high. There is much debate regarding what should be seen as a desirable intake of total fat and total carbohydrate; this issue is discussed in other chapters.

The above explanation for DVs may seem rather confusing. However, DVs are very easy to use in practice. The "% Daily Value" helps consumers easily see whether a food contributes a little or a lot of a nutrient.

Using the Nutrition Facts Label

Let us now summarize the key rules for reading labels:

- Read the list of ingredients.
- Learning all the rules is ideal, but most people do not have the inclination for that. The next best thing is to focus on four key numbers: calories, sodium, saturated fat, and dietary fiber. Start by figuring out reasonable targets for each of these. For an active adult man who is well motivated to keep himself healthy, appropriate targets are 2500 calories, 1800 mg sodium, 20 grams saturated fat, and 38 grams fiber; for a sedentary adult woman, the numbers are 2000, 1800, 20, and 25, respectively.
- For each food determine these four values. This must be based on the amount actually eaten. The user may well consume more than the serving size shown on the label; a label that states that the package contains two servings may, in reality, be only one serving for some consumers but three servings for others. The food can then be evaluated based on either the actual amounts or the percentages. As a simple litmus test, if the numbers for these four values are consistent with a healthy diet, then everything else will probably fall into place.

Finally, we will look at how the calorie content of food is calculated. We will use the food label shown in Fig. 41.1 as an example. Fat contains 9 calories/gram, while carbohydrate and protein each have 4. So, one serving of the food has 72 calories as fat (8 times 9), 148 as carbohydrate (37 times 4), and 12 as protein (3 times 4). This adds up to 197 calories. The small difference from the number on the label is because of rounding errors. Knowing how to make these calculations can be useful. For example, examination of a food label followed by a quick calculation may reveal that half the energy in a cake comes from fat.

While reading food labels can obviously be very informative, many people may wish to know the total nutrient and energy content of their diet. Appendix B gives websites that allow this to be done at no cost.

Front-of-Package Food Labels

The labels described in the previous sections appear on the back of food packages. For that reason, they are known as back-of-package (BOP) labels. A recent trend is the use of front-of-package (FOP) labels. These are much simpler than BOP labels and are intended to enable shoppers to select healthy foods quickly and easily. A variety of designs are now in use around the world. Some designs present information on a small number of substances, most commonly saturated fat, sugar, and sodium (or salt). Another design strategy is a summary label. Labels of this type summarize how healthy the food is using a single value and expressed in a very simple manner such as stars or a tick. A third design, originally developed in Chile, is based on warning labels, similar to those shown on cigarette packages. These are placed on food packages to warn shoppers that the food is unhealthy because of its relatively high content of substances such as sugar or salt. The effectiveness of different FOP labels was recently reviewed by Temple [5].

The only one of these FOP labels that has attained widespread use in the USA is Guiding Stars. It was also adopted by a chain of supermarkets in Canada. This summary label denotes the health value of the food with zero, one, two, or three stars.

Health Claims

Health Claims on Food Labels

About a dozen health claims may be stated on food labels. They are displayed prominently on the front of food packages. These claims are authorized by the US Food and Drug Administration (FDA) and inform shoppers that the food – as part of an overall healthy diet – may reduce the risk of a specific disease. The claims are based on evidence about the food itself or that the food has a high or low amount of particular nutrients or other substances. In making this determination, the FDA carries out an extensive review of the scientific literature. The health claims are authorized if there is significant scientific agreement (SSA) among experts that the claim is supported by the totality of the available scientific evidence that the substance affects the risk of disease.

Here is a list of the approved health claims for food labels:

- Sodium and hypertension
- Calcium, vitamin D, and osteoporosis
- Folic acid and neural tube defects
- *Dietary lipids and cancer
- Fiber-containing grain products, fruit, and vegetables and cancer
- Fruit and vegetables and cancer
- *Dietary saturated fat and cholesterol and risk of heart disease
- Fruit, vegetables, and grain products that contain fiber, particularly soluble fiber, and risk of heart disease
- Soluble fiber from certain foods and risk of heart disease
- Plant sterol/stanol esters and risk of heart disease
- Dietary noncariogenic carbohydrate sweeteners and dental caries

The two claims marked with * are based on evidence that is now widely seen as questionable. As new evidence emerges, the FDA will review all the claims and update the approved list as necessary.

Other health claims are termed "qualified" as the supporting evidence is somewhat less strong than with the above health claims. Accordingly, the phrasing allowed by the FDA must include a "qualifier" that dilutes the claim. These health claims are authorized based on an Authoritative Statement by Federal Scientific Bodies. Examples of this type of health claim are as follows:

- Whole grain food and risk of heart disease and certain cancers
- Whole grain foods with moderate fat content and risk of heart disease
- Potassium and the risk of high blood pressure and stroke
- Fluoridated water and reduced risk of dental caries
- Substitution of saturated fat in the diet with unsaturated fat and reduced risk of heart disease

In addition to "health claims," food labels may also contain nutrient content claims. These words now have strict definitions as listed in the following:

- Free: Synonyms include "zero," "no," "without," "trivial source of," and "dietarily insignificant source of"
- Low: Synonyms include "little," "few" (for calories), "contain a small amount of," and "low source of"
- Reduced/less: Synonyms include "lower" ("fewer" for calories)

Using Labels to Make Misleading Implicit Health Claims

Food marketing is very sophisticated but can often be misleading. Here are two examples of this. Sugar-sweetened beverages are widely seen as unhealthy. In 2000, a new product appeared called VitaminWater. It comes in a variety of formulations. This beverage contains roughly 5.5% (5.5 g/100 ml) sugar, about half the concentration found in Coca-Cola, plus vitamins and assorted other substances. The manufacturers have succeeded in achieving the best of each world: consumers have the taste of a sugary beverage, while the product's name conveys an implicit message that it is healthy.

The second example is Sunny D. The name is highly suggestive of sunshine and of the vitamin D that the body produces when exposed to sunshine. The label has images of fruit. In reality, the main ingredient (after water) is sugar; it also contains a lesser amount of fruit juice. Many other food products also have large colored images of fruits on their labels. For example, some brands of fruit juice consist mainly of a cheap fruit juice, such as apple juice, but with a small amount of berries. The image will typically display the reverse of this, namely, large brightly colored images of berries.

What these examples demonstrate is why we need front-of-package labels that provide honest, easy-to-understand information. Consumers need to be vigilant to avoid being deceived by deceptive labels, such as products with misleading names or the presence of misleading images.

Major Nutrient Contributions of the Food Groups and of Various Foods

Below is listed the major nutrient(s) found in each of the food groups.

- **Fruit**: Vitamins A and C, folate, potassium, and fiber.
- **Vegetables**: Vitamins A, C, E, and K, folate, magnesium, potassium, and fiber. The vitamin A supplied by fruits and vegetables is provided in the provitamin form (β-carotene).

- **Grains**: Grains are available as either refined or whole grain. Refined grains include white flour, white bread, white rice, corn flakes, and rice krispies. Almost all refined grains are enriched with several vitamins, such as thiamin, riboflavin, and niacin. Refined grains also contain added folic acid (the form of folate used as an additive). However, refined grains are a poor source of several nutrients including vitamins B_6 and K, magnesium, potassium, and fiber. Whole grains include whole grain flour, whole grain bread, rye bread, brown rice, shredded wheat, and oats. Compared with refined grains, these foods have a much higher content of several nutrients including vitamins B_6, magnesium, potassium, and fiber.
- **Meat, fish, poultry, and eggs**: Protein, niacin, thiamin, vitamins B_6 and B_{12}, iron, magnesium, potassium, and zinc.
- **Legumes and nuts**: Protein, folate, thiamin, vitamin E, iron, magnesium, potassium, zinc, and fiber.
- **Milk, yogurt, and cheese**: Protein, riboflavin, vitamin B_{12}, calcium, magnesium, and potassium. In addition, vitamins A and D are present if the food is fortified.
- **Oils**: See below.

Food Sources of Select Nutrients

Lipids

Polyunsaturated fatty acids (PUFA) consist of two main types: n–6 PUFA and n–3 PUFA.

Rich sources of n–6 PUFA include most of the common vegetable oils, such as corn oil, sunflower oil, and most brands of soft margarine. However, some vegetable oils have a much lower content of n−6 PUFA, notably olive oil and canola oil (rich sources of monounsaturated fatty acids) and tropical oils (rich in saturated fatty acids).

Rich sources of n–3 PUFA include fatty fish, such as sardines, mackerel, salmon, trout, and herring. Fish oils are particularly rich in the long-chain n–3 PUFA (DHA and EPA). The n–3 PUFA in plant oils are mainly linolenic acid. Sources include flaxseed oil (a rich source), followed by soybean oil and then canola oil.

Saturated fatty acids: Most animal fats including whole milk, cream, butter, and cheese; fatty cuts of beef, pork, poultry, and lamb products; and tropical oils including palm and coconut oils.

Trans fatty acids: Common food sources in the past included hard margarine (made with hydrogenated oils), cakes, cookies, donuts, pastry, and crackers. This fat has been almost entirely removed from foods sold in the USA.

Cholesterol: Eggs (main dietary source), liver, milk products (if high in fat), meat, poultry, and shellfish.

Dietary Fiber

Fruits, vegetables, and legumes; whole grain products such as whole grain bread, oats, and rye bread. Especially rich sources include wheat bran, bran flakes, All-Bran, and oat bran.

Vitamins and Minerals

Food sources of vitamins are shown in Table 34.1 of Chap. 34. Food sources of minerals are shown in Table 35.1 of Chap. 35.

Phytochemicals

Phytochemicals are a diverse class of bioactive substances found in a wide variety of plants. Fruits, vegetables, whole grains, and legumes are good dietary sources.

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Suggested Further Readings

FDA. This website provides an explanation of how to understand and use the Nutrition Facts Label. https://www.fda.gov/food/food-labeling-nutrition.

Health Canada. A Canadian website can be found by doing a Google search for “nutrient value of some common foods”. This provides detailed information on the nutrition content of large numbers of foods.

Part VIII

Opinions Concerning Supplements

Supplements to Our Diets: Navigating a Minefield

42

Norman J. Temple

Keywords

Dietary supplements · Dietary Supplement and Health Education Act · Herbal preparations · Marketing of dietary supplements · Multivitamin supplements

Key Points

- In this chapter, dietary supplements refer to any substance taken in addition to regular food. This includes vitamins, minerals, amino acids, herbs, enzymes, and various substances extracted from plants and animals. Some of these products are not technically dietary supplements.
- The use of dietary supplements has much increased over the last 30 years; around half of people in North America regularly use supplements.
- A wide variety of supplements are sold. In many cases, there is firm evidence supporting their efficacy, but in many other cases, there is little or no supporting evidence.
- Some herbal preparations have toxic effects and should therefore only be used with much caution.
- Supplements are marketed by a variety of different methods, including health food stores, multi-level marketing, bulk mail, spam e-mails, internet websites, advertising on TV and in newspapers, and infomercials on TV. This marketing often involves giving unreliable or dishonest information that is not supported by scientific studies.
- The marketing of supplements in the USA is weakly regulated.
- Suggestions are given on counseling patients so that they can better evaluate claims made for supplements.

Introduction

Hope springs eternal in the human breast. (A. Pope, Essay on man, Epistle i)

N. J. Temple (✉)
Centre for Science, Athabasca University, Athabasca, AB, Canada
e-mail: normant@athabascau.ca

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There are a number of different ways to classify "dietary supplements" used by the FDA and other organizations. In this chapter, dietary supplements refer to any substance taken in addition to regular food. This includes vitamins, minerals, amino acids, herbs, enzymes, and various substances extracted from plants and animals. Some of these products are not technically dietary supplements. For example, herbal preparations are more akin to drugs. However, these substances are included here as they are marketed and used much like true dietary supplements. By definition, these products are not conventional foods. They are intended to improve health and body functioning and prevent or treat disease.

There has been a substantial increase over the past 30 years in the sales of dietary supplements in the USA. Much of this can be traced to the passing of the Dietary Supplement and Health Education Act (DSHEA) in 1994, a law that gave the supplement industry much wider freedom. Sales of dietary supplements in the USA have been steadily increasing since and now total roughly $42 billion per year [1]. Surveys reveal that around half of adults in the USA take supplements regularly [2–4]. Canadian surveys are broadly similar [5]. The people most likely to use dietary supplements are female, older, white, nonsmokers, regular exercisers, and better educated [2, 3].

Physicians and other health professionals need to be aware of issues related to supplements. Patients may seek advice from their physician concerning supplements. Ideally, physicians should be able to give reliable information. This does not mean that physicians should have a detailed knowledge of all supplements, but rather that they should have a good basic knowledge while also knowing where to obtain additional information. Unfortunately, most physicians have only a weak knowledge of supplements [6].

Common Supplements

Many types of supplements are sold. With some, the evidence of their efficacy is strong, but for many others, it is weak.

Vitamins and Minerals

The story of vitamin D in recent years has been both fascinating and confusing. It had been well known for decades that vitamin D plays a critical role in calcium balance and bone health. Starting around the year 2000, epidemiological studies generated impressive evidence suggesting that a poor intake increases the risk of cardiovascular disease, cancer, and osteoporosis (and therefore of bone fractures).

Based on this evidence, it was widely believed that supplements of vitamin D would help prevent these major health problems. Many randomized controlled trials (RCTs) have been carried out, but the results have been mostly negative [7, 8]. Our best evidence at present is that only limited groups of people may benefit from a supplement. One is frail older people [8]. The other is people who are likely to have low blood levels of the vitamin, including those with dark skin, those with little skin expose to the sun, and inhabitants of northern latitudes, including the northern states of the USA. An appropriate supplement provides about 400−800 IU (10−20 μg) per day [8]. It must be stressed that as the evidence is full of contradictions, conclusions are tentative. A recent review by three experts went one step further. They argued that people with a low body level of vitamin D, a group that includes most Black people who live at northern latitudes, should take a supplement that provides 4000 IU (100 μg) per day. They believe that this would lower their risk of several diseases [9].

Another popular supplement is calcium, often taken by middle-aged and older women in the hope that it will help protect against osteoporosis. Alas, findings from RCTs have been mostly negative regarding the value of this supplement [8].

Supplements of iron and folic acid can be of value for many women during their reproductive years. Iron supplements may also be beneficial to many vegetarians who have a tendency to become anemic.

Multivitamins – meaning pills containing a broad spectrum of vitamins and minerals and that are typically taken once a day – are the most popular type of dietary supplement. These are certainly advisable for people at risk of malnutrition as may be the case with people who habitually consume a low-calorie diet which is often the case with elderly people and those with anorexia, drug addiction, or advanced cancer. But what about healthy adults? Much valuable evidence has come from prospective cohort studies. These are a type of epidemiological study where people's diets are recorded and the subjects are tracked for around 5 to 15 years. Findings consistently reveal that people who consume a multivitamin supplement gain no benefit in terms of a reduced all-cause mortality [10–12]. Several RCTs have taken place in order to determine whether multivitamins have any value in the areas of cardiovascular disease, cancer, or cognitive impairment. A paper published in 2013 in the journal *Annals of Internal Medicine* summarized the findings and drew a firmly negative conclusion [13] The paper had the unambiguous title: "Enough is enough: Stop wasting money on vitamin and mineral supplements."

Antioxidants

Many supplements are sold with a claim of being "rich in antioxidants," the obvious implication being that these products improve health or prevent disease. In support of this, it has been firmly established that antioxidants are important components of some of the body's defense mechanisms. Based on these findings, it seemed logical to assume that supplements of antioxidants will help prevent various diseases. This possibility was tested in the following studies.

Several dozen RCTs have been conducted in order to test the three major antioxidant vitamins, namely, β-carotene, vitamin C, and vitamin E. The goal of the RCTs was to determine the effectiveness of these vitamins for either primary or secondary prevention. The great majority of the subjects in these studies had cardiovascular disease or other conditions that meant that they were at an elevated risk of disease. The dose has typically been far above what would typically be obtained from the diet. Very little evidence has been forthcoming from these RCTs that either β-carotene or vitamin C prevents disease [7]. The results with respect to β-carotene and cancer were discussed in Chap. 14. More importantly, meta-analyses of RCTs indicate that supplementing with these vitamins does nothing to reduce all-cause mortality [7, 14]. Vitamin E presents a more confusing story. It seems to have modest value in the prevention of cardiovascular disease [7], but other evidence suggests that it may lead to a slight increase in all-cause mortality [7].

There is convincing evidence that foods naturally rich in antioxidants, such as fruit and vegetables, reduce the risk of various diseases, such as heart disease and cancer. But these benefits are likely to be the result of the combined action of many different substances including phytochemicals, antioxidants, various vitamins and minerals, and dietary fiber. By contrast, there is minimal evidence that the health benefits obtained from foods rich in antioxidants can also be obtained from purified antioxidants. Therefore, when advertisements for supplements state that a product is "rich in antioxidants," that is weak evidence that it will have a positive effect on health.

Probiotics

The study of the microbiome and its relationship to health has emerged as a hot topic in recent years. The focus has been on the bacteria present in the colon. The rationale for giving supplements of probiotics, preparations containing particular bacteria in a concentrated form, is to establish more beneficial bacteria in the colon. Findings from RCTs provide some supporting evidence that specific probiotics are of value for a small number of medical purposes, such as preventing antibiotic-associated diarrhea. Some evidence suggests that probiotics may also improve immune function [15]

and help with weight loss [16]. Supplement manufacturers have seized on this limited evidence; they are marketing probiotics to healthy people by much exaggerating the possible benefits. Advertisements for such supplements are commonly seen on TV. Before probiotics can be recommended to healthy people as a way to improve health, we need clear supporting evidence from well-designed RCTs, but no such studies have been published [17].

Herbs

A great many different herbal preparations are used in North America and around the world. They are employed for both prevention and treatment of a wide variety of disorders. As noted earlier, herbal preparations are not technically dietary supplements but rather more closely resemble drugs.

Supporting evidence for the value of herbal products is highly contentious. Unlike conventional drugs, they generally lack standardization of active ingredients. There can be much variation between different brands of what is supposedly the same herb due to such factors as the actual species of plant used, the part of the plant used, and the extraction method. Adding to these problems, many herbal products sold in North America do not contain the herbal product stated on the label. This was shown in a study published in 2013 which reported that about half the samples of herbal products tested did not contain the species stated on the label [18].

Let us suppose that a RCT is carried out, and the findings strongly suggest that a particular herbal product is effective for the prevention or treatment of a particular condition. Does this mean that the product can be recommended? The author argues that the answer must be no. This is because the various problems listed above with the formulation of herbal products mean that one cannot be confident that an herbal product purchased by patients will contain the same active ingredients at a similar concentration as that present in the product tested in the RCT.

Here we look at some examples of herbal treatments that have been much researched.

- Echinacea. This herb is widely used in North America and Europe for the prevention and treatment of the common cold. A review concluded that: “The overall evidence for clinically relevant effects is weak” [19].
- St John’s Wort. Evidence suggests that it may be effective in the treatment of mild to moderate depression [20]. This herb therefore appears to be in the small minority where there is solid supporting evidence of efficacy. However, for reasons noted above, because the herbal treatment achieved positive results in clinical trials, that is no guarantee that a preparation purchased in a health food store will have the same chemical composition or will be as effective.
- Ginseng. This very popular herb is often claimed to boost mental and physical performance. But this claim relies in no small part on its use in traditional Asian medicine over many centuries. As is often the case with herbal products, research studies are inconsistent regarding the medicinal benefits of ginseng. Another potential problem is that there are several species of plant that are called ginseng. Overall, there is very little solid evidence that ginseng really deserves the many claims routinely made for its effectiveness [21].
- Cinnamon. This supplement is often used by persons afflicted with type 2 diabetes. It is claimed to improve blood glucose levels. This product may achieve a modest beneficial effect [22].

These examples illustrate the general problem with herbal treatments. First, most have little or no supporting evidence. Second, even where clinical trials have generated positive findings (often using a carefully selected preparation of known composition), it is a leap of faith to conclude that the herb will achieve similarly positive results when used for self-treatment by the average consumer.

Supplements Promoted to Stimulate Detoxification and the Immune System

For the sellers of supplements, detoxification is much like the word antioxidants: it provides a simple concept that most people can easily grasp and that can be used to provide an apparently scientific reason why a particular product will do wonders for health. Detoxification is, of course, a well-established biochemical process. However, herbal treatments, in particular, are routinely sold with the promise that they will stimulate the liver – and perhaps other organs as well – so that detoxification is accelerated and the body is cleansed. This will then lead to all sorts of benefits. However, supporting empirical evidence is lacking.

Many supplements come with the claim that they somehow stimulate the immune system. Much like detoxification, this is usually associated with herbs. However, there is a serious lack of supporting evidence.

Glucosamine and Chondroitin

Supplements of these substances are popular for the treatment of osteoarthritis. While some positive effects have been reported in a few trials, especially for chondroitin, our most reliable evidence is that neither supplement is of clinical value [23].

Prevagen

This supplement consists of a protein extract from jellyfish. It is frequently advertised on TV in North America. It is claimed that it aids the memory. The marketing campaign was so grossly dishonest that in 2017, the Federal Trade Commission and the New York State Attorney General took action [24, 25]. These agencies: "…charged the marketers of the dietary supplement Prevagen with making false and unsubstantiated claims that the product improves memory, provides cognitive benefits, and is 'clinically shown' to work." New York Attorney General Eric Schneiderman stated: "The marketing for Prevagen is a clear-cut fraud… It's particularly unacceptable that this company has targeted vulnerable citizens like seniors in its advertising for a product that costs more than a week's groceries, but provides none of the health benefits that it claims." Incredibly, 3 years later, in 2021, the advert was still appearing on cable TV.

CoQ

Another supplement frequently advertised on TV in North America is CoQ (also known as CoQ10 or coenzyme Q10). Findings from RCTs are not consistent and do not justify claims that it will improve health [26].

Weight-Loss Products

With the huge obesity epidemic that has swept North America, it is scarcely surprising that supplement manufacturers have jumped on the bandwagon. Many products have been marketed. Typically, such products come with thin promises based on even thinner evidence. But what they do produce, very often, is a photo of a young woman with a BMI of about 20. A recent review evaluated the

effectiveness of ten supplements promoted for weight loss and came to the following conclusion: "Contrary to popular belief, results of this review suggest that the use of natural supplements for weight loss are unlikely to contribute to meaningful weight loss and in some cases may contribute to harm" [27]. Table 42.1 briefly describes some of the more commonly sold supplements that come with the claim of enhancing weight loss.

A Repeating Story

What we see, time and time again, is weak evidence dressed up as solid science. The marketers of different types of supplements often use scientific evidence the way a drunk uses a lamp post: more for support than illumination. A major reason that this marketing strategy has been so successful is because most of the population has a weak grasp of science, especially biomedical science [30].

Potential Hazards from Supplements

A common mantra from those in the supplement industry is that supplements are safe. However, many hundreds of cases of undesired side effects induced by supplements have been reported [31]. The true figure likely runs into the thousands as most cases are probably never reported. A study published in 2015 estimated that 23,000 visits occur each year to emergency departments in the USA as a result of harm caused by supplements [32]. This is likely to be a substantial underestimate as it excludes cases where the emergency room physician failed to make a connection between the medical problem and the use of supplements. The type of supplements most often linked to this problem is those recommended for energy and weight loss.

Table 42.1 Features of common ingredients found in weight-loss supplements

Supplement	Claimed action	Effectiveness	Safety[a]	Is it recommended?
Bitter orange	Increases energy metabolism and the breakdown of fat; decreases appetite	Possible small increase in energy metabolism. Effect on weight probably negligible	Some concerns	No
Caffeine	Increases energy metabolism	Small increase in metabolism. Possible small increase in weight loss	Safe	No
Green tea	As caffeine	Effect on weight probably negligible	Safe	No
Chitosan	Reduces fat absorption	Possible small decrease in fat absorption. Effect on weight probably negligible	Safe	No
Chromium	Increases muscle mass and fat loss and decreases appetite and food intake	Possible small increase in weight loss	Safe	No
Conjugated linoleic acid (CLA)	Reduces body fat	Possible small increase in loss of body fat and weight	Safe	No
Garcinia cambogia (hydroxycitric acid)	Suppresses the appetite	Effect on weight probably negligible	Some concerns	No
Hoodia	Suppresses the appetite	None	Possibly unsafe	No

Sources of information: Medline Plus [28] and National Center for Complementary and Alternative Medicine [29]
[a]All products are potentially hazardous if taken in excess

Some supplements sold with the claim that they enhance sexual function have been shown to be adulterated with drugs [33]. A chemical analysis was conducted on traditional Ayurvedic medicines that were being sold in the USA via the internet. The findings revealed that 21% of these herbal preparations exceeded one or more standards for acceptable daily intake of lead, mercury, or arsenic [34]. Recent studies carried out in the USA and Canada have reported that many supplements contain high levels of fillers or contaminants [18, 35]. Again, this problem is most often associated with herbal products. Quite apart from toxic contaminants, many herbs interact with various drugs.

How Dietary Supplements Are Marketed

Dietary supplements are marketed in diverse ways [36]. They can be purchased in pharmacies, supermarkets, and health food stores (HFS), directly from people engaged in multilevel marketing and by mail order. Their sales are promoted using all forms of marketing methods, including advertisements in newspapers and on TV, bulk mail, e-mails and internet websites, as well as by infomercials on TV.

Direct Contact with Consumers

HFS are a popular source of dietary supplements. A request for advice will typically be responded to by a recommendation to take a particular supplement: advice that usually suffers from a serious lack of credible supporting evidence. Studies in Hawaii, Canada, and the UK have shown that when the same question is asked in different HFS, there is a huge variation in the advice that is given [36].

It is usually a different story in pharmacies. As pharmacists are trained health professionals and must abide by a code of ethics, customers requesting advice are far less likely to be given misleading information. This was confirmed in a study conducted in Canada [37]. It was found that 90% of the time that questions were asked in HFS, customers were given recommendations that were either unscientific or were poorly supported by the scientific literature. By contrast, this occurred for only 39% of questions in pharmacies. Conversely, on more than half of visits to pharmacies, staff gave advice considered to be fairly accurate or accurate, but this seldom occurred in HFS.

Multilevel Marketing

Dietary supplements are also sold by direct marketing – a strategy in which company salespeople recruit other salespeople. The foot soldiers and everyone up the chain receive a commission from their sales. My observations of how this form of marketing is carried out in the area of supplements strongly suggest that, much like HFS, claims are often made that are either unscientific or are poorly supported by the scientific literature. On one occasion, flyers were distributed in Edmonton promoting a particular product where the person behind it was described as “the world’s leading viroimmunologist.”

Advertising

Dietary supplements are advertised in diverse ways. Advertising on TV and in newspapers is a common method. Infomercials are another method. They resemble regular TV programs. They typically last for 30 min and air during the night. Bulk mail (“junk mail”) is a common form of advertising, especially for supplements that promise weight loss. Spam e-mails are a cheap and easy way for manufacturers to promote their dietary supplements to tens of thousands, if not millions, of people. As a result, large numbers of products are being touted. In recent years, vast numbers of spam e-mails

have been sent out promoting sex-related nutritional supplements. Spam e-mails typically work by directing potential customers to a website. There are many websites selling all types of supplements; they are, in effect, virtual HFS. They often flout US law [38].

Regulations on the Marketing of Supplements

The USA

In 1994, Congress passed a law regulating the marketing of dietary supplements: the Dietary Supplement and Health Education Act (DSHEA). This law freed dietary supplement manufacturers from many FDA drug regulations [39]. Whereas under the former law manufacturers were required to prove that a dietary supplement is *safe*, now, under DSHEA, the onus in on the FDA to prove that a supplement is *unsafe*. This shift in regulatory policy places burdens on a federal agency with important public health responsibilities but limited resources [31].

As a result of DSHEA, marketers of supplements are free to make health-related claims (structure/function claims) but are not permitted to state explicitly that the product will cure or prevent a disease. They must also state that the FDA has not evaluated the agent. What this means is that a marketer may now claim that a supplement "boosts the immune system," "makes the body burn fat while you sleep," or "fights cholesterol," provided they stop short of saying that the supplement prevents infectious disease, cures obesity, or prevents heart disease. Needless to say, most consumers will be confused by the distinction between the two sets of claims.

Another major flaw in DSHEA is that herbal preparations are regulated together with vitamins and minerals. As a result, these products escape proper regulation. As mentioned earlier, it would be more accurate to call these products drugs rather than dietary supplements [40].

DSHEA was passed by Congress after heavy lobbying that was orchestrated by the supplement industry [39]. Over the years following passage of DSHEA, there have been countless cases of sellers of supplements making unscientific claims, unsupported by any good evidence, and claiming that these are established facts.

In 2003, the *Journal of the American Medical Association* [41] published an editorial deploring this state of affairs: "The public should wonder why dietary supplements have effectively been given a free ride. New legislation is needed for defining and regulating dietary supplements." A similar article was published in 2002 in the *New England Journal of Medicine* [40] with a focus on herbal supplements. The author believes that these comments are as true today as when they were written.

Canada

Canada provides an object lesson for the USA on how not to reform the system for the production and marketing of supplements. In 1999, the government of Canada created a new organization, the Natural Health Products Directorate, to regulate dietary supplements. The regulations require a pre-market review of products to assure Canadians that label information is truthful and health claims are supported by appropriate scientific evidence. When these regulations were announced, the clear impression was given that the marketing of supplements would become much more evidence-based and honest. The supplement industry was given several years to implement the regulations, which came into force in 2004. Much evidence, some of which was referred to in this chapter, indicates that the new regulations have failed to achieve any real impact [42]. In that respect, the situation in Canada is still every bit as bad as that in the USA. In the author's opinion, the clear lesson is that regulations are worth little if the regulators are unable or unwilling to enforce the regulations.

Helping Patients Make Informed Choices About Dietary Supplements

As mentioned earlier, the use of supplements by patients can pose hazards, including both harmful side effects and interference with the action of prescription drugs. These problems arise most often with herbs. Patients often do not tell their physician about their use of supplements. Physicians and other healthcare professionals need to be aware of these problems. In addition, as the general population is exposed to enormous amounts of marketing activity for supplements, much of which is misleading; physicians therefore have a responsibility to assist their patients in evaluating health claims. Indeed, physicians are well positioned to help counter the bogus marketing of supplements as they are widely seen as a credible source of information. Moreover, every year, millions of people talk to a physician.

Physicians and other healthcare professionals can offer the following simple rules to help their patients/clients evaluate product authenticity. First, suspicious claims for supplements often have the following features:

- Money-back guarantee
- The use of testimonials
- A claim that the product is a "scientific breakthrough"
- Touting the product as an effective treatment for a broad range of ailments. If things are too good to be true, they probably are.

Additional guidelines that other healthcare professionals can usefully convey to patients are as follows:

- Ignore advice given by persons who have a financial interest in selling supplements, especially when they appear to have no relevant qualifications. This includes staff in health food stores and people engaged in multilevel marketing, and statements on flyers that arrive in the mail, on infomercials, and on websites of supplement manufacturers.
- If in doubt about a supplement, obtain advice from a licensed health professional, such as a physician, dietitian, or pharmacist.
- Always use common sense. People should view all types of marketing of supplements with a healthy dose of skepticism.
- For further information, check credible sources of information. This is a consumer's best protection against fraudulent and misleading marketing. Information on supplements is easily found on the websites of several health-related organizations. Here are three of the best:
  - Mayo Clinic; http://www.mayoclinic.org/drugs-supplements [43]
  - National Center for Complementary and Alternative Medicine (NCCAM); http://nccam.nih.gov/ [29]
  - Medline Plus; http://medlineplus.gov/ [28]

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Examples of False and Misleading Information

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Norman J. Temple

Keywords

Blood groups · Conflict of interest · Detoxification · Dr. Oz · False information Misleading information · Nutritionist training program

Key Points

- False and misleading information is a common problem across many areas of nutrition.
- This chapter briefly examines some examples including Dr. Oz and his TV show, unscientific weight-loss treatments, diet programs and approaches to treating illnesses that are based on a person's blood group, and approaches to the prevention and treatment of disease based on detoxification.
- This chapter also looks at training programs for nutritionists that lack scientific credibility.
- Problems of food companies interfering in scientific research and of conflict of interest in research are discussed.

Introduction

The previous chapter discussed dietary supplements, including how they are marketed. That chapter stressed that much of this marketing is based on delivering false and misleading information to potential customers. This chapter continues the subject of how the problem of false and misleading information is common in other areas of nutrition. This problem has a long history across the medical sciences. In Victorian times, a common belief was that masturbation was a major cause of blindness and insanity. In the 1970s, a great many people believed that if they were feeling irritable and lacking in energy, this was a sure sign of low blood sugar. This epidemic mysteriously disappeared only to be replaced by newer epidemics such as an allergy to gluten, an overload of toxins, and a yeast infection (*Candida*). More recently, millions of parents have become convinced that some types of vaccination pose a significant risk to children. The resulting decrease in the proportion of children who have been

N. J. Temple (✉)
Centre for Science, Athabasca University, Athabasca, AB, Canada
e-mail: normant@athabascau.ca

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vaccinated has led to many cases of measles and some deaths. The problem of false and misleading information is continuously evolving. It is clearly impossible, therefore, to cover all aspects of this problem. This chapter is intended only to present some illustrative examples.

Physicians and other healthcare professionals need to be cognizant of the problem. This is because, first, out of any random group of patients, several will probably believe that some of the medically related false ideas being widely circulated (usually on the Internet) are scientifically accurate, and, second, because these false ideas can cause harm to patients.

The Case of Dr. Oz

Dr. Mehmet Oz is a highly accomplished heart surgeon. He has had a TV show for several years that has been watched by millions of people across North America. He dispenses advice on many topics in the general area of health. Researchers from the University of Alberta in Edmonton, Canada, made a careful analysis of the accuracy of his claims [1]. They estimated that 39% of his advice was in the area of diet. The researchers were able to find evidence in support of 46% of the recommendations, while 15% were contradicted by the evidence. That left 39% of the recommendations where no supporting evidence could be found. In other words, at least half of the recommendations made by Dr. Oz lacked supporting scientific evidence.

One of his claims landed him in hot water. Dr. Oz was called before Congress to testify at a Senate hearing about deceptive advertising for over-the-counter diet supplements after he sang the praises of green coffee bean extract as a "miracle" weight loss pill [2]. Sen. Claire McCaskill, who chairs the Senate's Consumer Protection panel, blasted him for making such claims on his show when "you know it's not true." In reply Dr. Oz defended himself by pointing to his right to suggest ways that may assist with weight loss by using various products. However, he failed to provide specific supporting evidence for his claims.

Weight-Loss Treatments

If diet books worked, then the obesity epidemic would have been vanquished years ago. But for the past several decades, the diet book industry has been growing in parallel with American waistlines. A search at Amazon shows that thousands of books are published each year on the subject. A perusal of the titles reveals obvious indicators that false and misleading information is a common ingredient. For example, 170 books were published in 2018 that included the words "quick and easy weight loss" in the title (or a slight variation of these words). Similarly, the words "belly fat" appeared in the titles of 120 books. This problem extends to magazines. Woman's World is a supermarket tabloid sold across North America. It regularly features the latest "lose a pound per day" diet on its front page.

Blood Types and Health

In 1991 James D'Adamo published a book with the title *The Blood Type Diet: Your Personalized Diet and Exercise Program*. The theme of this book is that people should select their diet, as well as their exercise program, based on their ABO blood group. Over the years, several other authors jumped on the publishing bandwagon with books making similar claims. These books claim that a person's blood group can be used as a guide in order to select a diet that will help both prevent and treat an assortment of health problems including cancer, heart disease, diabetes, arthritis, and overweight.

How much evidence is there to justify the many claims made in these books? There is, in fact, surprisingly strong evidence that blood groups do affect health. Folks who have blood group O have a significantly reduced risk of cardiovascular disease, some types of cancer, as well as of all-cause mortality [3]. This suggests that the antigens that are the basis of blood groups have complex effects on disease etiology. Perhaps one day this information will be translated into practical advice on reducing risks to health if your parents bequeathed you a bad blood group. But there is no evidence to support the claims of those promoting particular diets, or other types of treatment, based on a person's blood group. A systematic review on this subject was published in the *American Journal of Clinical Nutrition* [4]. The researchers concluded that: "No evidence currently exists to validate the purported health benefits of blood type diets."

Detoxification

Detoxification was discussed in the previous chapter where it was pointed out that many dietary supplements, mainly herbal ones, are sold with the claim that they enhance health by speeding detoxification. This claim is devoid of supporting evidence. However, the claims made in the area of detoxification go well beyond supplements.

The American chapter of the story started a century ago. Benedict Lust immigrated to the USA from Germany late in the nineteenth century. In 1918, he wrote the following: "The natural system for curing disease is based on….the employment of various forces to eliminate the poisonous products in the system…" [5]. Lust later became one of the founding fathers of naturopathy in the USA.

The concept of detoxification is based on the general claim that the accumulation of toxins in the body is involved in much sickness and that disease can be both prevented and cured using treatments to eliminate these toxins. This concept is still the basis for various naturopathic therapies today. Indeed, a survey of naturopaths in the USA reported that 92% stated that they employ detoxification therapies [6]. Detoxification is often advocated to enhance weight loss. The treatment at the center of detoxification is fasting, often accompanied with fruit or vegetable juices. As noted above and in the previous chapter, the supplement industry has jumped on the bandwagon and promotes many products as aids to detoxification. In recent years, the concept has gained much popularity in nutritional and health circles that clearly lie well outside the mainstream. There has also been an explosion of books on the subject in recent years.

A variation of this approach is autotoxicity where the focus is on removing toxins from the colon, often with the aid of an enema. A more extreme variation is colonic irrigation, a procedure that is potentially harmful as it can hyperextend the colon [7, 8]. The irony of this treatment is that the same effect can be achieved by a few teaspoons of wheat bran at far less risk, far less discomfort, and far less cost!

There is very little credible evidence that detoxification treatments, such as dietary changes, consumption of herbs and supplements, fasting, or colonic irrigation, can remove toxins from the body [9]. Moreover, there is no evidence that these treatments improve health.

Training Programs for Nutritionists

The usual dietitian training program in North America is a 4-year degree in nutrition followed by a supervised clinical internship. But a Google search using the term "nutritionist training program" reveals many programs, most of which are seriously lacking in scientific credibility.

Here is one example of a program. The American School of Natural Health (http://www.americanschoolofnaturalhealth.com) [10] offers a training course to become a "nutrition consultant." Their

courses emphasize the importance of "detoxification and cleansing." Programs of this type typically take about 1 or 2 years to complete which is considerably less than conventional nutrition programs. But for many people that is too long. One option for people in a rush is the American Fitness Professionals & Associates (www.afpafitness.com) [11]. They will train a person to become a "Certified Nutrition & Wellness Consultant" in only 100 hours.

Some schools offer a more in-depth program. The International College of Natural Health and Traditional Chinese Medicine (http://www.internationalhealthcollege.com), based in Ontario, Canada, has a 24-month program called the "Orthomolecular Nutrition Diploma Program" [12]. Some indications of what students will learn during the program are indicated by a description of books from the approved reading list:

(i) "The 4-Week Ultimate Body Detox Plan shows you how to get rid of toxins using a simple and effective step-by-step approach."
(ii) "Control the level of acid in your body and reclaim your health with this simple, step-by-step program. Beginning a healthier lifestyle can be as easy as starting your day sipping a glass of water with a squeeze of lemon juice. Drinking this simple drink is only one of the many ways, all outlined in The Ultimate pH Solution that you can change your body's pH and ward off disease."
(iii) "The only Self-Help Guide to make alterative cancer therapies work for YOU. A bold revelation of what this [20th] century's early naturopaths learned about not only the causes of cancer, but also effective treatments and what you CAN DO NOW to save your life with this vital knowledge."

The Problem of Food Companies Interfering in Scientific Research

There is an enormous amount of money tied up in the results of research studies in the area of nutrition science. Reports have appeared that suggest that conflict of interest exists and is distorting the findings of some research studies. Here is one illustrative example. An analysis was made of research studies and review papers published between 1999 and 2003 on soft drinks, juice, and milk [13]. Those reports where the authors had industry financing were at least seven times more likely to report a finding favorable to industry than was the case with reports where there was no industry financing. A study of papers published in 2018 in the area of nutrition research produced remarkably similar findings [14].

How should these findings be interpreted? My viewpoint is as follows. These findings do not necessarily indicate that deliberate dishonesty has taken place. Rather, they raise suspicion that the research process has been corrupted. This can occur in various ways such as by designing randomized trials in such a way that the results desired by the funders are more likely to be observed, by analyzing the data so as to make the conclusions as close as possible to what the paymasters wants to hear ("if you torture the data long enough, it will eventually confess"), and by only allowing the findings of studies to be published if they report the "right" results.

Journals are well aware of this problem, especially in the area of drug research. As a result, most journals now insist that all authors of papers state whether there is any potential conflict of interest. But that is only a partial solution to the problem as the following example illustrates. A paper was published in a nutrition journal in 2014 that reviewed the value of vitamin supplements [15]. The paper strongly argued the case that such supplements are of much value. A note at the end of the paper stated that funding for the work came from Pfizer but failed to mention that Pfizer is the manufacturer of Centrum multivitamins, which is the leading brand of multivitamins sold in North America. Now it may well be that the author of this review was completely free of bias and carried out a first-class piece of work. But the point is that readers of the review should be fully informed of potential conflicts of interest.

Starting around the year 2000, an impressive body of evidence appeared linking sugar-sweetened beverages with the epidemic of obesity. This poses an obvious threat to Coca-Cola. They have responded by funding research that emphasizes the role of physical activity in obesity while ignoring the role of diet [16]. In China, Coca-Cola succeeded in taking a large measure of control over obesity research and policy development. As a result, the Chinese policy on obesity, especially during the years 2000–2013 emphasized physical activity over diet [17]. In another significant action, Coca-Cola set up an organization called the Global Energy Balance Network [18]. The game plan was for the organization to be perceived as being both independent and scientifically credible while promoting interpretations of the science of obesity that are favorable to the commercial interests of Coca-Cola.

Conclusion

Much of what has been written in this chapter will doubtless be out of date within a few years. But creative minds will dream up many new forms of false and misleading information. Some will do it because they are deluded, some because they love the publicity, and others because of greed. There is little that can be done to stop these people. A society that values free speech allows people to say that HIV does not cause AIDS and that megadoses of vitamin C cure cancer. The general public is easily misled by this misinformation as only a small minority has the scientific education that allows them to identify which claims are probably correct and which should be ignored. This places the onus on health professionals to be aware of this never-ending problem, to explain the problem to their clients, and to provide sound information.

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Part IX

Final Thoughts

Postscript

44

Ted Wilson, Norman J. Temple, and George A. Bray

Research studies over the last several decades convincingly demonstrate that the disease pattern seen across the Western world is a direct result of lifestyle and that diet plays a major role in this. This information has been of tremendous value in showing how health may be enhanced and diet-related diseases prevented. Indeed, it is no exaggeration to say that these discoveries in nutrition science represent one of the most important advances in the field of public health during the past half century. That is the essence of this book. It is the fervent hope of the editors that this book will be a valuable resource for physicians and other healthcare professionals thereby enabling them to enhance the service they provide to their clients.

The changes in nutrition that enable improved health have come about as a result of either avoidance of a diet or acceptance of the dietary lifestyle that is right for the individual. The following studies provide excellent summaries of the importance of nutrition (and lifestyle) to health.

- A wide range of highly processed foods are now often referred to as ultra-processed foods. These include those foods where the main ingredients are sugar, refined flour, and added fats, plus much salt. Almost 60 percent of the calories in the American diet come from these foods [1]. Solid evidence has shown that people who have a relatively high intake of ultra-processed foods have an appreciably increased risk of several chronic diseases including cardiovascular disease, cancer, and obesity, as well as all-cause mortality [2]. Recognizing the need to avoid ultra-processed foods is paramount.
- A meta-analysis of cohort studies concluded that people who consume a relatively healthy diet benefit from a significantly lower risk for all-cause mortality, cardiovascular disease, cancer, diabetes, and neurodegenerative diseases [3].

T. Wilson (✉)
Department of Biology, Winona State University, Winona, MN, USA
e-mail: twilson@winona.edu

N. J. Temple
Centre for Science, Athabasca University, Athabasca, AB, Canada
e-mail: normant@athabascau.ca

G. A. Bray
Pennington Biomedical Research Center, Baton Rouge, LA, USA
e-mail: george.bray@pbrc.edu

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- It is important to bear in mind that other aspects of lifestyle, in addition to diet, also have a major impact on health. This was well illustrated by the following meta-analysis of cohort studies [4]. People were categorized based on the extent to which they follow a generally healthy lifestyle. Lifestyle factors included not only diet but also smoking, physical activity, and body weight. Risk of cardiovascular disease was 67% lower in those who followed a healthy lifestyle in comparison with those who did not.

In a perfect world, a book about nutrition would simply state the established facts, and everyone would be on the same page. But that is far from the case. We can illustrate nutritional divergence with a geographical metaphor. The rivers of Montana flow to three different seas. One river flows west to the Pacific, a second goes north through Canada to Hudson Bay and thence to the Arctic Ocean, and the third joins the Missouri, then the Mississippi, and continues to the Gulf of Mexico. The world of nutrition is like these rivers: many streams can merge into major rivers of thought, action, and direction, but these rivers can also flow in opposite directions and interact in complex ways with the total landscape of nutritional health. These opposing thoughts and actions are sometimes seen in the chapters of this book. Here are a few examples:

- The effects of different foods on the body reflect the synergistic interactions between the many substances present in foods, including micronutrients, phytochemicals, fats, sugar, and dietary fiber. The relationship between diet and disease is best explained in terms of foods rather than single nutrients. This concept is known as food synergy and is now widely accepted [5, 6].
- Major changes have also been seen in recent years in our understanding of the role of different components of the diet in the causation of obesity (e.g., the relative importance of fat and carbohydrate) and of heart disease (e.g., the relative importance of saturated fat).
- Several different dietary patterns are now being recommended, often in competition with each other. These include the Mediterranean diet, the DASH diet, and the vegetarian diet.
- The ideal design of food guides has changed radically in recent years. The American food guide has changed from a pyramid (with recommendations regarding the number of servings from each food group) to a plate (with few quantitative recommendations).
- The general public is often confused by the information they receive. There are several reasons for this. Nutrition experts endeavor to convey scientifically accurate information to the general public, but, quite often, the supposedly authoritative statement by one nutrition expert is contradicted by other experts. Adding to the confusion, new discoveries regularly refute what had for years been widely believed. A major source of confusion is that many self-proclaimed “experts” are highly active in disseminating a river of false and misleading information. In particular, the food industry, through its advertising, encourages the population to feast on unhealthy foods. Likewise, there is a vast amount of dishonest marketing for dietary supplements.

At the time that this book moved to printing, the world was in the midst of the COVID-19 pandemic. This created immense short-term challenges to providing improved nutrition [7]. COVID-19 has affected food delivery systems, nutrition, physical activity, weight management, and the simple ability of a patient to receive effective nutrition counseling.

We as clinicians and researchers have been deluged with a flash flood of publications on all aspects of COVID-19. Many of the hypotheses and initial reports will be found to be incorrect or of negligible importance. But one finding is based on solid evidence: people who have preexisting conditions related to nutrition, such as obesity, cardiovascular disease, or diabetes, are at high risk of serious illness after developing COVID-19. This emphasizes yet again the crucial importance of a healthy diet (as well as a generally healthy lifestyle) to prevent those conditions and thereby greatly reduce the risk of serious illness or death if a person develops COVID-19.

Much research is being carried out into many other aspects of nutrition that may have an impact on COVID-19. Nutrition may be of relevance to both prevention (by enhancing the body's immunological defenses) and to improve outcomes in infected patients, as well as their nutritional needs following recovery. In the coming years, the COVID-19 flood will recede and as it does the quality of our understanding will be better understood. These important lessons will probably be equally true when the next pandemic arrives.

Clearly, a person who wishes to be well informed about nutrition faces challenges. In particular, the ability of health professionals to communicate accurate information to patients continues to be ever more difficult. This book enables the reader to keep their knowledge of nutrition updated. However, as a sad irony, despite the overwhelming evidence that nutrition has such enormous potential to improve human well-being—at modest cost—there is still a chasm between nutrition knowledge and its full exploitation for human betterment. This, hopefully, is what our readers will now be inspired to do, and this is our final takeaway message.

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Appendix A: Aids to Calculations

Weight

1 gram = 0.035 oz
1 kg = 2.20 lb
1 oz. = 28.35 grams
1 lb. = 454 grams

Length

1 cm = 0.393 in
1 meter = 39.37 in
1 in = 2.54 cm
1 ft. = 30.4 cm

Volume

1 pint (US) = 0.473 L = 16 oz
1 quart (US) = 0.946 L = 32 oz
1 fluid oz. = 29.57 mL
1 L = 2.11 pints (US)
1 cup = 8 oz. = 236 mL (commonly rounded to 250 mL)
1 teaspoon (tsp) = 5 mL
1 tablespoon (tbs or T) = 3 teaspoons = 15 mL

Temperature

To change Fahrenheit (°F) to Celsius (°C), subtract 32, then divide by 1.8
To change °C to °F, multiply by 1.8, then add 32

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Boiling point 100 °C = 212 °F
Body temperature 37 °C = 98.6 °F
Freezing point 0 °C = 32 °F

Energy

1 kcal = 4.2 kJ (kilojoules)

Energy in Food Components (Kcal per Gram)

Fat: 9
Carbohydrate: 4
Protein: 4
Alcohol: 7

Body Mass Index (BMI)

BMI = weight (kg) divided by height $(m)^2$ or [weight (lb) x 703] divided by height $(in)^2$

Appendix B: Sources of Reliable Information on Nutrition

Books

Duyff R. American Dietetic Association complete food and nutrition guide. Geneva, Il: Houghton Mifflin Harcourt; 2012.

Temple NJ, Wilson T, Jacobs DR, eds. Nutritional health: strategies for disease prevention, 3rd ed. New York: Humana Press; 2012.

US Department of Health and Human Services; US Department of Agriculture. 2015–2020 Dietary Guidelines for Americans. eighth ed. Washington, DC: US Dept of Health and Human Services; December 2015. http://www.health.gov/DietaryGuidelines.

Internet Websites

http://www.mayoclinic.com

This is operated by the Mayo Clinic and provides much information on health and disease, including diet and supplements. It also sells books written by Mayo Clinic experts.

http://www.healthfinder.gov

A source of health information on many topics. The website is run by the U.S. Department of Health and Human Services.

http://medlineplus.gov

This website is operated by agencies of the US government and provides extensive information on many aspects of health and medicine (Also in Spanish).

http://www.ncbi.nlm.nih.gov/PubMed

MEDLINE. This is the "big brother" of MedlinePlus. It provides direct access to a database of well over 25 million articles (more than a million per year) published in thousands of scholarly journals in all areas of the biomedical sciences.

http://www.eatright.org

American Dietetic Association. Resource for nutrition information.

http://www.nhlbi.nih.gov

National Heart, Lung, and Blood Institute. Provides much valuable information on heart disease and related subjects.

http://www.heart.org

American Heart Association. Another resource on heart disease.

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http://www.cancer.gov

National Cancer Institute. This provides extensive information on all aspects of cancer. (Also in Spanish).

http://www.diabetes.org

American Diabetes Association. Extensive information on all aspects of diabetes. (Also in Spanish).

http://www.aap.org

American Academy of Pediatrics. Information on all aspects of pediatrics, including nutrition.

http://win.niddk.nih.gov

National Institute of Diabetes and Digestive and Kidney Diseases. Information on diabetes and diseases of the digestive tract, kidney, and liver. Other topics covered include nutrition and weight control.

The following two organizations run websites that give reliable information on various health frauds:

National Council Against Health Fraud (NCAHF): http://www.ncahf.org

Quackwatch: http://www.quackwatch.org

People can obtain an analysis of their diet, at no cost, at the following websites. In each case, a diet record is entered, and the website provides extensive information on nutrient content.

http://www.nutritiondata.com. Operated by NutritionData.

A Canadian website can be found by doing a Google search for "nutrient value of some common foods." This provides detailed information on the nutrition content of large numbers of foods.

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