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

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

Nutrition Guide for Physicians and Related Healthcare Professionals

Second Edition

Humana Press

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Adrianne Bendich, Ph.D., FACN, FASN,
Connie W. Bales, Ph.D., R.D., Series Editors

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

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

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

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To Zac, my adorable grandson

—Norman

This book is dedicated to my beloved Jack, Dirk, Karen, and Moki, as well as the physicians and veterinarians whose help keep us healthy and happy.

—Ted

To my wife Mitzi with whom I have shared so many wonderful meals.

—George

Preface

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

Many advances took place in our understanding of basic nutrition 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, and vegetables.

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 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 [3]. Nevertheless, there are still many gaps in our knowledge. For example, we cannot properly explain why taking a vitamin supplement pill seldom delivers any 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 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 a registered dietitian. *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 opening six chapters (Part 1) 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 7–19 (Part 2) summarize the role of nutrition in the prevention and management of chronic conditions frequently seen in clinical practice, including obesity, diabetes, coronary heart disease, hypertension, cancer, gastrointestinal disorders, liver and pancreatic disease, chronic kidney disease, osteoporosis, eating disorders, inherited metabolic disorders, and food allergies and intolerances. This is followed by Chaps. 20–27 (Part 3) that look at different aspects of the diet, including vitamins, minerals, and dietary fiber, and recommendations for vegetarian diets, organic food, and alcoholic and nonalcoholic beverages. Chapter 28 (Part 4) then summarizes our current knowledge regarding the relationship between diet and health. That chapter concludes with an overview of various food guides. This theme continues in Chaps. 29–31 (Part 5) that explore diverse sources of information including Dietary Reference Intakes, food labels, and useful approaches for persuading patients to make healthful behavior changes. The final five chapters cover several diverse topics (Part 6). Chapter 32 examines issues related to dietary supplements, especially the problem of dishonest marketing. Chapter 33 then looks at the widespread problem of misleading information in the area of nutrition. Finally, Chaps. 34–36 consider three other topics: drug interactions with foods, methods for assessing nutritional status, and bariatric surgery.

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 three quotes illustrate our changing understanding of what constitutes nutritional and medical wisdom.

Herman Boerhaave (1668–1738) was a great Dutch physician. One story is that he left a book in which he had set out all the secrets of medicine. After he died it was opened and all the pages were blank except one on which was written: "Keep the head cool, the feet warm and the bowels open."

It was not so long ago that vegetarians were seen as cranks. 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 carcase; 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].

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

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Series Editor Page

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

"Nutrition Guide for Physicians and Related Healthcare Professionals, Second Edition," edited by Norman J. Temple, Ted Wilson, and George A. Bray is a very welcome addition to the **Nutrition and Health Series** and fully exemplifies the Series' goals. This volume represents a critical updating of the chapters that were so well received when the first edition was published in 2010. The volume is designed as 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. The 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. Certainly, the obesity epidemic remains a major concern especially as the comorbidities, such as the metabolic syndrome, type 2 diabetes, hypertension, and hyperlipidemia, are seen even in young children. The editors have made great efforts to provide health professionals with the most up-to-date and comprehensive volume that highlights the key, well-accepted nutrition information available to date. 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. Clear definitions and distinctions are made concerning commonly asked patient questions such as what are the differences between the different 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 two chapters that review the essential vitamins and essential minerals. This volume includes 36 review chapters that contain Key Points and Key Words as well as over 900 targeted references, 65 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 six 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.

The editors of this volume are experts in their respective fields and represent the medical profession as well as the academic research community. Norman J. Temple, Ph.D., is a member of the faculty of Centre for Science at Athabasca University, Athabasca, Alberta, and serves as Professor of Nutrition. Dr. Temple has more than 100 peer-reviewed publications and book chapters. 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 and published in 2003**; "Nutritional Health: Strategies for Disease Prevention, Second edition,"** edited by Norman J. Temple, Ted Wilson, and David R. Jacobs and published in 2006; **"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 and published in 2016.

Dr. 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 and dietary supplements including pistachios, low-carbohydrate diets, cranberries, cranberry juice, apple juice, grape juice, wine, resveratrol, creatine phosphate, soy phytoestrogens, eggplant, coffee, tea, and energy drinks. He has examined the associations between these dietary factors and the development of heart failure, diabetes, and obesity. Diet-induced changes that have been studied include physiological evaluations of plasma lipid profiles, antioxidants, vasodilation, nitric oxide, platelet aggregation, and glycemic and insulinemic responses using in vivo and in vitro models. Dr. Wilson is a member of the American Physiological Society, American Society for Nutrition, and Institute of Food Technologists and serves on the editorial board of the *Journal of Food Processing*. As mentioned above, Dr. Wilson has coedited the first and second edition of **"Beverages in Nutrition and Health,"** the three editions of **"Nutritional Health: Strategies for Disease Prevention,"** and **"Nutrition Guide for Physicians."** He also enjoys teaching courses entitled Nutrition, Cardiovascular Physiology, Cell Signal Transduction, and Cell Biology.

Dr. George C. Bray is a world-recognized expert in obesity research. He became the first Executive Director of the Pennington Biomedical Research Center in Baton Rouge, Louisiana, in 1989 and oversaw the growth of the facility from 25 employees and a million dollar budget to a flourishing

research center with over 70 scientists, 350 employees, and an annual budget of nearly $20 million. Dr. Bray is University Professor emeritus at Louisiana State University and the Boyd Professor at the Pennington Biomedical Research Center of Louisiana State University in Baton Rouge, Louisiana. He is Principal Investigator for the Diabetes Prevention Program Outcomes Study and the Look AHEAD study, two multicenter NIH-funded clinical trials. He is a Master in the American College of Physicians and a Master of the American College of Endocrinology. He is a member of numerous professional societies including the Obesity Society, the Endocrine Society, the American Diabetes Association, the American Association of Clinical Endocrinologists, and the American Physiological Society. In 1982 he founded the North American Association for the Study of Obesity (NAASO, now the Obesity Society), and he was the founding editor of *Obesity Research*, as well as co-founder of the *International Journal of Obesity* and the founding editor of *Endocrine Practice*. In recognition of his critically important contributions to the fields of obesity and human metabolism research, Dr. Bray received the Goldberger Award from the American Medical Association, was elected to the Society of Scholars at Johns Hopkins University, and received the Osborne–Mendel Award from the American Society for Nutrition, the McCollum Award from the American Society of Clinical Nutrition, the Mead-Johnson Award, the Tops Award, Stunkard Award, and the Presidential Medal from the Obesity Society. Dr. Bray was also a coeditor of the first edition of **"Nutrition Guide for Physicians."**

Part 1: Nutrition Across the Lifespan

The six introductory chapters in the first part provide readers with the basics of nutritional requirements during pregnancy, lactation and weaning, childhood nutrition, adolescent nutrition, unique needs of the menstruating female, and healthy aging. The chapters describe investigations into the mechanisms and factors affecting nutrient metabolism and the changes that occur at each life stage. Descriptions of the nutritional and immunological value of breast milk are included 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. The introductory chapters also provide reviews of the major clinical studies and national guidelines for each age and life stage. The chapter on adolescence and young adults examines the development of eating disorders including obesity, anorexia, bulimia, and binge eating. Healthy aging is particularly relevant as the population is growing older. By 2030 one out of every five people in the USA will be 65 years of age or older. Lifestyle changes and changes in body functions (sight, hearing, taste, digestion, bone, muscle, etc.) can affect food choices and vice versa. This sensitive chapter provides a wealth of important advice to health professionals.

Part 2: Nutrition in the Prevention and Management of Chronic Conditions

Part 2 contains 13 chapters that examine, in the first 4 chapters, 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. Separate chapters review the pathophysiology of the metabolic syndrome, type 1 and type 2 diabetes, hypertension, and hyperlipidemia, and relate these to the mechanisms behind the alterations in metabolism that increase chronic disease risk. Practice guidelines and tools for obesity management including up-to-date information on medical nutrition therapy and surgical obesity treatments and their implications for improving human health and

reducing obesity-related diseases are tabulated for the reader. Two chapters examine the importance of dietary intake in the prevention and treatment of cardiovascular disease and hypertension. 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 and the Trial of Hypertension Prevention are but two examples.

There are separate chapters dealing with the gastrointestinal tract and the liver and pancreas. Topics include malabsorption diseases, GERD, ulcers, constipation, diarrhea, diverticulosis, food allergies, cirrhosis, nonalcoholic fatty liver disease, and acute as well as chronic diseases including cancers of these organ systems. Renal function and its critical role in fluid balance as well as the value of a medical nutrition practice for patients with kidney diseases are discussed in Chap. 15. An important, clinically related chapter examines the nutritional requirements of individuals who have the most common forms of inherited metabolic disorders. The next chapter provides an in-depth look at the differences between food allergies and food intolerance and the resultant differences in treatments. Bone health is discussed with regard to age appropriate requirements for specific nutrients. The importance of calcium, phosphorus, vitamin D, and parathyroid hormone to both kidney and bone health becomes apparent after reading these chapters. The final chapter in this part deals with cancer and the nutritional as well as physical activity needs for prevention as well as during treatment. The comprehensive chapters are practice oriented and detailed and include a number of relevant tables and figures.

Part 3: Food, the Substances in Food, and Their Effects on Health

The eight chapters included in the third part review the major food categories of fat, fiber, vitamins and minerals, alcoholic and nonalcoholic beverages and also examine the benefits and risks associated with vegetarian as well as vegan diets. 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. There are several comprehensive tables found in these chapters including the in-depth tables concerning vitamins and minerals.

Part 4: Diet and Health: A Summary

The summary chapter by Dr. Temple encompasses the key information in the preceding chapters and provides helpful information for health providers who are treating patients and/or clients who have nutrition-related questions.

Part 5: Sources of Nutritional Information

Of importance to physicians and other health professionals who provide advice concerning diet, foods, nutrition, and clinical management of nutritionally related conditions and/or diseases is identification of reputable sources of nutrition information. Part 5 provides chapters that review these relevant resources. The first chapter examines the national food guides that review the components of a healthy diet. These recommendations differ across nations and both the US and Canadian guidelines are examined. In the USA, there are several national departments that oversee dietary guidelines

including the US Department of Agriculture (USDA) and the Food and Drug Administration (FDA); the government-independent National Academy of Sciences publishes the Dietary Reference Intakes for essential nutrients. Thus, there are several sources of professionally generated recommendations for health professionals as well as consumers. Moreover, many university nutrition departments have posted their own evaluations on the Internet. Adding to the confusion, food labels and other information on the label, such as claims statements, are reviewed by the FDA as well as the Federal Trade Commission (FTC) in the USA. The three chapters in this section provide important guidance to physicians and others who provide advice to patients and consumers.

Part 6: Other Selected Topics

The last six chapters in this comprehensive volume examine patient-related topics including chapters that review the potential for physicians to alter patient dietary habits and a review of the many types of dietary supplements, their contents and potential for containing unacceptable components especially in weight reduction and body-building products. Patients and consumers are concerned about many claims that are made for common foods, such as juice drinks, soy products, novel fruits, genetic modification of foods, and other areas of interest. Chapter 33 examines these and other provocative areas of diet information. The final three chapters provide clinically relevant information on drug-nutrient interactions, assessment methods of nutritional status, and nutritional effects of bariatric surgery. These three chapters provide a wealth of timely information for any health professional.

Appendices

The volume includes three 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 and a tabulation of the current Dietary Reference Intakes.

Conclusions

Drs. Temple, Wilson, 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 be the benchmark in the field because of its extensive covering of the most important aspects of clinical nutrition including complex interactions between diet, health, and disease. The editors have chosen 57 of the most well-recognized and respected authors from around the world to contribute the 36 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 three useful appendices including a detailed table of major conversions used in nutrient calculations, suggested sources of reliable nutrition information on the web, and a copy of the dietary reference intake tables from the US Institute of Medicine. The volume also contains more than 50 detailed tables and figures, an extensive, detailed index, and more than 900 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 and Related Healthcare Professionals, Second Edition,"** edited by Norman J. Temple, Ph.D., Ted Wilson, 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 healthcare 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. The editors are applauded for their efforts to develop this volume 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

About the Series Editors

Adrianne Bendich, Ph.D., F.A.S.N., F.A.C.N. has served as the "Nutrition and Health" Series Editor for 20 years and has provided leadership and guidance to more than 200 editors that have developed the 70+ well-respected and highly recommended volumes in the series.

In addition to "Nutrition Guide for Physicians and Related Healthcare Professionals," Second Edition, edited by Norman J. Temple, Ted Wilson, and George A. Bray, major new editions published in 2012–2016 and expected to be published shortly include:

1. Arginine in Clinical Nutrition, edited by Rajkumar Rajendram, Vinood Patel, and Victor Preedy, 2016
2. Preventive Nutrition: The Comprehensive Guide For Health Professionals, Fifth Edition, edited by Adrianne Bendich, Ph.D., and Richard J. Deckelbaum, M.D., 2015
3. Beverage Impacts on Health and Nutrition, Second Edition, edited by Ted Wilson, Ph.D., and Norman J. Temple, Ph.D., 2015
4. Nutrition in Cystic Fibrosis: A Guide for Clinicians, edited by Elizabeth H. Yen, M.D., and Amanda R. Leonard, MPH, RD, CDE, 2015
5. Glutamine in Clinical Nutrition, edited by Rajkumar Rajendram, Victor R. Preedy, and Vinood B. Patel, 2015
6. Nutrition and Bone Health, Second Edition, edited by Michael F. Holick and Jeri W. Nieves, 2015
7. Branched Chain Amino Acids in Clinical Nutrition, Volume 2, edited by Rajkumar Rajendram, Victor R. Preedy, and Vinood B. Patel, 2015
8. Branched Chain Amino Acids in Clinical Nutrition, Volume 1, edited by Rajkumar Rajendram, Victor R. Preedy, and Vinood B. Patel, 2015
9. Fructose, High Fructose Corn Syrup, Sucrose and Health, edited by James M. Rippe, 2014
10. Handbook of Clinical Nutrition and Aging, Third Edition, edited by Connie Watkins Bales, Julie L. Locher, and Edward Saltzman, 2014
11. Nutrition and Pediatric Pulmonary Disease, edited by Dr. Youngran Chung and Dr. Robert Dumont, 2014
12. Integrative Weight Management, edited by Dr. Gerald E. Mullin, Dr. Lawrence J. Cheskin, and Dr. Laura E. Matarese, 2014
13. Nutrition in Kidney Disease, Second Edition, edited by Dr. Laura D. Byham-Gray, Dr. Jerrilynn D. Burrowes, and Dr. Glenn M. Chertow, 2014
14. Handbook of Food Fortification and Health, Volume I, edited by Dr. Victor R. Preedy, Dr. Rajaventhan Srirajaskanthan, and Dr. Vinood B. Patel, 2013
15. Handbook of Food Fortification and Health, Volume II, edited by Dr. Victor R. Preedy, Dr. Rajaventhan Srirajaskanthan, and Dr. Vinood B. Patel, 2013

16. Diet Quality: An Evidence-Based Approach, Volume I, edited by Dr. Victor R. Preedy, Dr. Lan-Ahn Hunter, and Dr. Vinood B. Patel, 2013
17. Diet Quality: An Evidence-Based Approach, Volume II, edited by Dr. Victor R. Preedy, Dr. Lan-Ahn Hunter, and Dr. Vinood B. Patel, 2013
18. The Handbook of Clinical Nutrition and Stroke, edited by Mandy L. Corrigan, MPH, RD, Arlene A. Escuro, MS, RD, and Donald F. Kirby, MD, FACP, FACN, FACG, 2013
19. Nutrition in Infancy, Volume I, edited by Dr. Ronald Ross Watson, Dr. George Grimble, Dr. Victor Preedy, and Dr. Sherma Zibadi, 2013
20. Nutrition in Infancy, Volume II, edited by Dr. Ronald Ross Watson, Dr. George Grimble, Dr. Victor Preedy, and Dr. Sherma Zibadi, 2013
21. Carotenoids and Human Health, edited by Dr. Sherry A. Tanumihardjo, 2013
22. Bioactive Dietary Factors and Plant Extracts in Dermatology, edited by Dr. Ronald Ross Watson and Dr. Sherma Zibadi, 2013
23. Omega 6/3 Fatty Acids, edited by Dr. Fabien De Meester, Dr. Ronald Ross Watson, and Dr. Sherma Zibadi, 2013
24. Nutrition in Pediatric Pulmonary Disease, edited by Dr. Robert Dumont and Dr. Youngran Chung, 2013
25. Magnesium and Health, edited by Dr. Ronald Ross Watson and Dr. Victor R. Preedy, 2012.
26. Alcohol, Nutrition and Health Consequences, edited by Dr. Ronald Ross Watson, Dr. Victor R. Preedy, and Dr. Sherma Zibadi, 2012
27. Nutritional Health, Strategies for Disease Prevention, Third Edition, edited by Norman J. Temple, Ted Wilson, and David R. Jacobs, Jr., 2012
28. Chocolate in Health and Nutrition, edited by Dr. Ronald Ross Watson, Dr. Victor R. Preedy, and Dr. Sherma Zibadi, 2012
29. Iron Physiology and Pathophysiology in Humans, edited by Dr. Gregory J. Anderson and Dr. Gordon D. McLaren, 2012

Earlier books included 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 Physicians, 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-Gray, 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 is President of Consultants in Consumer Healthcare LLC and is the editor of ten books including Preventive Nutrition: The Comprehensive Guide for Health Professionals, Fifth Edition, coedited 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. Dr. Bendich is Adjunct Professor at Rutgers University. She is listed in Who's Who in American Women.

Connie W. Bales, Ph.D., R.D. is a 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.*

About the Volume Editors

Norman J. Temple, Ph.D. is professor of nutrition at Athabasca University in Alberta, Canada. He has published 85 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.

Ted Wilson, Ph.D. is a 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* (Humana/Springer Press Inc, 2010). He also enjoys teaching courses in Nutrition, Cardiovascular Physiology, Cell Signal Transduction, and Cell Biology. When not in the laboratory he enjoys family time, the outdoors, and farming.

George A. Bray, M.D., M.A.C.P., M.A.C.E. is a 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, and the Presidential Medal from the Obesity Society. 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 89. Bray has had a long interest in the history of medicine and has written articles and a book on the history of obesity.

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Contributors

Kelly C. Allison, PhD Department of Psychiatry, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA

Kathryn Alp, BSc, RD Registered Dietitian, Replenish Nutrition, Ottawa, ON, Canada

Asima R. Anwar, BSc Recreation and Parks Department, Mississauga, ON, Canada

Laura A.G. Armas, MD, MS Diabetes, Endocrinology and Metabolism, University of Nebraska Medical Center, Omaha, NE, USA

Bruno Borsari, PhD Department of Biology, Winona State University, Winona, MN, USA

Alice N. Brako Department of Physiology, School of Medical Sciences, University of Cape Coast, Cape Coast, Ghana

George A. Bray, MD Pennington Biomedical Research Center, Louisiana State University, Baton Rouge, LA, USA

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

Catherine M. Champagne, PhD (RDN, LDN, FADA, FAND, FTOS) Department of Nutritional Epidemiology, Pennington Biomedical Research Center, Louisiana State University, Baton Rouge, LA, USA

Cindy D. Davis, PhD Office of Dietary Supplements, National Institutes of Health, Rockville, MD, USA

Karen M. Davison, PhD Department of Biology, Kwantlen Polytechnic University, Surrey, BC, Canada

Gianna Ferretti, PhD Dipartimento di Scienze Cliniche Specialistiche e Odontostomatologiche, Università Politecnica delle Marche, Ancona, Italy

Jennifer J. Francis, MPH, RD Dietetics Program, Southern Maine Community College, South Portland, ME, USA

Marion J. Franz, MS, RDN, CDE Nutrition Concepts by Franz, Inc., Minneapolis, MN, USA

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

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

Corrine Hanson, PhD, RD, LMNT, FAND Medical Nutrition Education, University of Nebraska Medical Center, Omaha, NE, USA

Janetta Harbron, PhD, MSc, BSc, RD Division of Human Nutrition, Department of Human Biology, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa

David W. Harsha, PhD Pennington Biomedical Research Center, Louisiana State University, Baton Rouge, LA, USA

Christina M. Hopkins, BS Department of Psychology and Neuroscience, Duke University, Durham, NC, USA

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

Kerrie Kaspar, PhD Ocean Spray Cranberries, Inc., One Ocean Spray Drive, Lakeville-Middleboro, MA, USA

Carol J. Klitzke, PhD, RD Department of Nutrition and Dietetics, Viterbo University, La Crosse, WI, USA

Christopher Larson, PA-C, RDN 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

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

Margaret A. Maher, PhD, RDN Department of Biology, University of Wisconsin—La Crosse, La Crosse, WI, USA

Claire T. McEvoy, PhD Institute for Global Food Security (Centre for Public Health), Queen's University Belfast, Belfast, Northern Ireland, UK

Caroline McGirr, BSc Institute for Global Food Security (Centre for Public Health), Queen's University Belfast, Belfast, Northern Ireland, UK

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

Johnson W. McRorie, PhD Global Clinical Sciences, Procter & Gamble, Mason, OH, USA

Davide Neri, PhD Dipartimento di Scienze Agrarie, Alimentari e Ambientali, Università Politecnica delle Marche, Via Brecce Bianche, Ancona, Italy

Roman E. Perri, MD Gastroenterology, Hepatology and Nutrition, Vanderbilt University School of Medicine, Nashville, TN, USA

Marise M. Pinheiro, MSc Centre for Science, Athabasca University, Athabasca, AB, Canada

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

Sharon A. Ross, PhD, MPH Division of Cancer Prevention, National Cancer Institute, National Institutes of Health, Rockville, MD, USA

Eleanor D. Schlenker, PhD, RDN Department of Human Nutrition, Foods and Exercise, Virginia Polytechnic Institute and State University, Blacksburg, VA, USA

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

Scott P. Segal, PhD Department of Biology, Winona State University, Winona, MN, USA

Joanne M. Spahn, MS, RD, FADA J. Spahn Consulting, LLC, Fairfax Station, VA, USA

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

Brittany Stotmeister, RDN, CD Department of Family Medicine & Community Health, University of Minnesota, Minneapolis, MN, USA

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

Elaine B. Trujillo, MS, RDN Division of Cancer Prevention, National Cancer Institute, National Institutes of Health, Rockville, MD, USA

Bernard Joseph Venn, PhD Department of Human Nutrition, University of Otago, Dunedin, Otago, New Zealand

Desirée de Waal, MS, RD, CD, FAND Department of Nephrology, University of Vermont Medical Center, Burlington, VT, USA

Sheila M. Wicks Department of Clinical Anatomy and Cell Biology, Rush University, Chicago, IL, USA

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

Jayne V. Woodside, PhD Institute for Global Food Security (Centre for Public Health), Queen's University Belfast, Belfast, Northern Ireland, UK

Zhuoshi Zhang, RD Department of Human Nutrition, University of Otago, Dunedin, Otago, New Zealand

Part I
Nutrition Across the Lifespan

Chapter 1
Pregnancy: Preparation for the Next Generation

Michelle C. McKinley, Jennifer J. Francis, and Jayne V. Woodside

Key Points

- Ideally, good nutrition practices begin in the preconception period.
- Weight gain during pregnancy should be based on prepregnancy body mass index (BMI).
- Most nutrient requirements during pregnancy can be met through a carefully selected diet. However, all women of childbearing age should take a folic acid supplement, and some high-risk women can benefit from iron and/or calcium supplements.
- Nutrition remains an important concern during the postpartum period, especially for women who choose to breastfeed their infants.
- Referrals should be made for women in high-risk pregnancies, low-income women with high risk for poor nutrition, and women with concerns about breastfeeding.

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

Introduction

Nutrition is a modifiable factor that has a tremendous 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.

More and more evidence is coming to light 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].

M.C. McKinley, Ph.D. • J.V. Woodside, Ph.D. (✉)
Centre for Public Health, Queen's University Belfast, Belfast, Northern Ireland, UK
e-mail: j.woodside@qub.ac.uk

J.J. Francis, M.P.H., R.D.
Dietetics Program, Southern Maine Community College, South Portland, ME, USA

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Ideally, good nutrition practices should be encouraged beginning at the preconception period and continue on through 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 [2]. 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 obese women lose weight before pregnancy to improve menstrual functioning, ovulation, and metabolic profile and reduce infertility and that 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 [3].

Since eating habits can be difficult to change, it is essential to establish positive behaviors before conception. Habits that promote optimal nutrition include

- Eating three meals and—two to three snacks per day
- Choosing minimally processed foods rather than foods with added salt, sugar, and fat
- Following the recommendations of the USDA Dietary Guidelines for Americans (www.choosemyplate.gov)
- 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, vegan diets, pica, use of megadose vitamin and mineral supplements, use of herbal supplements, and extreme weight loss/fad diets.

Women with preexisting disease conditions with a nutrition component should be referred to a registered dietitian (RD) 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 [4] 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 [5] and may be least likely to use supplements [6].

Nutrition During Pregnancy

The goal of nutrition during pregnancy is twofold 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.

Table 1.1 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 second and third trimester (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]

Source of information: Ref. [3]
[a]Assumes a weight gain of 1.1–4.4 lb (0.5–2 kg) in the first trimester

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. Weight gain guidelines are outlined in Table 1.1 [3]. 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 1.1. 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 kcal/day in the second trimester and by 450 kcal/day in the third trimester. 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 by approximately 25 g/day, for a total of 71 g/day. 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 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 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 neurodevelopment of the child, including cognition and visual acuity [7, 8]; however, evidence from RCTs is inconclusive [9].

Table 1.2 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. [10, 11]

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.

Fluid needs during pregnancy are generally accommodated for in response to increased levels of thirst. Water, milk, and 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 1.2 for recommended intakes for selected nutrients [10, 11].

Folate is essential in the earliest days of pregnancy for proper closure of the neural tube, and for this reason folic acid supplements (400 μg/day) are recommended for all women who could become pregnant in order to prevent neural tube defects such as spina bifida. In addition, adequate folate may have a protective effect against the risk of a host of other adverse outcomes via its role in converting homocysteine to methionine. Elevated levels of homocysteine throughout pregnancy have been linked to the risk for rupture of the placenta, stillbirth, preterm delivery, preeclampsia, congenital defects, and low birth weight. In this light, it seems wise to continue folic acid supplementation even after the critical period for preventing neural tube defects. Women should also be encouraged to choose a diet rich in folate including legumes, green leafy vegetables, and citrus fruits, as well as foods fortified with folic acid (cereals, pasta, and breads).

For women who have previously been pregnant with a child affected by neural tube defects, a supplement of 4 mg/day of folic acid is recommended for prevention of recurrence [4]. This amount has not been shown to be harmful even though it exceeds the Upper Limit (UL).

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 vitamin D. In such cases, increased intakes of fortified dairy products and supplementation at levels consistent with the RDA (Table 1.2) are the preferred methods for increasing vitamin D status. However, in cases of actual deficiency, supplementation at higher doses may be necessary to prevent osteomalacia in the mother, or rickets in her offspring.

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 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 vitamin B_{12}.

Calcium metabolism changes dramatically during pregnancy. Absorption, bone turnover, excretion 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.

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, 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 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. 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 cheeses, 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 [12, 13]. Advice for women who are pregnant and breastfeeding is to eat 8–12 oz of a variety of fish each week from choices that are lower in mercury, such as salmon, shrimp, pollock, tuna (light canned), tilapia, catfish, and cod. Pregnant women should avoid eating shark, swordfish, king mackerel, and tilefish from the Gulf of Mexico, and albacore (white tuna) should be limited to 6 oz/week [12].

Translating Nutrition Guidelines into Practical Advice About Food

Women do not eat grams of macronutrients or milligrams of minerals, they eat portions of food. It is therefore reassuring to know that most nutrient needs will be met by a carefully selected, nutrient-dense diet. If women are familiar with a few basic concepts, they can make their food choices wisely. Food guidelines for pregnant and lactating women can be found at www.choosemyplate.gov.

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; often fresh air can also help.

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 help as well.

The hormones of pregnancy can alter the muscle tone of the gastrointestinal tract and cause constipation which may lead to hemorrhoids if there is much straining with bowel movements.

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 also be adequate.

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 non-food 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 non-food items replace nutritious foods in the diet, nutrient deficiencies can occur. Women with pica are also often found to be anemic. Whether pica is the cause of the anemia or if the reverse is true remains to be seen.

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 eastern 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 calcium supplementation during pregnancy in all women, at doses of 1.5–2.0 g elemental calcium/day, for the prevention of preeclampsia in areas where dietary calcium intake is low, especially in those at high risk of developing preeclampsia [14]. 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 normal, overweight, and obese women. 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) [3].

More research is needed to determine the exact nutrient requirements consistent with healthy outcomes.

Nutrition for Lactation

Breast milk is the gold standard for human nutrition [15]. 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 [16]. 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 increased need for some vitamins and minerals during lactation to support the mother's nutrition status. DRIs for selected nutrients are presented in Table 1.2. Women who are breastfeeding should, as during pregnancy, avoid eating fish known to contain high levels of mercury.

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 poor weight gain, hyperemesis gravidarum (excessive nausea and vomiting), chronically poor diets, phenylketonuria, chronic diseases such as hypertension and diabetes, or a history of substance abuse may be referred to a registered dietitian for medical nutrition therapy [17]. 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 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 treated using a team approach. Maternal nutrition continues to be important in the postpartum period, particularly for mothers who choose to breastfeed their infants. 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. Appropriate weight gain, adequate nutrient intakes, and avoidance of harmful substances, such as alcohol and tobacco, are the key components of optimal prenatal nutrition. Women in high-risk pregnancies should be referred to a dietitian for medical nutrition therapy.

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Chapter 2
Infants: Transition from Breast to Bottle to Solids

James K. Friel and Wafaa A. Qasem

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 (effect on cell or tissue), antioxidants, immunological defenses, minerals, and fatty acids not found in formula. These deficient elements may help explain the health benefits associated with breast milk. Formula manufacturers are trying to introduce these missing elements into formula.
- Complementary feeding should begin at 6 months of age with breast milk continuing until at least 1 year of age.
- Complementary feeding should help promote a positive association with hunger, food, appetite, and the person feeding. Infants should also learn gross motor skills and form relationships.

Keywords Infants • Breast milk • Breastfeeding • Complementary feeding • Formula • Growth

What Is the Best Milk for an Infant?

Breastfeeding is recommended for the first year of life [1, 2]. Exclusive breastfeeding is recommended for the first 6 months of life. Formula feeding is recommended only for those women who choose not to or cannot breastfeed. The consumption of whole or reduced-fat cow's milk is not recommended during the first year of life [3]. About two out of three mothers in the United States initiate breastfeeding and one out of five continues to 6 months.

J.K. Friel, Ph.D.
Department of Human Nutritional Sciences, University of Manitoba,
196 Innovation Drive, Winnipeg, MB, Canada, R3T 6C5

Department of Pediatrics, University of Manitoba, Winnipeg, MB, Canada

W.A. Qasem, Ph.D., M.D. (✉)
Department of Human Nutritional Sciences, University of Manitoba,
196 Innovation Drive, Winnipeg, MB, Canada, R3T 6C5
e-mail: qasemw@myumanitoba.ca

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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, and the use of most prescription and over-the-counter drugs should preclude breastfeeding.

With all the best intentions and technological expertise, "humanized" infant formulas cannot be compared with 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 [4]. 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 (due to lactase deficiency). While primary lactase deficiency develops as a result of genetic mutation of the intestinal enzyme lactase, secondary lactase deficiency does occur due to lactase shortage most often following surgery or a gastrointestinal disorder.

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: an equation 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's 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 manufacturers is due to (a) aggressive marketing, (b) 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 milk changes over time. The composition of human milk also changes during feeding so that most of the fat in human milk is concentrated in the latter part of feeding, probably saturating the infant and providing a signal for terminating feeding. It appears that breastfed infants have more control over the amount consumed at a feeding than do formula-fed infants [4]. 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 [5]. 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% of total) and whey (50–90% of total) proteins [6]. Milk fat globule membrane proteins and protein derived from cells

present in milk comprise 1–3%. For some years, manufacturers prepared their formula with either a whey or 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 [6]. 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 other long-chain (*n*-3) and (*n*-6) fatty acids such as docosahexaenoic acid (22:6, *n*-3) and arachidonic acid (20:4, *n*-6) [7]. 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 present in human milk, and recently 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 be used in certain formulas [4].

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 [8]. The levels of Zn, Cu, Rb, and Mo decrease over time, suggesting homeostatic regulation and possible essentiality for human infants [8]. 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 [9].

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 receiving less than a liter of formula. Minimum and maximum levels of vitamins are regulated for formulas so that they are complete. Formula labels state the amount of all nutrients, including vitamins, which 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 [10].

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 [11]. 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 [2, 11].

Current practice is for iron supplements to be deferred until 4–6 months of age. Some authorities [11] 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) [12]. Fluoride supplements once recommended for all infants are no longer recommended during the first year of life [11].

Formulas that conform to 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 have a low content of iron (<4 mg/L) which 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 [13]. See Fomon [4] 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 [14]. But fat-soluble vitamins and fatty acids are affected by the maternal diet [14]. It appears that there are mechanisms to ensure

constant supply and stability 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. To date many bioactive compounds have been identified in human milk including cytokines, immune factors, growth factors, hormones, antimicrobial agents, nucleotides, antioxidants, and enzymes (*see* review [15]). 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 thereby potentially exerting important physiological functions [15, 16].

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 make safe new foods with flavors already experienced in breast milk [17]. Again, 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 microbiome [18, 19]. It is believed that the human milk microbiome plays a major beneficial role in shaping the development of the infant's intestinal microbiota and their immune system, and may also play a role in other aspects of short- and long-term infant and maternal health [20]. Formula-fed infants have different microbiota profiles compared to breastfed infants; this may favor intestinal pro-inflammatory status thereby leading to negative health outcomes [21].

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 [22]. Antiviral and antibacterial factors exist in human milk with secretory IgA produced in the mammary gland being one of the major milk proteins [6]. There may even be a pathway from the infant back to the mother, which tailors production of antibodies against microbes to which the infant has been exposed.

Hamosh [15] 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 [15]. 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 digests polysaccharides that are not present in human milk. Amylase is important after the initiation of starch-containing foods such as cereals [15]. 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 focused on the antioxidant properties of human milk. Several groups have reported the ability of colostrum [23] and mature milk [24] 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 [16].

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 [14, 25]. Prior to advancements in hygiene, infants who were not breastfed did not fare well and mortality rates could be as high as 90% [4, 14]. Even with the use of current formulas, breastfed infants have lower incidences of many illnesses and are generally sicker for shorter times than formula-fed infants [26]. Previous work demonstrated that later in life breastfed infants have decreased risk of diabetes, cancer, and cardiovascular disease [26]. However, the recent results from the National Longitudinal Survey of Youth (NLSY) showed that longer duration of breastfeeding may not necessarily lead to long-term healthier childhood and well-being [27].

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 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, the relevance of less growth in breastfed infants is questionable as no negative effects on functional outcomes have been observed. We found infants who had consumed home-made formulas of evaporated milk grew more than either formula-fed or breastfed babies [28], yet they did not perform as well as breastfed infants on tests of visual function [29].

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 [30]. Small differences have been seen even in later childhood [30]. 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 [31]. We found enhanced visual acuity in full-term breastfed infants compared to formula-fed infants which was related to blood fatty acid levels [29]. 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 [30] reporting improved neurological development in breastfed infants sparked a major debate on which factors really explained increased cognitive development. It is reasonable to assume that the long-chain polyunsaturated fatty acids, enzymes, hormones, 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 year 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 [32].

The timely introduction of complementary foods should begin at 6 months of age. Most infants start consuming complementary foods at 3–4 months. 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 [14, 26]. Delaying complementary feeding allows for the infant to gain more benefits from breast or formula feeding.

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 [32]. 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 [33]. Currently, meats are not consumed regularly until 7–8 months of age, with other food groups starting at 4–6 months.

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. 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 to 8 months and then increase to 3–4 meals per day to the end of toddlerhood. 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 for the food.

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 [34]. There have been correlations made between unbalanced diets in infancy and being overweight or obese later in life [35]. The protein content of the infant's diet is of concern for obesity risks. Diets high in protein in infancy have been shown to be associated with obesity 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 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 [33]. 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 for the majority of infants. 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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Chapter 3
Young Children: Preparing for the Future

Jennifer J. Francis and Kathryn Alp

Key Points

- A carefully chosen diet can provide the energy and nutrients that children need to grow, learn, and play.
- The Centers for Disease Control and Prevention (2000) growth charts are typically used to monitor growth.
- The Dietary Guidelines for Americans and the MyPlate resource are appropriate tools to support healthy food choices for children.
- Childhood overweight is a multifactorial problem which requires a very broad approach, including diet, physical activity, psychological support, behavior modification, and caretaker involvement.
- Food insecurity, iron-deficiency anemia, and food allergies are all issues which may affect dietary quality and may require referrals to registered dietitians or food assistance programs.
- Nutritional and vitamin supplements are not necessary for well-nourished children.

Keywords Children • Growth charts • Child obesity • Dietary guidance • Physical activity • Food allergies • Iron-deficiency anemia • Food insecurity

Introduction

Early childhood nutrition is essential for growth and development and can establish dietary habits that last into adulthood. It is important for children to receive a balanced diet that provides a variety of foods in order to ensure that their energy and nutrient intake are adequate. Parents and caregivers play an important role in modeling healthy eating behaviors, and care should be given to delineate the role of the adult and that of the child during mealtime [1]. Poor nutrition in childhood can increase the risk of illness and obesity and can affect intellectual and physical capacities [2].

J.J. Francis, M.P.H., R.D.
Dietetics Program, Southern Maine Community College, South Portland, ME, USA

K. Alp, B.Sc., R.D. (✉)
Registered Dietitian, Replenish Nutrition, Ottawa, ON, Canada
e-mail: alpkaty@gmail.com

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Monitoring Growth

The Centers for Disease Control and Prevention [3] recommends that healthcare providers in the United States use the World Health Organization (WHO) growth standards to monitor the growth of children under 2 years of age and the CDC growth charts for children age 2 years and older [3]. 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, standing for measure of stature. The growth charts 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 an indication of nutritional risk [4]. It is important to note that single data points should not be used, but, rather, trends should be monitored, and other factors, such as gestational age, chronic illness, and the biological parents' stature, should also be taken into account [4].

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; however, it is not a diagnostic tool, and additional assessment is necessary to evaluate the child [5]. A BMI below the 5th percentile for age indicates underweight, between the 85th and the 95th percentile indicates overweight, while a BMI greater than the 95th percentile indicates obesity [4].

Nutrition Guidance

Energy and Nutrient Needs

Total estimated energy requirements are based on the age, weight, height, sex, and level of physical activity. Table 3.1 states the estimated energy requirements for different age and gender groups. The table also states the Recommended Dietary Allowance amounts and Adequate Intakes for selected nutrients. Requirements for energy and most nutrients steadily rise with age.

A diet rich in fiber provided by fresh fruits and vegetables, whole grains, and legumes is essential for preventing constipation [7]. 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 [8–10]. 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 [11]. The USDA 2015–2020 Dietary Guidelines now recommend that fiber intake is 14 g/1000 kcal. For children this can range from approximately 14 to 20 g/day [12].

Table 3.1 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

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

Source: Institute of Medicine [6]

Fluids in the diet should be provided primarily by water and milk. Children should be offered approximately 500 mL of milk or a fortified soy beverage a day [13, 14]. This provides several micronutrients including calcium, vitamin D, and protein. 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 [13, 14]. The requirement for fluid is increased with physical activity, fever, vomiting, diarrhea, and other medical conditions as well as hot, dry, or humid weather.

Sugar-sweetened beverages, including soft drinks and artificial fruit beverages, 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 dental caries [15–17]. The WHO [16] recommends limiting sugars added to food and beverages, as well as those naturally occurring in fruit juice, honey, and other syrups to less than 10% of total energy intake. Much the same recommendation is made in the USDA 2015–2020 Dietary Guidelines. Parents should be encouraged to offer children water or milk when they are thirsty and to limit other beverages offered.

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, iron, calcium, and vitamin D intakes are often below the RDA in the diets of children. Dietary strategies for increasing iron intake and absorption include limiting milk or soy beverage intake to less than 750 mL/day, consuming meat and meat alternatives with a source of vitamin C to increase absorption, and including fortified breakfast cereals in the diet. Calcium can inhibit iron absorption; calcium-rich products should therefore be consumed at a different time than foods containing iron.

If calcium intake is a concern, intake can be increased by offering a variety of low-fat dairy products and calcium-fortified foods such as cereal. Children who do not consume 500 mL of milk or fortified alternative a day should be given a supplement that supplies 400 IU of vitamin D a day in order to ensure adequate intake [18].

Dietary Guidance

The Dietary Guidelines for Americans are applicable for children aged 2 years and above [19]. The recommendations include:

- Half of all grains consumed should be whole grains
- For children aged 2–3 years, fat should comprise 30–40% of calories and for older children fat intake should be reduced to 25–35% of calories, primarily from unsaturated fats.

The fat content of the diet should be provided by whole foods and should come primarily from monounsaturated fatty acids (MUFAs) and polyunsaturated fatty acids (PUFAs), such as those found in fish, nuts, and seeds.

The MyPlate Daily Checklist can be personalized for children and adolescents by entering their age, sex, and physical activity level. The USDA also offers Supertracker that can provide a personalized plan based on age, sex, physical activity level, height, and weight. Following the personalized recommendations can help children meet their energy and nutrient needs and encourage physical activity.

Recommendations for exercise are also of major importance, including:

- Children age 1–4 should engage in at least 180 min of activity per day
- Children age 5–11 should do at least 60 min of energetic play per day [20].

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. Evidence shows that the more pressure parents use to coerce their children to eat or to try new foods, the less likely they are to succeed [21]. Likewise, being overly restrictive about certain foods can increase the desirability of those foods. Parental tactics regarding food intake (e.g., requiring that a child "clean their plate") can diminish the child's internal cues about hunger and satiety, leading to a decreased capacity for food self-regulation [22]. Research is still limited on the effect of parental feeding and childhood weight; however, pressuring children to eat has been associated with increased fussiness and food refusal [21, 23].

Ellyn Satter's 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. [24] 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 [25].

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

- Eat regular mealtimes together as a family as much as possible. Mealtimes should be social and pleasant, not a time for television, arguing, or conducting work.
- Model good food choices; do not expect children to eat a better diet than their parents.
- Discourage "grazing" throughout the day. Rather, offer three meals and two or three snacks each day, giving the child a chance to build up an appetite between eating occasions.
- Snacks should be chosen from the major food groups, i.e., whole grains, fresh fruits and vegetables, dairy, and protein-rich foods.
- 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 appropriate portion sizes. A reasonable portion size for children up to 2 years of age is one to two tablespoons. For children up to 4 years, portion sizes are about two-thirds the size of adult portions.
- Be tolerant of infant and toddler-feeding skills. Self-feeding and food exploration allows the child to become familiar with new tastes and textures.
- Serve new foods in small portions, along with familiar foods, at the beginning of the meal when the child is hungry. A new food may need to be offered up to 15 times before it is accepted.
- Offer a variety of foods from infancy onwards.
- Never force a child to eat.
- Avoid using food as a reward, and never withhold food as a punishment.

Nutrition Concerns During Childhood

Childhood Obesity

The prevalence of overweight in children has been rising steadily over the past three decades. According to CDC data for 2014, 10.2% of children aged 2–5 and 17.9% of those aged 6–11 are overweight, defined as a BMI for age greater than the 95th percentile [26]. Besides the social and

emotional problems associated with overweight, these children are also at higher risk for chronic diseases, including hypertension, the beginnings of atherosclerosis, and type 2 diabetes [27].

The causes of overweight are multifactorial, and approaches for prevention and treatment must address not only diet and physical activity but also psychological support, behavior modification, and caretaker involvement. The goal of treatment is to slow the rate of weight gain and allow 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 more difficult to achieve sufficient intake of vitamins and minerals; nutrient-dense foods must therefore be emphasized.

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 overweight 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. 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 that use very little energy above basal metabolic rates, and time spent viewing television replaces physical activity in the daily schedules of children. Screen time should be avoided in children under two, limited to an hour or less in children 2–4, and limited to 2 h or less in children 5–11 [19]. Screen time can also contribute to exposure to food advertising and encourage mindless snacking.

Sugar-sweetened beverages have been shown to be a significant factor in the development of obesity in children [15, 27]. These beverages, including soft drinks and artificially sweetened fruit beverages, offer little or nothing in the way of nutrition and should be offered in child-sized portions on special occasions; they are not appropriate for daily use.

Food Insecurity

An estimated 20% of American children aged under age 17 live in households that are food insecure, that is, households in which there is no access at all times to enough food for active, healthy lives for all family members [28]. Characteristics of households more likely to be food insecure include: incomes below the poverty level; education of parents less than high school diploma; headed by a single mother; and black, Hispanic descent, or American Indian/Alaska Native descent. Chronic food insecurity can result in poor nutrition, poor academic performance, and behavioral problems. 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. The foods that most commonly cause allergies are peanuts, tree nuts, milk, eggs, wheat, soybeans, fish, and shellfish, with peanuts being the most common. Children may outgrow allergies to milk, eggs, and soy. When a true food allergy is present, the only remedy is strict avoidance of the food. Children with food allergies must be taught skills to

recognize and refuse foods to which they are allergic and to recognize symptoms of an 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 offending food. 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. 17 for more about food allergies.

In contrast, children with food sensitivities or intolerances may experience symptoms, including nausea, vomiting, headache, or hives, but without an antibody response. Foods that are commonly implicated in intolerances include monosodium glutamate (MSG) and lactose-containing dairy products.

Iron-Deficiency Anemia

In the United States, 3.4% of children between birth and age 5 years have iron-deficiency anemia, and this number increases up to 64% in Africa [29]. Low-income children are at greater risk [29]. Studies have shown associations between iron-deficiency anemia and poor motor and mental development [30]. Strategies to increase iron intake were discussed earlier. When dietary measures to increase iron intake do not resolve the problem, iron supplements may be necessary. If iron deficiency is suspected, it is important to evaluate serum markers before suggesting iron supplementation.

Vitamin and Mineral Supplementation

When children consume a carefully selected 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 that is 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. Care must be taken to keep iron supplements out of children's reach as iron 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

Childhood nutrition has a major impact on growth and development. It also affects health outcomes and habits much later in life. It is therefore important to ensure that children are offered a variety of nutrient-rich unprocessed foods early on. Energy-dense foods, such as refined carbohydrates and sugar-sweetened beverages, should be limited as they displace nutrients and can lead to adverse health outcomes. Furthermore, developing healthy eating habits is also important, and 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*" [31]. In addition to a healthy diet, children should also be encouraged to play and engage in physical activity every day, and television viewing should be limited. Ultimately, parents/caregivers should act as role models and should model healthy living behaviors for their children.

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Chapter 4
Nutrition in Adolescence

Jamie S. Stang and Brittany Stotmeister

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.
- 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 obese adolescents or those with a family history of cardiovascular disease and/or type 2 diabetes.

Keywords Adolescent • Adolescent nutrition • Disordered eating • Adolescent obesity

Nutrition, Growth, and Development

Adolescence is a time of dramatic physical, social, and cognitive development, which directly affects nutritional status. Since chronological age of sexual maturation varies dramatically, Tanner 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 stages 2 and 3 of the Tanner stages of sexual maturation); 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 pounds (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.

J.S. Stang, Ph.D., M.P.H., R.D.N. (✉)
Division of Epidemiology and Community Health, University of Minnesota School of Public Health, Suite 300, West Bank Office Bldg, 1300 South 2nd Street, Minneapolis, MN 55454, USA
e-mail: stang002@umn.edu

B. Stotmeister, R.D.N., C.D.
Department of Family Medicine & Community Health, University of Minnesota, Minneapolis, MN, USA

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Consequently, body composition changes tremendously within females which places them at risk for body dissatisfaction, dieting, 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 14 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 alter eating habits in ways that place adolescents at risk of nutrition deficiencies. Some of the common behaviors are described below. A more detailed description of nutritional recommendation to treat eating disorders is included in the chapter by Allison and Hopkins.

Nutrition Behaviors and Their Effects on Nutritional Status

US adolescents do not consume adequate amounts of many nutrients including: folic acid; vitamins A, B6, C, and E; and iron, zinc, magnesium, phosphorus, and calcium [5]. Dietary fiber intake is generally low while teens exceed recommendations for total and saturated fats, sodium, and added sugar. Only about 17% of male and 14% of female teens meet recommendations for vegetable intake (excluding fried potatoes), while 24% of males and 20% of females meet recommendations for fruit intake [6]. Alarmingly, more than 5% of teens consume no fruit and up to 8% consume no vegetables on an average day [6].

Meal skipping is common among adolescents and increases with age. More than 27% of teens skip breakfast on an average day, with less than 40% reporting daily breakfast consumption [6–8]. Almost one in every four teens skips lunch and about 8% skip dinner on any given day [9]. Skipping meals can reduce 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 [10]. Snacks provide about 25% of daily energy intake, but up to 39% of daily added sugar intake [11–15]. Soft drinks are the most common snack reported by adolescents and are the single largest source of energy and added sugar in their diets [15]; soda accounts for 9% of daily calories and 45% of daily sugar intake alone [15]. 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 and low-fat cheese, whole grain ready-to-eat cereal and low-fat milk, or hummus with vegetables or pita chips.

For the purpose of dieting and weight-control, adolescents may consider the use of diet beverages. Consumption of these artificially sweetened beverages typically increases with age and is more common among females [16]. While diet beverages contain little or no calories, using them as a tool for weight loss remains controversial [16–18]. Research has demonstrated inconsistent findings regarding the association of artificially sweetened beverages with obesity and other health risks [16–18]. Health professionals should talk with adolescents to ensure diet beverages are not used as an overly

restrictive dieting tool or as a means of justifying the consumption of alternative calorie dense foods that are of poor nutritional quality such as potato 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 67% of Hispanic, 63% of white non-Hispanic, and 55% of black non-Hispanic girls diet during any given month [19]. Dieting is also common among males, with 42% of Hispanic, 26% of black, and 31% of white males reporting dieting. This is particularly concerning given unhealthy food patterns that are often associated with dieting such as fasting (not eating for 24 h or longer) 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 [20, 21]. They are discussed in more detail in Chap. 7.

- Anorexia nervosa: An eating disorder characterized by extreme weight loss, poor body image, and an 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 in order 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 [22]. 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% [19, 22]. 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 physical activity, combined with growth and development, increase adolescents' needs for energy, protein, and select vitamins and minerals. Athletes should be encouraged to eat a pre-event meal at least 2–3 h prior to exercise but should not consume foods high in fat, protein, and/or dietary fiber for at least 4 h prior to exercise as those foods may bring about indigestion and physical discomfort [23, 24]. Post-event meals should contain approximately 400–600 kcal and should comprise high-carbohydrate foods and adequate amounts of non-caffeinated fluids [23]. Teen athletes should consume at least 6–8 oz (180–240 mL) of fluid prior to exercise, 4–6 oz (120–180 mL) every 15–20 min during physical activity, and at least 8 oz (240 mL) fluid following exercise to maintain proper hydration [23].

In certain instances, 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 justified [25]. However, they are not always necessary, safe, or effective. 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 [19, 26–30]. The Youth Risk Behavior Surveillance Survey (YRBS) and other US data reveal that steroids are used by up to 6% of male and 5% of female adolescents; their use appears to peak during ninth grade and then decreases [19]. Steroids and other ergogenic aids are administered orally, injected, or absorbed through transdermal patches; they are often supplied by coaches [19, 26–30]. Substances are often used during training but not during active competition to avoid detection in situations where urine testing may be used. Steroids and precursors are often "stacked" over a period of several months so that the peak dose of one supplement overlaps the introduction of another [28]. 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. The use of steroids has been linked to infertility, hypertension, physeal closure, depression, aggression, and increased risk of atherosclerosis [28, 30].

DHEA and androstenedione are testosterone and estrogen precursors. Androstenedione is a controlled substance used by up to 4% of teens, while DHEA is widely available as an over-the-counter supplement [28–30]. The advertised effects include increases in lean body mass with decreases in body fat, increased insulin sensitivity, and increased immune response; however, little reputable scientific evidence support such claims. Androstenedione and DHEA may induce similar side effects to steroids including irreversible gynecomastia and prostate enlargement among males and hirsutism (increased hairiness) among females [28–30].

Growth hormone (GH) is purported to decrease subcutaneous body fat while strengthening ligaments and tendons and is often used to improve performance while decreasing injuries [28–30]. Side effects of use by teens may include physeal closure, hyperlipidemia, insulin resistance, and myopathy [28–30]. The extent of illegal use of GH among adolescent athletes is unknown.

Creatine is widely sold as a supplement to increase lean body mass. It is one of the most commonly used sports supplements: use of it is estimated at 11% among adolescent athletes and may be as high as 51% for male athletes [28–30]. Creatine use is most prevalent among those participating in football, gymnastics, hockey, wrestling, and baseball. It appears to be a safe and effective way to enhance performance and increase muscle mass among high volume/intense training athletes [25]. However, for the typical adolescent who is not participating in high volume/intense training, more than adequate amounts of creatine are formed in the liver and kidney through the consumption of meat.

Nutrition Management of Chronic Health Issues

Overweight and Obesity

Appropriateness of weight status for teens is best assessed by calculating body mass index (BMI). BMI is a measure of a person's weight (kg) divided by their height^2 (m^2). The Centers for Disease Control and Prevention BMI calculator is available online at http://nccd.cdc.gov/dnpabmi/Calculator.aspx. This is an accurate and quick way to calculate BMI values for youth. These values must be compared to age- and gender-appropriate percentiles to determine the appropriateness of weight status. Adolescents with a BMI greater than the 85th but lower than the 95th percentile are considered overweight while those with a BMI above the 95th percentile are considered obese [31]. Growth curves based on BMI values for children and adolescents are available from the National Center for Health Statistics and should be incorporated into the medical records of all teens.

More than one-third of adolescents in the USA are overweight and one-fifth are obese [32]. There are dramatic differences by race and ethnicity (Table 4.1). A range of medical and psychosocial complications accompanies overweight among adolescents, including hypertension, dyslipidemia, insulin

Table 4.1 Prevalence of at-risk for overweight and overweight by race and gender among 12- to 19-year-olds in NHANES 2009–2010

	Overweight	Obese
Males		
White	32.2	17.5
Black	37.4	22.6
Hispanic	42.9	23.9
Male Total	34.6	19.6
Females		
White	27.6	14.7
Black	45.1	24.8
Hispanic	41.9	19.8
Female Total	32.6	17.1

Source: All data taken from Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of obesity and trends in body mass index in US children and adolescents, 1999–2010. JAMA 2012;307:483–90

Table 4.2 Recommended indices for common chronic health issues in adolescents

	Acceptable	Borderline	Unacceptable
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)
Apolipoprotein A-1 (mg/dL)	>120 (>1.2 g/L)	115–120 (1.15–1.2 g/L)	≤115 (≤1.15 g/L)
Apolipoprotein B (mg/dL)	<90 (<0.9 g/L)	90–109 (0.9–1.09 g/L)	≥110 (≥1.1 g/L)
Hemoglobin (g/dL)			
Males	≥12.5 (12–15 years) (≥125 g/L)		
	≥13.3 (16–18 years) (≥133 g/L)		
	≥13.5 (>18 years) (≥135 g/L)		
Females	≥11.8 (12–15 years) (≥118 g/L)		
	≥12.0 (16+ years) (≥120 g/L)		
Hematocrit (%)			
Males	≥37.3 (12–15 years)		
	≥39.7 (16–18 years)		
	≥39.9 (> 18 years)		
Females	≥35.7 (12–15)		
	≥35.9 (16–18 years)		

Source: Based on: Bright futures nutrition. 3rd ed. Holt K, Wooldridge N, Story M, Sofka D, eds. Elk River, IL: American Academy of Pediatrics; 2011

resistance, type 2 diabetes mellitus, sleep apnea and other hypoventilation disorders, orthopedic problems, hepatic diseases, body image disturbances, and lowered self-esteem [33, 34]. 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, diabetes, and asthma among adults who were overweight or obese during adolescence [34].

All adolescents should be screened for appropriateness of weight-for-height on a yearly basis, or more frequently if there are concerns about excessive weight gain (or loss). Teens with multiple risk factors for obesity require an in-depth medical assessment to diagnose potential comorbid complications [31]. Adolescents who are assessed as overweight should have their blood pressure and fasting lipid panels measured; those with a family history of premature cardiovascular disease or diabetes should also have AST, ALT, and fasting glucose levels measured [35]. All teens found to be obese

Table 4.3 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. • Overweight teens: Provide Step 1 counseling or refer to a registered dietitian/nutritionist for weight management counseling; schedule follow-up appointment. • Obese adolescents: 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 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 overweight and obese adolescents to appropriate weight management program.
Blood lipids	• Review blood lipid indices with teen and family. • Order blood lipid panel for overweight or obese adolescents. • Overweight adolescents: 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. • Obese adolescents: 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-days 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 importance of limiting sedentary activity, with no more than 2 h/day of screen time
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 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 overweight and obese teens to a comprehensive weight management program.

Adapted from: U.S. Department of Health and Human Services, National Institutes of Health, National Heart, Lung and Blood Institute: Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents. Summary report. NIH Publication No 12-7486A, October 2012. Available at http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf. Last accessed February 1, 2016

should have the previously mentioned laboratory values measured with the addition of microalbumin. Table 4.2 lists cut-points for common indices of chronic disease, while Table 4.3 provides an overview of assessment and referral recommendations based on an adolescent's personal risk factors.

Treatment for overweight and obesity among adolescents is based on the degree of excessive body fat and the presence of comorbid health conditions [35]. 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 (excluding French fries and other fried potato products)
- 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 and only consume 100% fruit juice

- Participate in 60 min of moderate to vigorous physical activity, which can be done in four to six 10–15 min intervals or in 1 or 2 longer intervals. Teens should be able to carry on a conversation but not sing when they are participating at an appropriate level of intensity.
- Limit discretionary screen time to 2 h/day or less
- 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 overweight adolescents with personal risk factors should begin treatment at Step 2 as should all obese teens. Recommendations for Step 2 include all of those in Step 1 plus:

- Limit discretionary screen time to 1 h/day rather than 2 h/day
- Introduce a structured meal plan of 1400–1800 kcal/day that follows DASH dietary guidelines (see Table 4.4)
- 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 obese teens 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 and their families.

Table 4.4 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)	1 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/weeks
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 oz./ week	<3 oz./ week	<5 oz./ week	<5 oz./ week

Source: Based on the U.S. Department of Health and Human Services, National Institutes of Health, National Heart, Lung and Blood Institute: Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents. Summary report. NIH Publication No 12-7486A, October 2012. Available at http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf. Last accessed February 1, 2016

- Supervised physical activity may be provided to assure that teens are safely able to exercise vigorously.
- Mental health screening with 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 significantly obese teens who 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 [24, 36]. Classification of blood pressure based on the average of three readings are:

- Normal blood pressure: <90th percentile for age, gender, and height
- Prehypertensive: >90th and <95th percentiles for age, gender, and height
- Stage 1 hypertension: >95th and <99th percentile + 5 mmHg for age, gender, and height
- Stage 2 hypertension: >99th percentile + 5 mmHg for age, gender, and height.

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 [36]. 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 4.4). Weight loss according to national guidelines (outlined previously in this chapter) should be recommended for teens that are overweight or obese.

Hyperlipidemia

About 25% of US teens have hyperlipidemia [24, 36]. Table 4.2 outlines suggested cut-points for blood lipid 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 [36]. 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 [36].

The National Institutes of Health, National Heart, Lung and Blood Institute (NHLBI) has developed the CHILD 1 (Cardiovascular Health Integrated Lifestyle Diet) diet and nutrition guidelines which integrate dietary approaches to prevention hypertension, hyperlipidemia, and obesity [36]. These guidelines include the DASH dietary guidelines (Table 4.4) 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 meal 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) [37]. Type 2 diabetes is harder to detect in adolescents due to the lack of obvious symptoms, thus prevalence data are not available. The majority of adolescents treated for type 2 diabetes are obese with 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) [37]. Prevention of type 2 diabetes among youth includes early intervention for overweight or obesity, 60 min of daily activity, and following the DASH diet or the Diabetes Prevention Program approach with careful attention paid to removing sugar-sweetened beverages and sugar-rich foods from the diet (Table 4.4).

The metabolic syndrome, the clustering of risk factors for CVD, affects between 2 and 9% of US adolescents; rates are much higher among obese youth, estimated at 12–44% [36]. Overweight and obese teens 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. The MyPlate Supertracker (available at http://www.choosemyplate.gov/tools-supertracker) is an online tool that teens can use to measure the impact of changes in their diet and physical activity patterns and to monitor their progress over time. The use of technology to facilitate nutrition education and counseling for adolescents should be implemented whenever possible to engage adolescents and to provide nutrition information. Communication methods such as text messaging, podcasts, YouTube, and social media (e.g., Instagram, Twitter, and Tumbler) are popular with adolescents and can be a highly engaging way to convey nutrition information.

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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Chapter 5
Nutritional Challenges of Girls and Women

Margaret A. Maher

Key Points

- Physical demands of females for reproductive function and child-bearing affect nutrition, appetite, and weight regulation.
- 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 their risk of disordered eating and their need for weight management assistance.
- 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 weight 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 carbohydrate craving, disordered eating, and other metabolic anomalies including the metabolic syndrome which includes overweight or obesity, insulin resistance and associated glucose intolerance. Weight and drug management and attention to carbohydrates in the diet may improve insulin sensitivity and reduce negative outcomes (lowered fertility, type 2 diabetes, and cardiovascular disease).
- Women may seek nutritional and medical management strategies for age-related weight and body changes and for relief of premenstrual, peri- and postmenopausal symptoms.

Keywords Reproductive stages • Female athlete triad • Polycystic ovary syndrome • Weight management • Disordered eating

M.A. Maher, Ph.D., R.D.N. (✉)
Department of Biology, University of Wisconsin – La Crosse, 1725 State Street, La Crosse, WI 54601, USA
e-mail: mmaher@uwlax.edu

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Introduction

There are long-recognized associations between 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. It follows, therefore, that clinicians providing care for girls and women need a solid understanding of nutritional issues specific to females. Thus, this chapter examines the unique nutrition-related challenges for girls and women to complement Chaps. 1 and 2 on pregnancy and infants, respectively.

It should also be emphasized that the leading causes of death in women—heart disease, stroke, 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 [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 is 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 in.) [2].

Specific Nutrient Challenges for Females

Dietary Fat

While no significant associations of total dietary fat with cardiovascular disease risk are present in the dietary current recommendations, types and sources of dietary fat are still of great interest. 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, 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. Added concerns include especially 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

nonheme iron sources with regard to bioavailability. Nonheme 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 who are vegans or vegetarians with a history of limiting animal protein sources 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, but 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. 4. Because of common preoccupation of girls and women with body weight they may consume low levels of foods that are typically rich in 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. The daily recommendations for calcium, vitamin D, and other nutrients are listed in Appendix C. Increased dietary calcium or calcium supplementation, beyond general recommendations, is unlikely to be beneficial for increasing bone mineral density (BMD) 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 premenstrual symptoms have, in the past, included reductions in salt, sugar, caffeine, and meal sizes. Individual nutrients, including vitamins B_6 and E, calcium, and magnesium, and herbal remedies, have been suggested for the management of premenstrual symptoms (PMS—premenstrual syndrome and PMDD—premenstrual dysphoric disorder) [12]. 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]. Well-controlled studies have not demonstrated much improvement over placebo and may not merit the potentially harmful side effects of routine use. Additional lifestyle interventions with limited evidence base include regular exercise,

relaxation, and stress reduction interventions for ameliorating mild to moderate symptoms. Certain selective serotonin reuptake inhibitors (SSRIs) are considered first-line pharmacotherapy for more severe PMS or PMDD [13].

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 for their effectiveness at alleviating painful menses with limited or inconclusive 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 can report dissatisfaction with their bodies, as women age, the self-reported importance of their body shape and size declines [14]. While both boys and girls undergo major 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 nutritional outcomes and mental and physical health. The passage of mental health parity legislation should improve treatment options for individuals and families struggling with disturbances in eating and body image.

Weight Management in Females

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 various life stages. However, 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. Risks and management of overweight and obesity are discussed further in Chap. 8 by Bray and Champagne.

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 between women and men, 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 [16]. 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 [16]. For example, consumption of beverages containing carbohydrates has been associated with reduction in premenstrual symptoms, an effect linked to carbohydrate craving and related to tryptophan and the serotonin system [17].

When weight reduction is indicated, recommendations with a strong evidence base 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 500–750 kcal/day for women are recommended. 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].

Success rates for weight-loss maintenance in overweight women and recovery from eating disorders are not encouraging. Eating disorders are explored in more detail in Chap. 7. It is important for clinicians to recognize that a one-size-fits-all approach to treatment of disordered eating issues and weight management, in both males and females, may be 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 [19].

Body Weight and Reproduction

A very high or low body mass index (BMI >35 or <20, respectively) is associated with reduced probability of conceiving; this is related to leptin and gonadal axis dysregulation [20]. Pregnancy and peripartum complications as well as the health of prospective children [21] are affected by prepregnancy weight and maternal weight gain. A history of dieting and dietary restraint has been associated with increased weight gain during pregnancy in all but underweight women [21]. The health benefits of a normal body weight for both mother and prospective children should be emphasized.

The Female Athlete Triad

The female athlete triad (TRIAD) is a spectrum of disorders 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 bone mineral density (BMD) [22, 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 conditions may occur with or without eating disorders and in girls and women prevalence of the TRIAD varies depending on the age group, number, and definition of components [22]. 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. Detection 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 diagnosis of the TRIAD should be followed by comprehensive evaluation and intervention, including a primary care provider, a behavioral health professional, and a registered dietitian [22, 23]. Detailed considerations for assessment of the TRIAD and for intervention planning are shown in Table 5.1.

The goals of TRIAD 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 restoration of normal physiological and reproductive function. Behavioral health support may be needed to

Table 5.1 Assessment for diagnosis, monitoring, and evaluation of the female athlete triad

Assessment category	Key tools
Screening and Behavioral	Use a questionnaire such as EDI, EAT-26, SCOFF. [24] Interview to assess body image, food, and/or exercise focus
History	Body weight, diet, physical activity, social, medical (evidence of bone injuries, pain)
Anthropometrics	Height, weight[a], BMI calculation, application to ideal body weight (IBW) range and % IBW, % usual body weight (UBW) if recent weight loss
Dietary	Use 24-h 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	Bone density (whole body and regional), % fat mass[a]

[a]Care should be taken with sharing this information with the patient, given fears and obsession with some numbers

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 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 [22, 23].

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 5.2. 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 [28]. 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 [29].

Indications of hyperandrogenism in women include hirsuitism (male pattern hair growth in females) acne, dysmenorrhea, and alopecia (head hair loss). The presence of insulin resistance and hyperinsulinemia are 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 [28, 29].

Dietary management of PCOS should emphasize foods low in saturated fat and high in fiber. In addition, specific nutrients, plant extracts, and supplements have been shown to improve some clinical features of PCOS. Counseling may also be indicated for mood disorder, help with body image and acceptance, and disordered eating if present [19, 28]. 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, stimulate 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 can improve physical and mental health outcomes and reduce the risks of chronic diseases and infertility later in life [28, 29].

Table 5.2 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 letrazole	Phytochemicals
Android pattern Overweight/obesity	Anti-obesity drugs [25]	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	Focus on carbohydrate amount and type, inclusion of cinnamon [26].
Ovarian cysts		Phytochemicals
Hirsuitism—Alopecia	Topical 5-alpha reductase inhibitors	Zinc supplementation [27]

Peri- and Postmenopause

The peri- and postmenopausal periods may pose challenges for women's health and well-being that may be influenced by nutrition [12]. Until recently, hormone replacement therapy was a mainstay of treatment for health problems associated with this period of a woman's life, but is not preferred for some women with concerns of increased cancer risk. Up to 80% of women turn to non-hormonal treatments including herbal remedies and use of supplements [30]. However, a recent North American Menopause Society review provides guidance and evaluation of the evidence base for non-hormonal treatments [30]. Multiple studies have reported that isoflavones, which may have differential agonist, partial agonist, or antagonist actions at estrogen receptors, may relieve menopausal vasomotor symptoms, better known as hot flashes [12, 30]. The most robust evidence related to isoflavones is with soy foods and extracts. There is insufficient evidence to recommend that consuming isoflavone-rich foods or supplements will provide relief from hot flashes in most women. The isoflavone source, bioavailability, and response of each consumer and her microbiome impacts effectiveness. Several studies have also suggested that soy isoflavones have cancer-preventing properties in multiple organs including the mammary gland. However, recent studies have shown that the cancer-preventing properties may be related to soy consumption earlier in life [31]. In general, isoflavone administration is not recommended in women without childhood exposure to isoflavones due to its inconsistent effects on the mammary gland and uterus, which may increase the risk of developing malignancies [31]. Caution should be taken in application of these findings due to limitations in these studies. Women who have had or are at increased risk of breast, uterine, or ovarian cancer, uterine fibroids, or endometriosis should be aware of the potential risks of using phytoestrogens [12, 30, 31].

Black cohosh is another nutritional supplement that has been reported to reduce menopausal-related hot flashes and improve mood [32, 33]. However, a 12-month study showed benefit for reducing hot flashes with estrogen therapy, but no benefit of black cohosh [34]. This study also reported no benefit with a multibotanical, either alone or with dietary soy. Other supplements commonly used to reduce menopausal symptoms include flaxseed, gingko biloba, and red clover. Moreover, St. Johns Wort may be taken and is mildly effective for mood improvement [34]. Though there are a growing number of studies that have been completed on the safety and efficacy of these complementary and alternative medicine treatment options, the body of evidence is often not sufficient to provide specific recommendations [12]. Of importance, women taking supplements may not inform their healthcare providers and may thus risk drug interactions or unrecognized adverse reactions. Encouraging women (but without being judgmental) to reveal their supplement use and referring them to reliable sources to explore the evidence base for supplement use will empower them to make informed decisions.

Women represent 80% of those affected by osteoporosis. During menopause, there are yearly bone losses of 3–5%. Adequate calcium and vitamin D intake during childhood and the early reproductive years promote bone formation that will extend the time until postmenopausal signs of osteoporosis appear [2]. A European study found that postmenopausal women consuming fortified dairy products with 1200 mg calcium per day for 12 months had more positive changes in biochemical indices of bone metabolism and bone mineral density (BMD) than those women taking the same amount of calcium in supplement form [35]. Reasons for greater bioavailability of calcium from dairy products may be due to the role of magnesium and milk protein in bone metabolism. Soy isoflavones have shown potential to promote bone formation and reduce bone loss [36]. However, lack of studies informing dosage, as well as contraindications for some women, prevent specific recommendations for intake. A healthy diet, weight-bearing exercise, avoiding smoking, and limiting alcohol intake can reduce bone loss as well as promote healthy body weight and image in the postmenopausal period [2, 37].

Summary

The unique physiology of females and significant changes in anatomy and physiology directed by sex hormones across the life span pose nutritional challenges that may require assessment and intervention. Helping girls and women navigate the vast, often contradictory, nutrition 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, especially coincident with puberty, pregnancy, and postpartum and perimenopausal periods. These may help detect and monitor conditions that warrant 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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Chapter 6
Healthy Aging: Nutrition Concepts for Older Adults

Eleanor D. Schlenker

Key Points

- A lifestyle that includes a healthy diet and regular physical activity, including strength training, delays the appearance of age-related changes and slows the development of chronic disease and disability.
- Age-related changes in nutrient requirements increase or decrease depending on the nutrient; energy needs decline underscoring the importance of nutrient-rich foods.
- Both inappropriate weight gain and debilitating weight loss add to chronic disease and disability; loss of muscle can be prevented or reversed with strength training.
- Nutrient supplements may be needed as energy intake declines, but attention to individual needs, current medications, and food intake avoids toxicity or dangerous interactions.
- Community nutrition programs providing congregate or home-delivered meals help maintain nutrient intake when loneliness, anorexia, limited resources, or disability interfere with obtaining or preparing adequate meals.

Keywords Aging • Anorexia of aging • Sarcopenia • Physiological changes of aging

Introduction

By 2030, one in five persons in the United States will be aged 65 or over [1]. The aging population carries implications for health providers, policy-makers, and programs such as Medicare. The rising prevalence of obesity and the growth in diverse populations, especially those vulnerable to hypertension and diabetes, accentuate the need for lifestyle intervention at all ages. Optimal nutrition and physical activity represent the golden key to good health in a patient's later years. Appropriate amounts and types of food slow the aging process and improve both short- and long-term outcomes. New discoveries continue to affirm the interaction of nutrients with the biology of aging.

E.D. Schlenker, Ph.D., R.D.N (✉)
Department of Human Nutrition, Foods and Exercise, Virginia Polytechnic Institute and State University, 338 Wallace Hall, 295 West, Campus Drive, Blacksburg, VA 24061, USA
e-mail: schlenkr@vt.edu

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Physiologic Aging and Nutrition

Age-related changes in physical vigor become more pronounced after age 70. Changes in body composition, gastrointestinal function, and renal function follow a similar progression across the population, but occur at different rates within each individual and influence nutrient needs. Accordingly, patients may require individualized nutrition recommendations.

Body Composition

Loss of lean tissue influences health. Loss of muscle (sarcopenia), and to a lesser extent organ tissue, lowers basal needs. A sedentary lifestyle accelerates muscle loss, promoting the risk of physical disability and frailty. Conversely, strength training can restore muscle mass in persons as old as 98 years, giving renewed ability for self-care [2]. Muscle serves as a repository for amino acids for producing immune factors or acute phase proteins or rebuilding tissue following illness or stress. Replacing muscle (75% water) with fat (15% water) lowers total body water, based on their relative water content, and adds to the risk of dehydration. Loss of bone mineral mass contributes to risk of falls and fractures. Increased protein intake coupled with strength training blunts age-related muscle loss.

Gastrointestinal Function

Except for gastric acid, gastrointestinal secretions remain adequate to digest and absorb protein, fat, and carbohydrate. Atrophic gastritis, affecting 30% of older adults, likely results from *Helicobacter pylori* infestation, not normal aging [3]. Reduced gastric acid adversely affects the absorption of vitamin B_{12}, folate, iron, and calcium and permits bacterial overgrowth further lowering vitamin B_{12} availability. If gallbladder dysfunction interferes with fat absorption, fat-soluble vitamin absorption also declines. Intestinal microflora change in number and composition in older versus younger individuals, as influenced by diet, degree of inflammation, and institutionalization [4]. These microorganisms regulate nutrient absorption, modulate gastric motility, and control the growth of pathogenic bacteria. Specific bacterial populations have been linked to chronic disease; prior treatment with antibiotics appears to predispose older individuals to *Clostridium difficile* infection with gastroenteritis. Alterations in gastric hormone activity, a decline in nitric oxide, and the loss of the stomach's ability to stretch when food is received lead to early satiety and anorexia among frail elders [5].

Renal System

Loss of nephrons and changes in the renin–angiotensin–aldosterone system lower the conservation of water and sodium. The renal conversion of vitamin D to its active form is less effective, adding to the risk of bone loss. High protein intakes mandate additional fluid to excrete added nitrogenous waste. Renal changes further heighten the risk of dehydration in patients with reduced thirst and limited fluid intake.

Nutrient Requirements of the Older Adult

Normal aging coupled with chronic disease and medications adds uncertainty to nutrient requirements. The Dietary Reference Intakes (DRI) define two age categories for older adults (51–70 and over 70), addressing the cumulative physiologic and functional changes that occur over adult life [6]. Although food intake and energy needs decline, other nutrient needs do not, emphasizing the need for nutrient-rich foods.

Energy Requirements

Energy intake presents a delicate balance between unwanted weight gain and inappropriate weight loss. Basal calories fall 1–2% per decade over adult life, and for sedentary older adults, basal needs may equal 75% or more of total energy expenditure. Energy intake drops by about 450 kcal in women and 750 kcal in men between ages 20 and 70 [7]. Estimated energy needs for people over age 50 are 2000–2800 kcal for men and 1600–2200 kcal for women, depending on activity level [8], but many persons fall below 1600 kcal, making it difficult to supply required amounts of essential nutrients. At least 130 g of carbohydrate is needed each day to provide glucose for optimum brain function [6]. Fat should make up 20–35% of total energy, with the upper range supplying additional energy if food intake declines. While some patients need to lower fat and energy intake to prevent unwanted weight gain, others are influenced by public health messages directed toward younger overweight individuals and reduce energy and fat to inappropriately low levels.

Protein

Dietary protein supports tissue repair and replacement and counters the progression of sarcopenia. Both the amount of protein consumed and its distribution across all meals are important for preserving muscle. Studies suggest the current DRI of 0.8 g/kg is insufficient to prevent muscle loss in older adults and an intake of 1.0–1.5 g/kg is more appropriate [9]. To stimulate on-going muscle protein synthesis, 25–30 g is needed at each meal. Although protein intake usually reaches or exceeds this amount at lunch and dinner, older adults often consume less than 15 g at breakfast, and, frequently, this is plant rather than animal protein. Adding a serving of milk or yogurt along with an egg or slice of cheese could raise protein intake at breakfast. Protein intakes over two times the DRI can tax the nitrogen and urea removal capacities of less efficient kidneys and are best avoided.

Micronutrients

Micronutrients play a significant role in aging and the etiology of chronic disease. In this section, we discuss selected new aspects and functions of these nutrients.

Fat-Soluble Vitamins (A, E, D, and K)

Preformed vitamin A (retinol) is supplied in animal foods such as milk, butter, and liver, whereas provitamin A, converted to retinol in the liver, is found in fruits and vegetables. Traditionally associated with vision, vitamin A also supports immune function and cell differentiation. Preformed vitamin A is well-absorbed and toxicity can occur with high potency supplements and/or excessive intakes of fortified foods. Excessive vitamin A has been shown to accelerate bone mineral loss [6]. In contrast, provitamin A (e.g., beta-carotene, cryptoxanthin) consumed in food is nontoxic.

Vitamin E, the major body antioxidant, helps prevent the oxidation of LDL cholesterol and neutralizes free radicals from both internal and external sources. However, vitamin E supplements exceeding the DRI are not beneficial and indeed increase mortality risk [10]. Those anticipating surgery need to be alerted to the anticlotting action of vitamin E supplements.

Vitamin K-dependent proteins, required for normal blood-clotting, also help form bone matrix and facilitate its mineralization. Green leafy vegetables are good sources. Patients taking anticoagulants should monitor their intake of vitamin K, as too high an amount can neutralize the action of the drug.

Roles of vitamin D—the "sunshine" vitamin—have expanded from regulation of bone health to cancer prevention, immune response, and muscle metabolism; recent evidence suggests a role in mental function, as older persons with poorer vitamin D status exhibit more rapid decline in memory and cognitive function [11]. Normally, skin synthesis can meet body needs, but changes in skin cells, use of sunscreen, and limited sun exposure put older adults at risk. Those with darker skin produce vitamin D at about one-sixth the rate of Caucasians. Current recommendations for persons aged 30 and over are noted in Table 6.1. Vitamin D-fortified dairy foods, soy milk, juices, and cereals supply about 100 IU (2.5 μg) per serving, but portions are often inadequate to meet the DRI, creating need for a supplement. According to national survey data, mean vitamin D intakes from food and beverages for persons age 60 and over are 5.3–5.6 μg/day for men and 3.9–4.7 μg/day for women [7]. African American and Hispanic elderly have lower serum vitamin D levels than Caucasians [11]. (Further information on vitamin D can be found in Chap. 25)

Water-Soluble Vitamins

Requirements for thiamin, riboflavin, and niacin do not change with age; yet intakes can be low as food intake declines. Alcohol interferes with thiamin absorption and long-term use of diuretics can result in thiamin depletion. Milk and cereals are major sources of riboflavin and intake suffers if these foods are not consumed regularly. Optimum protein supplies both niacin and the amino acid tryptophan for niacin synthesis. Vitamin C as an antioxidant may help prevent senile cataract and preserve immune function.

Vitamin B_6 requirements increase after age 50 and inadequate intake adversely affects immune function and synthesis of neurotransmitters. Vitamin B_6 acts with folate and vitamin B_{12} to modulate plasma homocysteine levels. Megadoses of B_6 (2000-fold the DRI) impair muscle coordination and lead to irreversible neural damage if prolonged.

Table 6.1 Dietary Reference Intakes for vitamin D and calcium

Age	Vitamin D	Calcium
31–50	600 IU (15 μg)	1000 mg (males) 1000 mg (females)
51–70	600 IU (15 μg)	1000 mg (males) 1200 mg (females)
Over 70	800 IU (20 μg)	1200 mg (males) 1200 mg (females)

From Ref. [12]

Current folate (folic acid) fortification policies directed toward the prevention of neural tube defects have implications for older adults. Folic acid (the form added to grain foods) is better absorbed than naturally occurring folate in plant foods (85% vs. 50%), which requires acid for best absorption [6]. High levels of available folate, however, can substitute for vitamin B_{12} in the production of red blood cells. As a result, it delays the appearance and diagnosis of pernicious anemia and B_{12} deficiency, while irreversible neural damage continues [6].

Vitamin B_{12} status is precarious for those with low gastric acid, as acid is needed to release B_{12} from animal food proteins and enable its absorption. Synthetic vitamin B_{12} used in food fortification does not require acid for absorption, so it is best that fortified foods be consumed two to three times a week. Older adults are vulnerable to the harmful effects of B_{12} deficiency based on its effect on cognitive function.

Minerals

In older adults, calcium intakes are well below the recommended amount (see Table 6.1). Dairy foods and calcium-fortified juices, cereals, and soy milk supply 300 mg per serving, and 3–4 servings per day of these foods will adequately meet calcium needs. Increasing evidence points to the risk of inappropriate calcium supplements with reported incidence of gastrointestinal distress, related hospital admissions, and development of renal calculi. Calcium supplement users, when compared with subjects given placebos, had a 27% increase in myocardial infarctions and greater risk of stroke [12]. Older adults should avoid aluminum-containing antacids that bind with phosphorus, leading to phosphate depletion and adult rickets (osteomalacia). It is suggested that calcium helps control blood pressure [11], yet another reason to eat calcium-containing foods.

Based on its role in opposing the pressor action of sodium on blood pressure, the DRI for potassium was set at 4700 mg [6]; however, low food intake, limited resources, and chewing problems can make it difficult to include the five to nine servings of fruits and vegetables needed to reach this goal. Unless kidney function is severely compromised, adding potassium in the form of food does not pose a risk. Potassium supplements require on-going medical supervision.

The optimum intake of sodium continues to prompt debate. As a means of controlling blood pressure, individuals over age 55, African Americans, and persons with heart disease were urged to lower their sodium intake from the Upper Tolerable Intake Level (UL) of 2300 mg to the Recommended Dietary Allowance (RDA) of 1500 mg [13]. A recent report by the Institute of Medicine concluded that sodium intakes below 2300–2400 mg are associated with higher mortality and hospitalization of heart patients and recommended that these individuals follow the guideline of 2300 mg set for the general population [13]. However, many older adults consume well over this amount. About 77% of sodium intake comes from processed foods; about 11% is added in home preparation or at the table; and only 12% is naturally occurring [6]. Elderly persons with limited mobility depend on canned or frozen items that are often high in sodium. Salt substitutes often exchange potassium for sodium.

Magnesium has an important role in forming bone mineral crystals. Dairy products are a major source and persons avoiding those foods can have low intake. Poor magnesium status has been associated with renal wasting related to diuretic therapy [6]. Hypermagnesemia is a threat for those abusing magnesium-containing antacids or cathartics.

Iron needs are minimal in older adults (8 mg daily), but risk of deficiency is increased by poor absorption related to low gastric acid, chronic use of aspirin, or other pathological conditions resulting in blood loss [6]. Once iron is absorbed, it is poorly excreted, so iron overload is a danger with regular use of iron supplements. Highly fortified cereals containing 18 mg of iron per serving pose a risk if multiple servings are eaten regularly. Alcohol enhances iron absorption.

Zinc deficiency causing loss of taste and impaired wound healing sometimes occurs in older people. Normal function is dependent on adequate zinc, but age-related changes or other nutrient deficiencies may play a part.

Fluid and Electrolyte Homeostasis

Changes in hormonal secretion coupled with cardiovascular disease and medications can upset a delicate fluid balance, increasing the risk of dehydration or fluid retention. Reduced ability of the kidneys to conserve fluid and changes in the hypothalamus that lower voluntary fluid intake increase risk of dehydration. Various medications interfere with thirst, and incontinent elderly may self-limit fluid intake. Dehydration can result in drug toxicity and heat stroke in uncontrolled environments. Conversely, inappropriate secretion of antidiuretic hormone leads to water intoxication or hyponatremia.

Electrolyte disorders are not uncommon among community-living older adults [14]. Hyponatremia is associated with changes in postural balance, falls, and bone fractures. Thiazide, loop diuretics such as furosemide, and potassium-sparing diuretics require special attention to electrolyte balance.

Current fluid recommendations call for 9 cups/day for women and 13 cups/day for men and include fluid from all beverages and high-fluid foods such as soup [6]. The debilitated older adult following the mandate to "drink eight cups of water a day", in addition to other fluids, is at risk of water intoxication. Elderly individuals should monitor their fluid intake and not depend on thirst as a guide.

Nutrition and Dementia

The role of nutrients other than vitamin B_{12} in preventing age-related cognitive decline is poorly understood. However, a recent report suggests that fish and its n-3 polyunsaturated fatty acids (PUFAs), particularly docosahexanoic acid, lower the risk of future cognitive impairment [15]. A meta-analysis of 21 studies involving nearly 182,000 participants revealed that one serving of fish per week reduced the risk of dementia and Alzheimer's disease; increased intakes may lower the risk of mild cognitive impairment and Parkinson's disease. Fatty fish such as herring, sardines, mackerel, trout, salmon, and tuna are good sources of these fatty acids. Two servings of fish per week may also help prevent cardiovascular disease.

Special Benefits of Plant Foods

The dietary fiber found in whole grains, fruits, and vegetables helps lower blood cholesterol, prevent constipation, and improve intestinal health. Older adults with diets low in fiber should be encouraged to *gradually* increase their fiber along with additional fluid. Phytochemicals (plant chemicals) such as lycopene and polyphenols act as antioxidants and may protect against chronic disease; however, to be effective, they must be consumed in food, not supplements, suggesting they interact with each other or other unidentified substances in food.

Dietary Supplements

Individual requirements and circumstances govern the need for dietary supplements. When energy intake is low, it is less likely that all vitamin and mineral requirements can be met from food alone. In that case, a multivitamin–mineral supplement, with a composition approximating the DRIs, is helpful [16]. Supplements containing more than 100% of the DRI of any nutrient can lead to adverse interactions or total intakes that exceed the ULs. Iron and folic acid supplements require medical supervision.

To the extent possible, food is the preferred way to supply nutrients. Unfortunately, herbal, botanical, and other supplements are being marketed to older adults who need to be aware of potentially dangerous interactions with medications. The problem of dishonest marketing of supplements is discussed by Temple in Chap. 32.

Body Weight in the Older Adult

Body weight management poses particular problems in the elderly. Involuntary weight loss and decreasing muscle mass lower functional capacity, whereas ill-advised weight gain aggravates any existing disabilities and chronic disease. Age-related changes in food intake regulation preclude appropriate responses to short-term changes in food intake [17]. Weight lost during serious illness or emotional distress is unlikely to be regained; conversely, weight gain associated with short-term overeating is likely to become permanent.

Low Body Weight

The anorexia of aging is complex in nature. Age-related changes in the hypothalamus controlling the food drive and delayed gastric emptying lead to early satiety. Many common medications, such as digoxin, influence appetite. ACE inhibitors bring changes in taste such that even favorite foods become unpleasant. Various diuretics result in dry mouth, affecting taste and making swallowing more difficult. Cachexia arising from chronic inflammation and the subsequent release of cytokines is resistant to even aggressive nutritional intervention. A body mass index (BMI) which falls from a higher level to <21 might indicate a need for intervention [18].

Overweight/Obesity

The optimum body weight for a person of a given height appears to differ between older and younger individuals, resulting in a U-shaped curve with excess mortality at very high or low body weights. Although the BMI range of 18.5–24.9 represents normal weight, a recent meta-analysis of deaths in persons aged 60 and over indicated that hazard ratios were higher at BMIs below <23, were lowest between 23 and 32, and rose again at a BMI >33 [19]. Weight-loss interventions should balance any functional benefits with the need for appropriate intakes of nutrients. It is vital that weight loss does not bring about loss of muscle tissue that further compromises mobility and self-care. Rapid weight loss likely reflects an occult medical problem rather than a successful weight-loss regimen.

Factors Influencing Food Intake in Older Adults

Socioeconomic Factors

Changes in social relationships influence food intake. Eating alone can be a difficult adjustment for a widow(er). Loss of close friends or nearby family, changes in the neighborhood, or fear of the future reduce interest in eating. Financial losses and rising prices present difficult choices on a fixed income

that must cover living expenses and medications. Food choices can be dictated more by available money than need for nutrients. Many older adults are eligible for the Supplemental Nutrition Assistance Program (the food stamp program), but relatively few apply.

Health Factors

Physical infirmity makes food shopping challenging, and if transportation or food delivery is infrequent, access to fresh produce and milk is curtailed. Severe arthritis interferes with food preparation and opening packages of pre-prepared foods. Attempting to manage chronic conditions with a highly restrictive diet is most often counterproductive. Meal patterns including familiar foods with attention to frequency and portion control are more successful. Chewing is painful for edentulous elderly with ill-fitting dentures or periodontal disease, and left untreated, periodontal disease leads to systemic infection.

Loss of taste and smell or distorted taste related to normal aging, radiation therapy, or medications discourage eating. Bitter medications delivered to the taste receptors via the blood may flavor the saliva and affect appetite. The interaction of nutrition and drugs is discussed more completely in Chap. 34.

Dry mouth (xerostomia) makes eating and swallowing difficult. The loss of saliva associated with this condition enables rapid bacterial growth with ulceration if continued. Dysphagia or difficulty swallowing and fear of choking influence the types of food that can be handled comfortably. Swallowing can be troublesome for those with neurological impairment as occurs with Parkinson's disease, diabetes, or radiation treatment.

Evaluating Nutritional Risk

Community programs providing congregate meals in a social environment or delivery of meals to the homebound provide nutritional support and promote independent living. Most are subsidized with local and federal funds and target elderly persons who have limited resources. Questions in Table 6.2 can assist in identifying those at risk who could benefit from such programs. For an expanded assessment tool that can be self-administered (SelfMNA® Mini Nutritional Assessment), see Suggested Further Reading. Contact information for community food programs can be found on web sites or telephone listings of county and state departments for the aging.

Health Promotion for the Older Adult

Positive changes in the quality or amount of food consumed are never without benefit, regardless of age or physical status. Increased intakes of fruits, vegetables, and whole grains, and good food sources of calcium, protein, and vitamin D add important nutrients and phytochemicals for resisting chronic

Table 6.2 Identifying risk factors for inadequate food intake

Do you ever have problems obtaining the food you need? (could relate to problems with shopping or lack of money to buy food)
Do you have any problems that make it difficult to eat? (may involve chewing, loss of taste, problems with swallowing)
Do you eat at least two meals every day? (amount of food eaten)
Have you gained or lost 10 pounds over the last 6 months? (involuntary weight loss or unwanted weight gain)

disease and enhancing immune response. Regular physical activity to the extent possible, including walking and strength training, helps maintain bone and muscle mass and extend independence. Small changes add up to make a significant difference in the well-being of the aging adult.

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Part II
Nutrition in the Prevention and Management of Chronic Conditions

Chapter 7
Eating Disorders: Disorders of Under- and Overnutrition

Kelly C. Allison and Christina M. Hopkins

Key Points

- Eating disorder diagnoses consist of anorexia nervosa (restricting type and binge-eating/purging type); bulimia nervosa; binge eating disorder; and otherwise specified feeding or eating disorder (including atypical anorexia, subthreshold bulimia nervosa and binge eating disorder, purging disorder, and night eating syndrome).
- Physical complications of anorexia nervosa affect most major systems in the body and are caused by starvation and the effects of purging. Most physical complications of bulimia nervosa are due to purging.
- Overweight and obesity are linked with binge-eating disorder and night eating syndrome. Patients typically request that weight loss be addressed with treatment.
- Anorexia nervosa is difficult to treat and may need initial inpatient treatment for refeeding. Subsequently, family therapy is recommended for patients still living with their families.
- Cognitive behavioral therapy is the first line of therapy recommended for bulimia nervosa, binge-eating disorder, and night eating syndrome. Interpersonal therapy has also been shown effective for bulimia nervosa and binge-eating disorder with similar efficacy as cognitive behavioral therapy at 12 months post-treatment.
- Selective serotonin reuptake inhibitors have been shown effective for treating bulimia nervosa, binge-eating disorder, and night eating syndrome, as has topiramate. Lisdexamfetamine is also effective for binge-eating disorder. Medication trials have not identified a drug that effectively addresses the inability to maintain a healthy body weight, the core symptom of anorexia nervosa.
- Prevention studies are in their infancy, but dissonance-based programs have shown promise.

Keywords Anorexia nervosa • Bulimia nervosa • Binge-eating-disorder • Night eating syndrome • Purging disorder • Therapy for eating disorders

K.C. Allison, Ph.D. (✉)
Department of Psychiatry, Perelman School of Medicine at the University of Pennsylvania, 3535 Market St., Suite 3027, Philadelphia, PA 19141, USA
e-mail: kca@mail.med.upenn.edu

C.M. Hopkins, B.S.
Department of Psychology and Neuroscience, Duke University, Durham, NC, USA

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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, where an individual severely restricts daily caloric intake while periodically consuming extremely large amounts of food. Alternatively, the extremes can be found by definition, as in anorexia nervosa, restricting type, and binge-eating disorder. Current diagnostic criteria for eating disorders are outlined in the Diagnostic and Statistical Manual–5th Edition (DSM 5) from the American Psychiatric Association [1] and include anorexia nervosa, bulimia nervosa, binge-eating disorder, and otherwise specified feeding or eating disorder (OSFED). There are several clinically significant forms of disordered eating that are included in the OSFED category that are growing in recognition, including night eating syndrome and purging disorder.

This chapter will provide diagnostic criteria for each of these forms of disordered eating and a brief overview of prevalence, assessment issues, treatment, and prevention efforts.

Anorexia Nervosa

Anorexia nervosa was first noted in the scientific community in the late seventeenth century and first appeared in the DSM-III in 1980 as a diagnostic entity. According to the DSM 5 definition, there are four key attributes. The first, a core feature, is significant weight loss or a persistent failure to gain weight, leading to a significantly low body weight for age and height. While there is variability across individuals by body type, ethnicity, and gender for what is a "significantly low weight", it is generally defined as weighing less than 85% of expected weight for height, or at or below a body mass index (BMI) of 17.5 kg/m^2. However, with the change of wording in the DSM 5, if a patient's weight is falling precipitously, the clinician does not have to wait until the BMI falls below these markers to diagnose anorexia nervosa, hopefully allowing patients access to treatment sooner, which typically increases odds for recovery. For adolescents and children, lack of weight gain, rather than active weight loss, would also be an appropriate measure of this criterion. Centers for Disease Control growth charts [2] should be reviewed to assess if a child or adolescent has fallen significantly below his or her original weight trajectory.

The second criterion describes an intense fear of gaining weight despite being underweight, or if patients are unable to express this fear (e.g., young children or adolescents may not be able to recognize such a fear), they show persistent behaviors that interfere with weight gain. The third criterion requires a distortion in the way that body weight and shape are viewed or a denial of the seriousness of the condition. Persons with anorexia nervosa evaluate their self-worth almost entirely by their perceptions of their body weight and shape, and these distorted beliefs help maintain the severe caloric deficits necessary to sustain their low weight. Amenorrhea, the absence of menstrual cycles for at least 3 months, is no longer included as a required criterion, but it remains a useful marker of recovery among postmenarchal females.

There are two subtypes of anorexia nervosa. The restricting type is classified by the strict use of caloric restriction and excessive exercise as a means of controlling their weight. The binge-eating/purging subtype describes those who engage in binge eating or inappropriate compensatory measures, such as vomiting or misuse of laxatives, diuretics, or enemas. Those with the anorexia nervosa, binge-eating/purging subtype differ from persons with bulimia nervosa who binge and purge because of their extremely low body weight. Thus, a diagnosis of anorexia nervosa supersedes a diagnosis of bulimia nervosa.

Almost every physical system is negatively impacted by anorexia nervosa; this is due to starvation and, when present, the effects of purging. Resulting abnormalities include bradycardia, arrhythmia,

hypothyroidism, low bone density, constipation, infertility, and perinatal complications. Gray matter volume in the brain is decreased. Atrophied neural networks may maintain sufferers' psychological delusions regarding their fears of fat and beliefs that they are not thin enough, as well as obsessions and compulsive rituals with food. Despite the gravity of their symptoms, those with anorexia nervosa do not typically complain of their ailments and deny the seriousness of their physical and psychological states. With this denial, many sufferers refuse medical treatment until they have been seriously medically compromised.

Paradoxically, excessive exercise and movement are observed in anorexia nervosa, perhaps due to lowered leptin levels that increase the drive for movement once associated with food-finding behaviors to avoid starvation. When excessive movement subsides and fatigue sets in, this may indicate severe depression, electrolyte imbalance, or severe dehydration. Cardiac functioning may also be poor at that point. One recent study in Germany followed patients for between 10 and 30 years after inpatient treatment at a large hospital. The investigators reported a 6% mortality rate; two-thirds of these occurred from natural causes, e.g., circulatory collapse, cachexia, organ failure, or infection. Of those who died from non-natural causes, two-thirds were attributable to suicide [3]. For these reasons, anorexia nervosa is considered the deadliest psychiatric disorder.

Bulimia Nervosa

The core features of bulimia nervosa are binge eating and subsequent use of inappropriate compensatory behaviors. These behaviors are used in an attempt to attain a low body weight or prevent weight gain. As with anorexia nervosa, there is undue influence of weight and shape on self-evaluation and self-concept. Diagnosis requires that the binge-eating episodes and inappropriate compensatory behaviors occur at least once per week for at least 3 months.

Inappropriate compensatory behaviors with bulimia nervosa may consist of purging and non-purgative methods, and patients often use a variety of methods. Purging behaviors most often consist of vomiting, used in 80–90% of cases [1], followed by laxative abuse. Many persons with bulimia nervosa become skilled at inducing vomiting so that they no longer need to use their fingers or another instrument and can vomit at will. Four common signs associated with vomiting include "Russell's sign" (scarring on the back of the knuckles due to self-induced vomiting), swollen cheeks associated with parotid gland enlargement, dental enamel erosion, and receding gums. Laxative abuse is commonly associated with peripheral edema and bloating. Constipation results when laxatives abuse is discontinued, but it generally resolves in less than a month with exercise and gradual increases in fluids and fiber. Both vomiting and laxative use are associated with electrolyte imbalance, fatigue, heart arrhythmias, and gastrointestinal problems, such as gastroesophageal reflux disease (GERD). Other compensatory behaviors are fasting (i.e., going without food for longer than 8 h) or excessive exercise [4, 5]. Driven exercise, or excessive exercise with the specific purpose of controlling weight and shape, is a common compensatory strategy in patients with bulimia nervosa. This excessive exercising is often described as obligatory and may occur even if the patient is experiencing pain during exercise or if exercising is disrupting social routines. If, for some reason, the patient is prevented from exercising, extreme guilt can follow.

Most persons with bulimia nervosa have a BMI in the healthy weight range, with some in the overweight and obese ranges. Individuals with bulimia nervosa feel free of their binge food after purging and consequently experience psychological relief (if only temporarily), but, in reality, many of the calories from their binge episodes are absorbed and metabolized. They may also restrict food intake between binge episodes and exercise, but not to the extent that is observed with anorexia nervosa, binge-eating/purging subtype. Malnutrition may still occur in bulimia nervosa, but most of the medical complications in this disorder are caused by the purging behaviors. While these medical complications

are not as severe as those observed in anorexia nervosa, persons with bulimia nervosa generally are less tolerant of their physical symptoms. Those with bulimia nervosa typically have more insight into their disorder than those with anorexia nervosa, often feeling guilt and shame related to their binge-eating and purging behaviors. The binge cycle is often part of a coping strategy to regulate emotions and acts as a focus for the patient's distress about other difficult issues he or she would rather avoid in life.

Binge-Eating Disorder

The hallmark of binge-eating disorder is eating large amounts of food, accompanied by a loss of control over-eating. Additionally, at least three of five of the following signs must be present during binge-eating episodes: (1) eating more rapidly than normal; (2) eating until uncomfortably full; (3) eating when not physically hungry; (4) eating alone due to embarrassment; and (5) feeling disgusted, depressed, or markedly guilty after an episode. Diagnosis requires that distress regarding the binge eating must be present, and the episodes must occur, on average, at least once per week for 3 months [1].

Most individuals with binge-eating disorder are overweight or obese, and many present primarily for weight loss. Persons with bulimia nervosa typically restrict more consistently between binges than do persons with binge-eating disorder, but in laboratory studies those with bulimia nervosa consume more energy during binges than those with binge-eating disorder. Persons with binge-eating disorder typically engage in binge eating in addition to eating normal to large-sized meals throughout the day. This general pattern of overeating coupled with the lack of compensatory behaviors contributes to weight gain and also seems to contribute to weight-related comorbidities, such as chronic pain conditions, diabetes, and hypertension.

Otherwise Specified Feeding or Eating Disorder (OSFED)

There are many forms of disordered eating that are serious and cause psychological and physical distress that do not fit the diagnostic criteria for anorexia nervosa, bulimia nervosa, or binge-eating disorder. These are captured in the OSFED category. Two of these disorders have been gaining more attention: night eating syndrome and purging disorder, while others are variations of the other eating disorders. Each of these is described below.

Night Eating Syndrome

The night eating syndrome was first described in 1955 as a disorder of morning anorexia, evening hyperphagia, and insomnia, usually accompanied by a depressed mood and stressful life circumstances [6]. Night eating syndrome did not receive much research or clinical attention until the 1990s. This renewed attention was likely influenced by the rise of the prevalence of obesity and the search for correlates and contributors of excessive weight gain. In 1999, awakenings with ingestions (*nocturnal ingestions)* were added to the provisional set of criteria [7]. However, as research advanced our understanding of night eating syndrome, different criteria sets were increasingly used, making comparisons across studies difficult.

The following diagnostic criteria were reached by consensus at the First International Night Eating Symposium in 2008 [8]. First, the daily pattern of eating must show greatly increased intake in the evening and/or night time, as manifested by one or both of the following: (a) at least 25% of food intake is consumed after the evening meal and/or (b) at least two eating episodes occur each week upon awakening during the night. Second, the clinical picture is characterized by at least three of five

of the following features: (a) a lack of desire to eat in the morning and/or breakfast is omitted on four or more mornings per week; (b) the presence of a strong urge to eat between dinner and bedtime and/or during the night; (c) sleep onset and/or sleep maintenance insomnia are present four or more nights per week; (d) presence of a belief that one must eat in order to get to sleep; and (e) mood is frequently depressed and/or mood worsens in the evening.

Persons who meet these criteria must also have awareness and recall of the evening and nocturnal eating episodes to distinguish the behavior from sleep-related eating disorder, which is a parasomnia marked by impaired consciousness and the consumption of unusual food or nonedible objects. Diagnosis requires that the night eating behaviors must be present for at least 3 months and there must be distress or impairment of functioning present in relation to the night eating.

One epidemiological and two clinical studies have shown a link between night eating syndrome and obesity. However, other studies have failed to verify this. Average caloric intake consumed during nocturnal ingestions is similar to regular snacks (approximately 300–400 kcal). An early report [7] suggested that carbohydrates dominate nocturnal food choices, but a subsequent report has shown no difference in the proportion of macronutrient content of foods consumed during the night vs. the day [9]. However, the repeated and persistent nature of the disorder likely contributes to weight gain among its sufferers and has been linked to poor diabetes control.

Purging Disorder

Purging disorder is generally defined as the regular occurrence of inappropriate compensatory behaviors (e.g., vomiting, laxative use, or diuretic misuse) in the absence of regular binge-eating episodes and with a body weight greater than 85% of that expected [10]. The frequency used for the purging criterion has varied between greater than once per week to greater than twice per week. Some studies have also included undue influence of weight and shape on self-evaluation. Thus, persons with purging disorder generally feel distressed after eating anywhere from a typical meal to a small snack and have an overwhelming urge to purge afterward.

The effects of purging are the same as those presented for bulimia nervosa. The impact of purging disorder can therefore be dangerous and debilitating. A feeding study showed that women with the disorder reported more postprandial fullness and gastrointestinal discomfort after a standardized meal than those with bulimia nervosa and greater release of cholecystokinin (CCK) [11], suggesting that physiological cues may contribute to the purging behavior.

Atypical Anorexia Nervosa

In atypical anorexia nervosa, the patient has lost a significant amount of weight, and all of the criteria for anorexia nervosa are met, with the exception of reaching a significantly low body weight. These patients remain normal weight, overweight, or obese based on their BMI, but they may be compromised medically by the pace of their weight loss and/or by the psychological symptoms that accompany their weight loss. This may occur after a behavioral weight-loss effort that started purposefully initially or after bariatric surgery where fear of weight regain turns into a pathological issue.

Bulimia Nervosa (of Low Frequency or Limited Duration)

In this iteration of bulimia nervosa, all diagnostic criteria are met except that the frequency of the binge episodes and compensatory behaviors is, on average, less than once per week for the past 3 months.

Binge Eating Disorder (of Low Frequency or Limited Duration)

All criteria for binge eating disorder are met in this category except that the binge episodes occur, on average, less than once per week for the past 3 months.

Unspecified Feeding or Eating Disorder

This diagnosis may be used when there are subthreshold symptoms for the previously mentioned disorders, but there is significant impairment in functioning, such as in occupational, familial, or social arenas, or distress present in relation to the eating issues. This category may also be used when there is not enough information known to make a full diagnosis (e.g., in an emergency situation).

Prevalence of Eating Disorders

Comprehensive lifetime prevalence of the eating disorders has been studied most comprehensively using DSM-IV criteria: anorexia nervosa occurred in 0.9% of women and 0.3% of men; bulimia nervosa in 1.5% of women and 0.5% of men; and binge-eating disorder in 3.5% of women and 2.0% of men [12]. Furthermore, subthreshold binge-eating disorder, which did not include the five descriptors (e.g., eating more rapidly than usual) or the distress criteria, was assessed, yielding prevalence estimates of 0.6% of women and 1.9% of men.

An estimate of night eating syndrome in the general population of the United States is 1.5% [13]. Epidemiological studies among women of purging disorder reveal rates of 5.3% in an Australian twin cohort, 1.1% in an Italian cohort, and 0.85% in an adolescent Portuguese cohort [for review *see* Keel, [10]]. The relative frequency of these estimates, as compared to the other eating disorders, has varied, with some studies finding purging disorder more common and others less common than bulimia nervosa and anorexia nervosa.

Treatment of Eating Disorders

Much progress has been made in treating bulimia nervosa, binge-eating disorder, and night eating syndrome. However, treatments for anorexia nervosa that have long-term effectiveness are still sorely lacking. Table 7.1 provides an overview of effective treatment modalities. The first step in assigning treatment is to assess how medically compromised a patient is. With anorexia nervosa, inpatient hospitalization may be warranted for refeeding. The next step down is residential treatment, followed by partial-hospitalization or day-treatment programs. These treatments typically involve a multidisciplinary team of professionals, including physicians, dietitians, psychologists, and in some cases, art therapists and occupational therapists. Interventions include both group and individual treatments. Therapeutic meals are included where patients are challenged to eat nutritionally balanced meals and snacks at regular intervals each day, typically every 3–4 h. Patients are encouraged to gain approximately 1–2 lb/week (0.5–1 kg/week), at an initial intake of about 1500 kcal/day (30–40 kcal/kg/day), increasing up to 70–80 kcal/kg/day [14], reaching up to 3500–4000 kcal/d for optimal refeeding. Liquid meal supplements are often used to help patients reach this goal. Patients must be carefully monitored after meals, particularly in the bathroom and their rooms, to prevent purging. Bulimia nervosa can typically be treated on an outpatient basis, but persistent or very severe cases require residential or partial treatment.

Table 7.1 Effective treatments for eating disorders[a]

Disorder	Cognitive behavioral therapy	Interpersonal therapy	SSRIs[b]	Other
Anorexia nervosa	Mixed	Mixed	No	Family-based treatment is most effective for adolescents; Inpatient/residential multidisciplinary treatment; no medications proven effective
Bulimia nervosa	Yes	Yes	Yes	Not buproprion
Binge-eating disorder	Yes	Yes	Yes	Lisdexamfetamine only FDA-approved medication for BED; topiramate shows some efficacy, as does behavioral weight loss
Night eating syndrome	Yes	Not tested	Yes	Topiramate (case reports only)

[a]Purging disorder is not included because specific treatment studies have not been reported
[b]Selective serotonin reuptake inhibitors

Psychotherapy

The most effective outpatient psychotherapy approach for eating disorders is cognitive behavioral therapy (CBT). A 20-session course of treatment is effective for bulimia nervosa and binge-eating disorder [15]. Sessions occur twice weekly for the first 2 weeks of treatment, followed by weekly sessions. Maintenance sessions are encouraged after the initial 20-week course. CBT produces abstinence from binge-eating and purging behaviors in varying proportions of study participants with bulimia nervosa, ranging from 24 to 71% [16]. Similarly, CBT in binge-eating disorder produces abstinence in binge eating ranging from 37 to 79% of study participants [17]. However, weight is not significantly reduced in CBT treatment among persons with binge-eating disorder, despite large reductions in binge episodes. Less impressive results have been reported for treatment of active anorexia nervosa, although CBT may be helpful in maintaining treatment gains. Only an uncontrolled study among patients with night eating syndrome has been tested to date with significant reductions in nocturnal ingestions and evening eating.

Interpersonal psychotherapy has been tested by several groups of researchers and applied successfully to bulimia nervosa and binge-eating disorder. Anorexia nervosa has not responded as robustly as bulimia nervosa and binge-eating disorder. As persons with eating disorders typically experience interpersonal or social dysfunction, interpersonal therapy for eating disorders focuses on how these social deficits contribute to binge-eating and purging behaviors. Interpersonal therapy focuses on one of four areas of interpersonal functioning, including unresolved grief, role transition (e.g., graduating high school or college), role dispute (e.g., problems in communicating with a boyfriend or parent), and interpersonal deficit. Interpersonal psychotherapy is not generally recommended as a first-line approach because it relieves symptoms at a slower pace than CBT. The treatment outcomes with interpersonal therapy at one-year follow-up indicate a slightly lesser degree of success than with CBT [16, 17]. However, if a patient does not respond to CBT or medication management, interpersonal therapy may be a good option.

Family-based treatment, originally known as the Maudsley Approach, has been shown to be the only effective psychotherapeutic approach for anorexia nervosa [18] and is also effective for those with bulimia nervosa [19]. It works particularly well for younger patients living with their families. Family-based treatment is the most well-validated family therapy approach for anorexia and is intended to reduce the need for inpatient treatment and to help parents successfully refeed their child, which is the first goal. This approach takes decision-making regarding eating away from the patient at a time when the malnourished brain is typically struggling to allow the self to make healthy decisions and places these decisions with the parents/caregiver. The second goal, once weight has increased and

cognitive functioning has improved, is for the adolescent to start to take control again of eating and weight gain, at a level appropriate to maturational status. Last, an overview of normal adolescent development is covered with the family, and the therapist helps to identify any other outstanding social–emotional issues for which the family may still need help.

Finally, behavioral weight-loss therapy reduces binge eating and produces weight loss in persons with binge-eating disorder [20]. However, abstinence rates from binge eating are not as high as those produced through CBT. Thus, if weight loss is strongly desired by a patient and their other psychiatry comorbidities, such as major depression, substance abuse, or an anxiety disorder, are not causing noticeable impairments in functioning, then a behavioral weight-loss program may suit those patients best.

Psychotropic Medications

Antidepressants are widely prescribed for the treatment of eating disorders for two reasons: they are effective in reducing binge-eating and purging behaviors, and they improve comorbid mood and anxiety symptoms. Unfortunately, they have not been shown to reduce the core symptom of anorexia nervosa, i.e., refusal to maintain a healthy body weight. Thus, there are currently no efficacious medications used for the treatment or maintenance of anorexia nervosa. However, antidepressants may still relieve comorbid depression or anxiety, when present.

Tricyclic antidepressants, monoamine oxidase inhibitors (MAOIs), and selective serotonin reuptake inhibitors (SSRIs) have all shown efficacy over placebos in reducing binge eating and purging [16, 17]. SSRIs have been commonly used, with typical reductions of 45–65% in binge eating. In recent developments, lisdexamfetamine has been approved for the treatment of binge-eating disorder [21]. Adults with BED were randomized to receive placebo, 30, 50, or 70 mg/day of lisdexamfetamine. Doses were titrated for 3 weeks and participants remained dose-stable for 8 weeks, totaling 11 weeks of treatment. At that point, individuals taking 50 or 70 mg/day of lisdexamfetamine demonstrated a significant decrease in binge eating days per week when compared to those taking placebo or 30 mg/day. Additionally, the number of binge eating episodes decreased significantly from baseline to week 11 for individuals taking 50 or 70 mg/day. These results suggest that lisdexamfetamine may be an effective treatment for BED.

The SSRI, sertraline, has also been shown to reduce evening hyperphagia and nocturnal ingestions significantly among those with night eating syndrome. Topiramate successfully decreases binge eating and purging as compared to placebo treatment and is associated with weight loss; however, cognitive side effects may be intolerable for some users. Case reports of topiramate in the treatment of night eating syndrome have also shown significant reductions in evening hyperphagia, nocturnal ingestions, and weight. Buproprion is not indicated for those with eating disorders as it has been associated with increased risk of seizures.

Prevention

Prevention programs aimed at reducing the incidence of eating disorders have been designed for children, adolescents, and college students. Dissonance-based interventions have been tested most rigorously and have been shown to have the greatest effect on reduction of eating disorder risk factors, symptoms, risk of onset, and future risk of development of obesity [22]. Cognitive dissonance programs involve having participants speak or behave in a manner that is opposite to their beliefs. As applied to eating disorders, women would be challenged to voice active criticism of the thin ideal; this is because internalization of the thin ideal is a risk factor for developing anorexia nervosa and bulimia

nervosa. Among college students, peer-led dissonance-based interventions have been shown effective among women considered at high and low risk for developing anorexia nervosa or bulimia nervosa.

Other approaches have focused on media literacy and advocacy, but more evidence is needed, particularly in light of the superior effectiveness of the dissonance-based programs. In peer-led programs, the media advocacy intervention is effective in reducing risk for disordered eating among high-risk women, but not those at low risk [23]. One trial of a cognitive behavioral therapy-based prevention program delivered through the internet showed reductions in the onset of eating disorders in two subgroups, those who were overweight and a subset of those who reported preexisting purging behaviors [24]. Finally, programs that focus on body shape and weight acceptance for children and adolescents have also been used in school programming, but little to no formal testing of the effects of these programs has been reported. As with other prevention approaches, more controlled studies are needed to confirm these results and to compare their efficacy with the dissonance-based and media advocacy approaches.

Conclusion

Eating disorders range from severe caloric restriction to severe overeating. Extreme dissatisfaction with weight and shape is present across the different diagnoses. In most diagnoses, there is also an uncontrollable urge to binge-eat. When medical complications are severe, inpatient treatment is warranted, particularly in anorexia nervosa. For most cases of bulimia nervosa, binge-eating disorder, night eating syndrome, and purging disorder, outpatient psychotherapy is the first line of treatment. Psychotropic medications, most recently SSRIs, have also been proven effective in treating bulimia nervosa, binge-eating disorder, and night eating syndrome. Lisdexamfetamine is now approved for use for binge-eating disorder. Prevention programs using dissonance-based interventions are promising for decreasing the incidence of eating disorders among college-age students, but other programs that target children and adolescents need to be formally evaluated.

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Chapter 8
Obesity: Understanding and Achieving a Healthy Weight

George A. Bray and Catherine M. Champagne

Key Points

- Obesity is a chronic problem that is increasing in prevalence, affecting both adults and children.
- A small positive energy imbalance causes obesity, but focusing on calories alone may not be as productive as modulating some of the economic and societal factors.
- Obesity increases risk of death and of many diseases; weight loss provides benefits in reducing health risks and improving the quality of life.
- Treatments must redress the energy imbalance with diet, lifestyle modification, and exercise as the cornerstones.
- Five drugs are approved by the FDA for long-term treatment, 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.

Keywords Obesity • Body mass index • Drug treatment • Bariatric surgery • Diet treatment

Introduction

Increased body weight, expressed in the body mass index [BW (kg)/Ht $(m)^2$], is one of the most widely used methods to assess the degree of overweight or obesity. Using this measure, the prevalence of obesity has been rising steadily as the epidemic of obesity has spread over the past 40 years [1]. Although obesity results from an imbalance between energy intake and expenditure, it is the

G.A. Bray, M.D. (✉)
Pennington Biomedical Research Center, Louisiana State University, 6400 Perkins Road, Baton Rouge, LA 70808, USA
e-mail: brayga@pbrc.edu

C.M. Champagne, Ph.D. (RDN, LDN, FADA, FAND, FTOS)
Department of Nutritional Epidemiology, Pennington Biomedical Research Center, Louisiana State University, 6400 Perkins Road, Baton Rouge, LA 70808, USA
e-mail: catherine.champagne@pbrc.edu

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connection between these two components of the first law of thermodynamics that can provide the clues about how we should understand, prevent, and treat this problem [1]. While nutrition is, of course, the ultimate "source" of a positive energy balance, many other factors impinge on whether an individual develops obesity.

The pathology of obesity can best be understood as an enlargement of fat cells, and in some individuals an increased number of fat cells [2, 3]. These enlarged fat cells release less adiponectin as well as more fatty acids and a variety of cytokines, including leptin, and tumor necrosis factor-a that can provide a basis for understanding how obesity produces insulin resistance and changes in the inflammatory, thrombotic, and coagulation systems.

There is a large industry offering various forms of treatment. Although we can treat obesity with some success, we rarely cure it, and a plateau in body weight during treatment with subsequent relapse when treatment is terminated is the common experience. Surgical intervention with gastric bypass, sleeve gastrectomy, or gastric banding is the most effective treatment but at an increased risk of mortality and with substantial morbidity. There are five pharmacologic agents currently approved for long-term use but they produce only modest weight loss.

Let us start with the premise that all of us want to have a healthy weight. Interest in obesity has taken a sharp upturn in recent years as its prevalence has increased. Obesity can be viewed as a chronic, stigmatized, neurochemical disease [4]. In this context, the goal is to return weight to a healthy level and to remove the stigma associated with the use of the word "obesity." To consider it in the context of a neurochemical derangement has the advantage of focusing on the underlying mechanisms that produce the distortion in energy balance resulting in an unhealthy state [4].

Definition and Prevalence of Obesity

Body Mass Index

Over the past 50 years, there has been a steady right-ward shift in the distribution curve for body weight. This trend can most effectively be traced using the BMI which provides a useful operating definition of overweight and obesity. A normal BMI is between 18.5 and 24.9 kg/m^2. A BMI between 25 and 29.9 is operationally defined as overweight, and individuals with BMI > 30 are obese, after taking into consideration other factors such as muscle builders, who have a high BMI, which may not be the most appropriate measure of weight status due to muscle. BMI also provides the risk measure for obesity [5].

Central Adiposity

If the BMI is elevated, the waist circumference provides a practical measure of adiposity by measuring its central distribution. It is a surrogate for more precise measures of visceral fat, such as a CT or MRI scan of the abdomen at the L4–5 position. Risk for diseases, such as diabetes, heart disease, and cancer, increases with a higher waist circumference. In the United States, a waist circumference of >40 in. in men and >35 in. in women is a high-risk category, but most of the rest of the world uses considerably lower cut-points (90–94 cm [35.5–37 in.] for men and 80 cm [31.5 in.] for women). When BMI and waist circumference were used to predict the risk of hypertension, dyslipidemia, and the metabolic syndrome, the waist circumference was shown to be a better predictor than the BMI [1, 6].

Prevalence

Based upon BMI, it is clear that there is a worldwide epidemic of obesity that began in the 1980s continues today although it may be slowing down [5, 7]. It affects children as well as adults. For example, among children and adolescents aged 6–19, almost one in 3 (33.2%) are considered to be overweight or obese, and 18.2% are considered to be obese, with somewhat higher rates in males than females. More than 2 in 5 black and Hispanic youth (more than 41%) are considered to be overweight or obese. About 25.7% of black, 22.9% of Hispanic, and 15.2% of white youth are considered to be obese.

We are now seeing a rise in the prevalence of type 2 diabetes in adolescents that is directly related to obesity. Obesity has a higher prevalence in Latino and African-American populations as well as in the Native Americans. Both height and weight have increased in adults aged 20–74 years between 1960 and 2000 but may have leveled off in adults between 2000 and 2010 [5].

Cost of Obesity

Obesity is expensive, costing between 3 and 8% of healthcare budgets [8]. Hospital costs and use of medication also increase with increasing BMI. In a large health-maintenance organization, mean annual costs were 25% higher in participants with a BMI between 30 and 35, and 44% higher in those with a BMI greater than 35, compared to individuals with a BMI between 20 and 25. Costs for lifetime treatment of hypertension, hypercholesterolemia, type 2 diabetes, heart disease, and stroke in men and women with a BMI of 37.5 were $10,000 higher than for men and women with a BMI of 22.5, according to data from the National Center for Health Statistics and the Framingham Heart Study (*see* [2]).

Etiology

Energy Imbalance

We become obese because we ingest more energy in carbon- and nitrogen-containing compounds from food than we expend over an extended period of time. While societal, genetic, and epigenetic factors may influence this relationship, they are only rarely the cause of obesity. We, and other animals, thus obey the first law of thermodynamics. Voluntary overeating (by subjecting individuals to repeated ingestion of energy exceeding daily energy needs) can increase body weight. When these individuals stop overeating, they invariably lose most or all of the excess weight. The use of overeating protocols to study the consequences of food ingestion has shown the importance of genetic factors in the pattern of weight gain [2].

Epidemiologic Model

An epidemiologic model may be a better way than the energy-balance model to conceptualize obesity as a disease (Fig. 8.1) [2, 3]. In an epidemiologic model, environmental agents act on a host to produce a disease. Disease is a function of the virulence of the agent and the susceptibility of the host. For obesity, the environmental agents include food, medications, toxins, physical inactivity, and viruses.

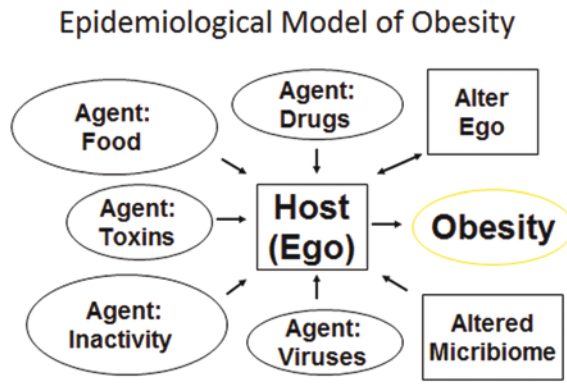

Fig. 8.1 An epidemiological model of obesity. The host at the center receives inputs from various environmental agents. Depending on the constitution of the host, obesity is one of the consequences [Adapted from Bray [3]]

In Western affluent societies, foods, particularly tasty, inexpensive, and convenient foods high in fat, are abundant. In addition, portion sizes have increased, providing more energy to people with each portion. Toxins are an interesting potential group of agents where more research is needed. Viruses are known to produce obesity and their potential role in obesity needs to be studied further. Physical activity within the general population has gradually been reduced, thereby decreasing energy expenditure. Some have described the current "environment" as a "virulent" or "toxic" environment that has heightened the risk for obesity. For the genetically susceptible host, this excess of food energy, environmental toxins, and viruses, along with the reduced level of physical activity, may lead to an accumulation of fat in fat cells. Genetics loads the gun; environment pulls the trigger (*see* [9]).

Environmental Agents

Intrauterine Factors

Several intrauterine events influence postnatal weight and lifetime weight gain and fatness [10]. These include, among other things, maternal weight gain, maternal diabetes, maternal smoking, and intrauterine undernutrition, all of which heighten the individual's risk for increased body weight and diabetes later in life.

Drug-Induced Weight Gain

In our current medicated society, it would not be surprising to find that drugs can cause weight gain. Table 8.1 is a list of medications that produce weight gain when used to treat various diseases such as psychosis, depression, allergies, and diabetes. Also listed in the table are alternative treatments that can be used to avoid the weight gain. In most instances, there are alternative strategies that can be used to treat a patient when weight gain is closely associated with the initiation of a new medication for one of these conditions. Several receptors, especially the histamine H_1, adrenergic α_{1A}, and serotonin (5-HT)-2C and −6 (5-HT_{2C} and 5-HT_6) receptors, explain much of the weight gain associated with atypical antipsychotic drugs (*see* [2]).

Table 8.1 Drugs that produce weight gain and alternatives

Category	Drugs that cause weight gain	Possible alternatives
Neuroleptics	Thioridazine, olanzapine, quetiapine, risperidone, clozapine	Molindone Haloperidol Ziprasidone
Antidepressants	Amitriptyline, nortriptyline	Protriptyline
Tricyclics	Imipramine	Bupropion
Monoamine oxidase inhibitors	Mirtazapine	Nefazodone
Selective serotonin reuptake inhibitors	Paroxetine	Fluoxetine Sertraline
Anticonvulsants	Valproate, carbamazepine Gabapentin	Topiramate Lamotrigine Zonisamide
Antidiabetic drugs	Insulin Sulfonylureas Thiazolidinediones	Acarbose Miglitol Metformin Sibutramine
Antiserotonin	Pizotifen	
Antihistamines	Cyproheptidine	Inhalers Decongestants
β-Adrenergic blockers	Propranolol	ACE inhibitors
α-Adrenergic blockers	Terazosin	Calcium channel blockers
Steroid hormones	Contraceptives Glucocorticoids Progestational steroids	Barrier methods Nonsteroidal anti-inflammatory agents

Diet

Many aspects of the diet may contribute to obesity. Portion size and consumption of sugar or high-fructose corn syrup (HFCS) in beverages have all been implicated in the current obesity epidemic. Consumption of soft drinks provides "invisible" energy which is not readily detected physiologically and which predicts future weight gain in children and adults [11].

Infant and Child Environment

Infants who are breastfed for more than 3 months may have a reduced risk of future obesity. In addition, children who sleep less have a higher risk for weight gain during school years. Children are in part a dietary product of their parental role-models, and the parental dietary and exercise patterns that lead to parental obesity predict childhood obesity.

Fat Intake

Epidemiologic data suggest that a high-fat diet is associated with obesity [2]. For example, the relative weights in several populations are directly related to the percentage of fat in the diet. A high-fat diet provides high energy density (i.e., more calories for the same weight of food), which makes overconsumption more likely. Differences in the storage capacity for various macronutrients may also be involved. The capacity to store glucose as glycogen in the liver and muscle is limited, so glucose must be continually replenished. In contrast, fat stores contain more than 100 times as many calories as

provided in the daily intake of fat. This difference in storage capacity makes eating carbohydrates a more important physiologic need that may lead to overeating when dietary carbohydrate is limited and carbohydrate oxidation cannot be reduced sufficiently.

Glycemic Index

The rate at which glucose is absorbed can be expressed as the glycemic index (GI). The GI is a way of describing the ease with which starches are digested in the intestine with the release of glucose that can be readily absorbed. A food with a high GI is readily digested and produces a large and rapid increase in plasma glucose levels. Conversely, a food with a low GI is digested more slowly and is associated with a slower and lower increase in glucose levels. Foods with a high GI suppress food intake less than foods with a low GI. Foods with a low GI include whole fruits and vegetables that tend to have fiber (but not juices) plus legumes and whole wheat. Potatoes, white rice, and white bread have a high GI. In a meta-analysis [12], the only difference between low GI/load and high GI/load diets was in plasma insulin favoring low GI/load diets, not in weight loss.

Calcium Intake

An inverse relationship has been reported between calcium intake and the risk of having a BMI in the highest quartile [13]. Others have reported similar inverse associations between body fat gain and calcium intakes in children and young women [8]. It has been suggested that a difference in calcium intake of 1000 mg/day is associated with an 8 kg difference in mean body weight, and, furthermore, that calcium intake explains roughly 3% of the variance in body weight [13]. These data suggest that low calcium intake may have a role in the current epidemic of obesity.

Most clinical trials, however, do not support a relation of dietary calcium to body weight. Diets high in dairy calcium do not necessarily translate into weight loss beyond that achieved in behavioral interventions. Thompson et al. [14] did not find that diets high in dairy products enhanced weight loss, stating that high-dairy (as opposed to moderate-dairy) and other specialized diets (e.g., low GI) should not be viewed as more effective without additional data from long-term randomized trials.

Frequency of Eating

The relationship between the frequency of meals and the development of obesity is not known. However, the frequency of eating does affect lipid and glucose metabolism. When normal-weight individuals eat several small meals per day, serum cholesterol concentrations are lower than when they eat a few large meals per day. Similarly, mean blood glucose concentrations are lower when meals are eaten frequently. One explanation for the difference between eating frequent small meals and a few large meals may be the greater insulin secretion associated with eating larger meals. One possible mechanism leading to weight gain might occur from the lower thermic effect of food and higher energy intake associated with irregular meal frequencies [15].

Restrained Eating

A pattern of conscious limitation of food intake is called “restrained” eating. It is a common practice in many, if not most, middle-aged women of normal weight. Higher restraint scores in women are associated with lower body weights. Weight loss is associated with an increase in restraint, indicating that higher levels of conscious control can maintain lower weight. Greater increases in restraint were correlated with greater weight loss but also with a higher risk of lapses, loss of control, and overeating.

Physical Activity

Low levels of physical activity correlate with weight gain. In a 10-year study of individuals aged 20–74 years in the National Health and Examination Survey (NHANES I), those with low levels of recreational activity gained more weight than did those with higher levels. The decline in moderate activity and increase in light and sedentary activity are correlated with the rising prevalence of obesity [16]. Low levels of baseline energy expenditure predicted weight gain in Pima Indians. Time spent watching television correlates with percent of overweight children (*see* [2]).

Smoking

Smokers have a lower body weight, and cessation of smoking is generally associated with weight gain.

Host Agents

Genetic Causes

There are several rare clinical forms of obesity. The Prader–Willi syndrome is the most common. This disease is transmitted as a chromosome/gene abnormality on chromosome 15 and is characterized by a "floppy" baby who has difficulty feeding. These children are mentally slow, short in stature, and obese [17]. The Bardet–Biedl syndrome is due, in at least one pedigree, to a defect in the chaperonin-like gene [17].

The leptin gene, the leptin receptor, the melanocortin-4 receptor gene, the proopiomelanocortin (POMC) gene, and agouti gene have significant effects on body fat and fat stores. MC4-receptor defects may account for up to 6% of obesity in early-onset, severely obese children [18]. Treatment of leptin-deficient children with leptin decreased body weight and hunger, indicating the importance of leptin for modulation of these processes in normal subjects. Heterozygotes for leptin deficiency have low but detectable serum leptin and have increased adiposity, indicating that low levels of leptin are associated with increased hunger and gain in body fat. Leptin can also increase energy expenditure and during reduced calorie intake, leptin attenuates the fall in thyroid hormones and the fall in 24-h energy expenditure.

The epidemic of obesity is occurring on a genetic background that does not change as fast as the epidemic has been exploding. Genome-wide association studies have found a large number of genes that have small effects on body weight. The FTO gene is the most potent and produces an additional 3 kg of body weight in those homozygous for the susceptibility variant [18]. At present, 97 genetic loci have been identified which accounted for 2.7% of the variation in BMI. Estimates made from these genome-wide surveys suggest that more than 20% of the variation in BMI may be accounted for by genetic variation [19].

Physiologic Factors

The discovery of leptin in 1994 opened a new window on the control of food intake and body weight. The response of leptin-deficient children to leptin indicates the critical role that this peptide plays in the control of energy balance. Leptin enters the brain, probably by transport across the blood–brain barrier. It then acts on receptors in the arcuate nucleus to regulate, in a conjugate fashion, the

production and release of at least four peptides. Leptin inhibits the production of neuropeptide Y (NPY) and agouti-related peptide (AGRP), both of which increase food intake, while enhancing the production of proopiomelanocortin (POMC), the source of α-melanocyte-stimulating hormone (α-MSH), which reduces food intake.

At least two other brain peptide systems have also been linked to the control of feeding. Melanin-concentrating hormone (MCH) is found in the lateral hypothalamus and decreases food intake when injected into the ventricular system of the brain. Orexin (also called hypocretin) was identified in a search of G protein-linked peptides that affect food intake. It increases food intake and plays a role in sleep.

Endocannabinoids are derived from membrane fatty acids. The endogenous cannabinoids (anandamide and arachidonoyl 2-glycerol) increase food intake by acting on CB-1 receptors in the brain. Antagonists to the CB-1 receptor reduce food intake.

Gut peptides, including glucagon-like peptide-1, polypeptide YY oxyntomodulin, and cholecystokinin, reduce food intake, whereas ghrelin, a small peptide produced in the stomach, stimulates food intake [2].

Metabolism of fatty acids in the brain may be another important control point. A chemical that blocks fatty acid synthase leads to significant weight loss in animal studies. Malonyl-CoA accumulates in this setting and has been suggested to be a molecule that modulates food intake.

Pathology and Pathophysiology of Obesity

Enlarged fat cells are the hallmark of obesity, and in some individuals there is also an increased number of fat cells.

Fat as an Endocrine and Inflammatory Organ

Two mechanisms can explain the pathophysiology of obesity: the first is increased fat mass, which can explain the stigmatization of physically obvious obesity, and the accompanying osteoarthritis and sleep apnea (Fig. 8.2; [2]). The second mechanism is the increased amount of peptides that are produced by the enlarged fat cells that act on distant organs. The discovery of leptin catapulted the fat cell into the arena of endocrine cells. In addition to leptin, there are increased amounts of cytokines, angiotensinogen, adipsin (complement factor D), etc. and metabolites such as free fatty acids and lactate. In contrast to the other fat cell products, adiponectin release is decreased in obesity. The products of the fat cell in turn modify the metabolic and inflammatory processes in other organs of the host. For the susceptible host, these metabolic and inflammatory changes increase fatty acids and estrogens leading to a variety of other processes, including hyperinsulinemia, atherosclerosis, hypertension, and physical stress on bones and joints.

Visceral Fat

Central, visceral, or ectopic fat has a stronger relationship with the complications associated with obesity than does total body fat [6, 20]. Central adiposity is also one of the key components of the metabolic syndrome, whose diagnostic criteria based on the recommendation of the National Cholesterol Education Program Adult Treatment Panel III is shown in Table 8.2.

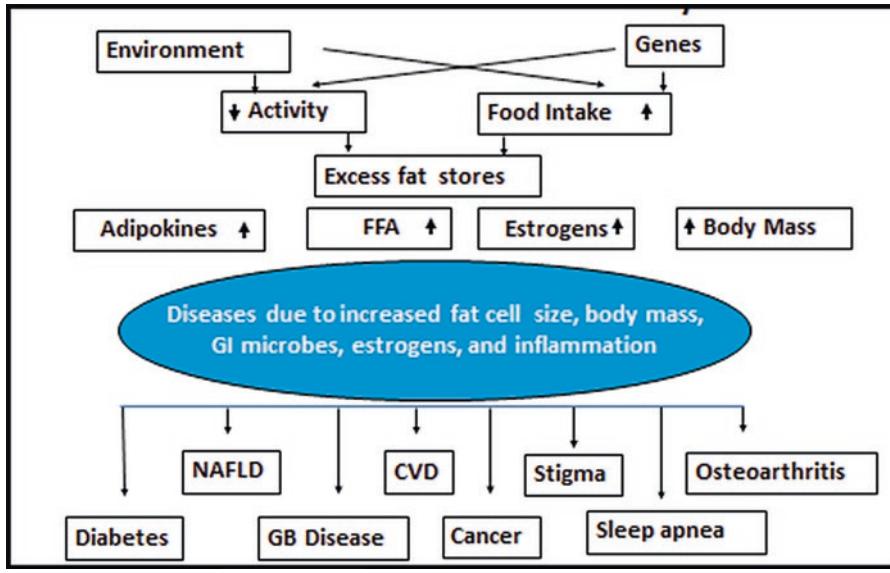

Fig. 8.2 Pathogenesis of health problems associated with obesity. The mass of fat and the responses to products produced by fat cells can explain most of the diseases that result from prolonged obesity. *NAFLD* nonalcoholic fatty liver disease, *CVD* cardiovascular disease, *GB* gall bladder. Adapted from [2]

Table 8.2 National Cholesterol Education Program Adult Treatment Panel III Criteria for the metabolic syndrome[a]

Risk factor	Defining level
Waist circumference (central adiposity)	
Males	>40 in. (102 cm)
Females	>35 in. (88 cm)
HDL cholesterol	
Males	<40 mg/dL
Females	<50 mg/dL
Triglycerides	>150 mg/dL
Blood pressure (SBP/DBP)	>130/>85 mmHg
Glucose (fasting)	100–126 mg/dL

[a]Modified criteria from the National Cholesterol Education Program Adult Treatment Panel III. The metabolic syndrome is present when three of these five criteria are abnormal

Complications of Obesity

Death

Obesity is associated with shortened life span and contributes between 100,000 and 400,000 excess deaths per year in the United States. Both the NCHS data and the Framingham data show that a BMI of 30 or more decreases life span by 3–5 years compared to normal weight [2]. Obesity is also associated with increased healthcare costs and diminished quality of life during the last years of life. This results from the comorbidities associated with obesity (i.e., sleep apnea, type 2 diabetes, osteoarthritis, heart disease).

Diseases

The curvilinear "J"-shaped relationship of BMI to risk of complications has been known for 100 years. As obesity increases, so, too, do the risks of type 2 diabetes, CVD, hypertension, arthritis, cognitive impairment, and some cancers. In the United States, diagnosed diabetes increased from 7.8 million cases in 1993 to 21 million in 2012; >8 million additional cases remain undiagnosed, and an estimated 86 million adults have prediabetes. Population-based studies have suggested that ~75% of all hypertension cases can be attributed to obesity, and approximately one-third of cancer deaths are linked to poor nutrition, excess weight, and a sedentary lifestyle. Worldwide, 44% of the diabetes burden, 23% of coronary heart disease, and 7–41% of certain cancers are attributable to excess weight. Obesity also decreases both health-related quality of life and life expectancy [21].

Prevention

A reduction in TV watching by children is associated with a smaller gain in BMI. In children, studies reveal that when the consumption of sugar-sweetened beverages, primarily soft drinks, is decreased, there is slower weight gain than when children are randomly assigned to soft drinks that do not contain sugar [2]. In addition, the youth in the upper half of the body weight range did not reduce calorie intake sufficiently to compensate for the beverage calories—thus, the beverage calories were partially "invisible" to these adolescents. In adults, there are unfortunately few successful programs that prevent obesity, but some individuals do lose weight and maintain it as demonstrated by the National Weight Control Registry of individuals who are "successful" weight losers for at least a year.

Treatment

Realities of Treatment

The Guidelines for Obesity provide an algorithm for evaluating the overweight patient [22]. It is a useful framework on which to hang the information that is collected during the evaluation of obese patients (Fig. 8.3).

Realism is one important aspect of treatment for obesity. For most treatments, including behavior therapy, diet, and exercise, the weight loss (measured as percentage loss from the baseline weight) plateaus after a loss of <10%. For many patients, this is a frustrating experience as their dream weight requires a weight loss of nearly 30%. A loss of <17% can be a disappointment to women entering a weight-loss program. It is thus important for the patient and physician to recognize that an initial weight loss of 10% is a success that will produce health benefits [22].

Diet

Diets Low in Fat, Carbohydrate, or Energy Density

A variety of diets, including low-fat foods, low-carbohydrate foods, or a balanced reduction of all macronutrients, have been used to treat obesity. Table 8.3 is a compilation of several of these diets. A meta-analysis of low-fat vs. conventional studies identified five studies lasting up to 18 months.

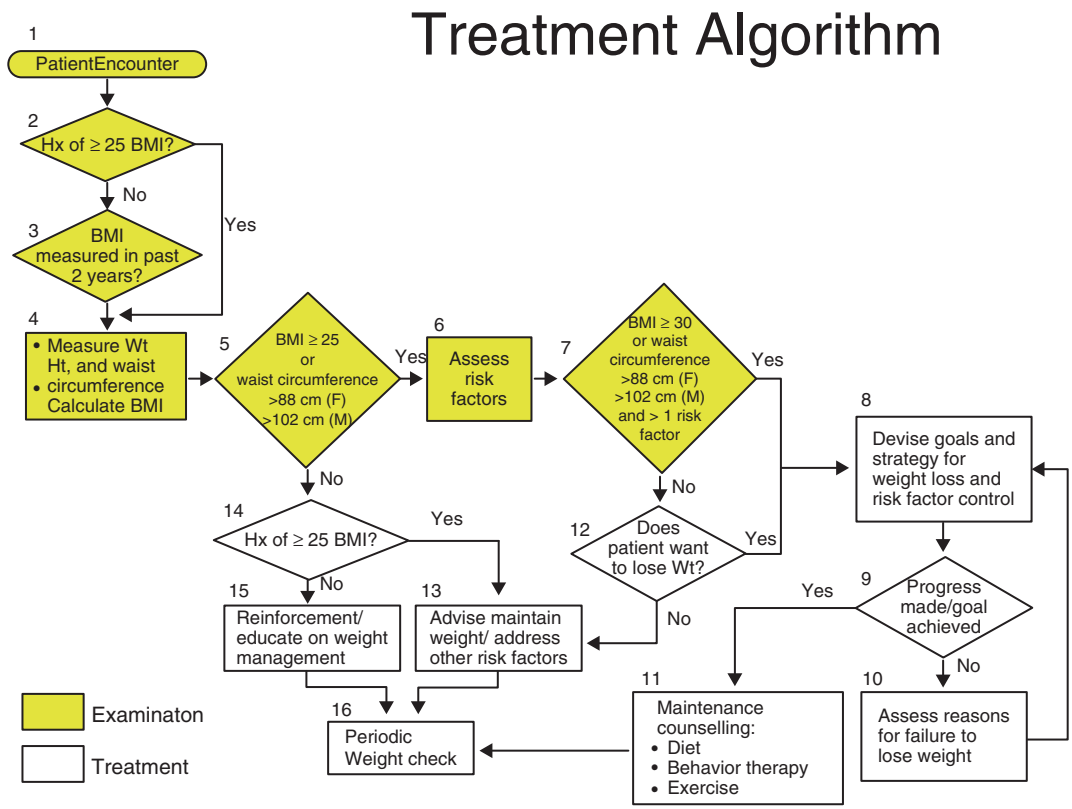

Fig. 8.3 Algorithm for diagnosis and treatment of obesity. Adapted from [22]

In comparing the weight loss at 6, 12, and 18 months, there were no statistically significant differences from control, leading the authors to conclude that low-fat diets produce weight loss, but not more so than other diets. In a meta-analysis comparing "named" diets, Johnston et al. [23] showed no consequential differences in weight loss at the end of 1 year.

Fat is an important component of energy density. If the diet is high in fat or low in water content, then it will have a high energy density (i.e., more calories per gram). In a recent trial, Ello-Martin et al. [24] reported a weight loss of 7.9 kg after 1 year by feeding a diet with a low energy density. The diet was low in fat diet and rich in fruits and vegetables with high water content. This underscores the role of energy density of the diet as a factor in weight loss. It is important to appreciate that little weight loss will occur unless the diet induces an energy deficit, but there may be a number of different ways to do that. This idea of low energy density is developed in the *Volumetrics* diet (Table 8.3).

Several controlled trials showed more weight loss with a low-carbohydrate diet than the control diet in the first 6 months but no difference at 12 months (Table 8.3). In two head-to-head comparisons of four popular diets, the average weight loss at 6 and 12 months was the same [25, 26]. The best predictor of weight loss for each of the diets was the degree of adherence to the diet [25, 26].

Portion-Controlled Diets

Portion control is one dietary strategy with promising long-term results. A trial in diabetic patients using portion-controlled diets as part of the lifestyle intervention (Look AHEAD Program) found that weight loss was increased across each quartile of portion control product use [27].

Table 8.3 Comparison of diet programs and eating plans compared 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/day	Low in fruits and vegetables, dairy, and whole grains High in saturated fat and unrefined carbohydrates	
Balanced nutrient, moderate-calorie approach	DASH Diet or diet based on 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, volumetrics	Carb: 55–60% Protein: 15–20% Fat: 20–30% Usually 1200–1800 kcal/day	Based on 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, other fats	Long-term compliance with some plans may be difficult because of 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	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: 1. Very low energy density—non-starchy fruits and veggies, nonfat milk, broth-based soups 2. Low energy density—starchy fruits/veggies, grains, breakfast cereal, low-fat meats and mixed dishes 3. Medium energy density—meat, cheese, pizza, fries, dressings, bread, etc. 4. High energy density—desserts, nuts, 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
Portion-controlled	Use of meal replacements, both liquid and solid meals			Weight loss at 1 year in the Look AHEAD trial related to frequency of consuming portion-controlled meals

Mediterranean style diets		Carb: 35–40% Protein: 12–20% Fat: 40–50% – Approximately 25–30% of energy from mono-unsaturated 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/day	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	Same weight loss at 6 months comparing <30 g/day 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	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% (note that I attached an abstract below)	Focus on low-GL foods	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 consumption of SSBs is related to 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
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), Medifast, Optifast	Less than 800 kcal/day	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	

Behavior Modification and Lifestyle Interventions

Behavioral modification in lifestyle programs has been an important part of programs for weight loss for more than a quarter of a century [27, 28]. Weight losses have been in the 5–10% range. 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 it 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. This has shown promising results [29].

Exercise

Exercise is important for maintaining weight loss, but when used alone does not generally produce much weight loss [30]. Comparisons of people who successfully maintain weight loss and those who do not show 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 allows counting of steps. Working toward 10,000 steps per day is a good goal.

Medications

The currently approved medications for the treatment of obesity are shown in Table 8.4. At present, five medications are approved for long-term treatment, and several others are approved for short-term use [2, 31].

Noradrenergic Drugs

Diethylpropion, phentermine, benzphetamine, and phendimetrazine are approved by the FDA for short-term use, usually considered to be up to 12 weeks. All of these drugs probably work by blocking reuptake of norepinephrine into neurons. Phentermine is among the most widely prescribed appetite suppressants. Clinical trials with these drugs are usually short term [2].

Orlistat

Orlistat blocks intestinal lipase and thus enhances fecal loss of fat. There have been several long-term clinical trials with orlistat. During the treatment period, patients receiving orlistat reached a maximum of 10% weight loss compared to about 5% with placebo. At the end of 4 years, there was still a 2.5% difference in favor of orlistat. In the subgroup that had impaired glucose tolerance, conversion to diabetes was reduced by nearly 40%. Orlistat blocks triglyceride digestion and reduces the absorption of cholesterol from the intestine; this accounts in part for the reduced plasma cholesterol found in patients treated with this drug [31].

Table 8.4 Drugs approved by the Food and Drug Administration for treatment of obesity

Drug and mechanism of action	Trade names	Dosage	Comments
Pancreatic lipase inhibitor approved for long-term use orally			
Orlistat (not scheduled)	Xenical	120 mg tid before meals	GI side effects from bloating and diarrhea are principal drawbacks
Serotonin receptor agonist approved for long-term use orally			
Lorcaserin DEA Schedule IV	Belviq	110 mg twice daily	Headache, dizziness, nausea, dry mouth, and constipation are generally mild. Do not use with other serotonin active drugs
Glucagon-like receptor-1 agonist approved for long-term use by injection			
Liraglutide (not scheduled)	Saxenda	3.3.0 mg/day—dose escalation over 5 week from 0.6 to 3.0 mg/day	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 DEA Schedule IV	Qsymia	3.75 mg/23 mg, first week; 7.5 mg/46 mg thereafter can increase to 15 mg/92 mg for inadequate response	Paresthesias and change in taste (dysgeusia) Metabolic acidosis and glaucoma are rare; do not use within 14 days of an MAOI antidepressant
Naltrexone SR-Bupropion SR (not scheduled)	Contrave	8 mg/90 mg tabs; take 2 twice daily after dose escalation	Nausea, constipation, headache; avoid in patients receiving opioids, MAOI, antidepressants, and with history of seizure disorder
Noradrenergic drugs approved for short-term use			
Diethylpropion DEA Schedule IV	Tenuate	25 mg tid	Dizziness, dry mouth, insomnia, constipation, irritability
	Tepanil	75 mg q AM	Cardiostimulatory
	Tenuate Dospan		
Phentermine DEA Schedule IV	Adipex	15–37.5 mg/day	Dizziness, dry mouth, insomnia, constipation, irritability
	Fastin		Cardiostimulatory
	Oby-Cap	15–30 mg/day	
	Ionamin slow release		
Benzphetamine DEA Schedule III	Didrex	25–50 mg tid	Dizziness, dry mouth, insomnia, constipation, irritability Cardiostimulatory
Phendimetrazine DEA Schedule IV	Bontril	17.5–70 mg tid	Dizziness, dry mouth, insomnia, constipation, irritability
	Plegine	105 mg qd.	Cardiostimulatory
	Prelu-2		

Lorcaserin

Lorcaserin is a specific serotonin 2c receptor agonist which is remarkable for its tolerability and low rate of adverse events. Echocardiograms performed in phase III trials found no statistically significant increase in FDA defined valvulopathy. The drug should not be used with serotonin reuptake inhibitors because of the risk of serotonin syndrome. It has not been studied with SSRIs, SNRIs, or other serotonergic agents, and extreme caution should be used in combining it with those agents [31].

Liraglutide

Liraglutide is a GLP-1 agonist with a 97% homology to GLP-1 which extends its circulating half-life. It has been used for management of diabetes at doses up to 1.8 mg, given by injection. It is now approved in the United States and EU for chronic weight management at a dose of 3.0 mg. Nausea has been one of the principal complaints in patients injecting this drug and a slow dose escalation over 5 weeks is recommended. There is also a small but significant increase in heart rate, but blood pressure tends to fall. GLP-1 agonists are associated with thyroid C cell tumors in animals but this has not been demonstrated with certainty in humans. Liraglutide should not be prescribed in patients with family or personal history of medullary thyroid cancer or multiple endocrine neoplasia. Acute pancreatitis, gall bladder disease, and hypoglycemia in diabetics are safety issues that require managing if they occur [31].

Combination of Phentermine and Topiramate: Extended Release

The combination of phentermine and topiramate as an extended release (ER) formulation (PHEN/TPM ER) uses lower doses of both (7.5/46 mg at the recommended dose) than are usually prescribed when either drug is used as single agent. This combination of medications is associated with greater mean weight loss than other available medications. Topiramate is associated with fetal toxicity (oral clefts) and a pregnancy test prior to initiating therapy and monthly thereafter is recommended. The most common side effects include paresthesias, dizziness, dysgeusia, insomnia, constipation, and dry mouth. A rare side effect of topiramate is acute myopia with glaucoma and the drug is contraindicated in glaucoma. The combination of PHEN/TPM ER is also contraindicated in hyperthyroidism and within 14 days of treatment with monoamine oxidase inhibitors (MAOIs). Other rare potential adverse risks include kidney stones (associated with topiramate) and increased heart rate (associated with phentermine) in patients susceptible to sympathomimetic drugs [31].

Combination of Naltrexone-Bupropion: Sustained Release

The combination of naltrexone SR/bupropion SR is approved for long-term management of patients with obesity. Bupropion is a reuptake inhibitor of dopamine and norepinephrine. Naltrexone is an opioid antagonist that has minimal effect on weight loss on its own. Naltrexone is thought to block inhibitory influences of opioid receptors activated by the β-endorphin released in the hypothalamus that stimulates feeding, thus allowing the inhibitory effects of α-melanocyte stimulating hormone (α-MSH) to reduce food intake. Naltrexone SR/bupropion SR can increase blood pressure and the combination should not be prescribed to patients with uncontrolled hypertension. Monitoring the patient's blood pressure during drug titration is advisable. Marketing was approved after a cardiovascular outcome trial was conducted. Nausea on initiating the drug mandates a dose escalation over 4 weeks. All antidepressants in the United States are required to carry a black box warning of suicidality and the combination's label includes this warning even though there were no signals for suicidality in phase III studies [31].

Surgery

Surgical intervention for obesity has become ever more popular [32, 33]. The Swedish Obese Subjects Study evaluated gastrointestinal operations for obese patients and provides one of the best sources of information about the outcomes of this surgery [34]. The control group comprised obese patients who

were treated with the best alternatives. Weight loss for many patients with gastric bypass exceeded 50 kg. There was a graded effect of weight change, measured at 2 and 10 years after the operation, on HDL cholesterol, triglycerides, systolic and diastolic blood pressure, insulin, and glucose [35]. Mortality was significantly reduced by 29% in the operated patients [36]. These patients also showed a reduction in myocardial infarction, stroke and reduced incidence of diabetes mellitus. Cancer was significantly reduced in the women [34].

To maintain successful weight loss after bariatric surgery requires that calorie intake remains low. Failure rates, that is, weight regain or inadequate initial weight loss, can occur in up to 40% of some studies indicating the importance of commitment to the goals of bariatric surgery—maintaining weight loss.

Conclusion

The challenge is to provide nonsurgical treatments that have dose-dependent effects on body fat stores, and thus the size of individual fat cells, as a treatment strategy aimed at reducing the complications of the disease of obesity. Treatment of patients with surgery shows that weight loss improves long-term health outcomes, but at a cost of significant short-term health problems. Effective medications for treatment of obesity, however, are few in number. With a disease that is affecting upward of 30% of the adult population and reducing life expectancy, there would appear to be a bright future for medicinal agents aimed squarely at treating this epidemic.

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Suggested Further Reading

The following websites contain good information or handouts to determine whether following a particular diet will be harmful or not:

The Federal Trade Commission, www.ftc.gov, which includes "Weighing the Evidence in Diet Ads"

The American Heart Association's *Fad Diets*, at www.americanheart.org

Chapter 9
Nutrition Therapy Effectiveness for the Treatment of Type 1 and Type 2 Diabetes: *Prioritizing Recommendations Based on Evidence*

Marion J. Franz, Zhuoshi Zhang, and Bernard Joseph Venn

Key Points

- Medical nutrition therapy for diabetes using a variety of nutrition interventions and multiple encounters can lower hemoglobin A1c by ~1–2% depending on the type and duration of diabetes.
- For persons with type 1 diabetes
  - Identify a usual or convenient schedule of foods/meals and physical activity
  - Integrate insulin therapy and dietary advice into the patient's lifestyle
  - Determine insulin-to-carbohydrate ratios, calculate insulin correction factors, and review goals
  - Provide ongoing support and education
- For persons with type 2 diabetes
  - Focus on metabolic control—glucose, lipids, and blood pressure
  - Implement nutrition interventions for glucose control
  - Encourage physical activity
  - Monitor outcomes to determine if goals are being met or if medications need to be added or changed
  - Provide ongoing support and education
- Research supports consistency in total amount of carbohydrate eaten, fiber intake for lowering of total and LDL cholesterol, no change in protein intake with normal renal function, and reduction in saturated and trans fatty acids and dietary cholesterol.
- Research on the glycemic index/load and micronutrient supplementation is controversial.

Keywords Type 1 diabetes • Type 2 diabetes • Nutrition therapy • Insulin therapy • Glycemic index

M.J. Franz, M.S., R.D.N. C.D.E. (✉)
Nutrition Concepts by Franz, Inc., 6635 Limerick Drive, Minneapolis, MN 55439, USA
e-mail: MarionFranz@aol.com

Z. Zhang, R.D. • B.J. Venn, Ph.D.
Department of Human Nutrition, University of Otago, PO Box 56, Dunedin, Otago 9054, New Zealand
e-mail: zhazh902@student.otago.ac.nz; bernard.venn@otago.ac.nz

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Introduction

Based on 2012 data, approximately 29 million people in the United States have diabetes, an increase of 5 million from 2007 [1]. The estimated prevalence of total diabetes was 12–14% in total US population. Up to 25–36% of people with diabetes are undiagnosed, a rate that has fluctuated between 25 and 30% over the last few years [2]. Worldwide, it is estimated that 415 million people have diabetes with projections of huge increases into the foreseeable future [3]. Diabetes prevalence increases with age, affecting approximately 25% of those 65 years and older. In North America, the disease is particularly prevalent in ethnic populations, such as African-Americans, Hispanic populations (Latinos and Mexican Americans), Native Americans and Alaska Natives, Asian-Americans, and Pacific Islanders. While much of the rise in the prevalence of type 2 diabetes is seen in the middle-aged and elderly, there is a trend to an earlier age of onset. Evidence shows a rise in type 2 diabetes among younger North Americans; in 10–19-year-olds, type 2 diabetes now accounts for around 9% of recent diagnoses in non-Hispanic whites and 50% or more in ethnic minority groups [4]. Studies have shown that medical nutrition therapy (MNT) can play an important role in assisting persons with diabetes to meet their glucose, lipid, and blood pressure goals and, therefore, should be a major component in the medical management of the disease [5, 6].

Medical Nutrition Therapy for Diabetes

Prior to 1994, nutrition recommendations for diabetes attempted to define an "ideal" nutrition prescription that would apply to all persons with the disease. The nutrition prescription was based on a theoretical calculation of required calories and an identified ideal percentage of carbohydrate, protein, and fat. Individualization, although recommended, needed to be done within the confines of this prescription, which did not allow for much, if any, individualization. Not surprisingly, persons with diabetes often found it difficult, if not impossible, to adhere to these recommendations.

In 1994, the American Diabetes Association (ADA) recommended a different approach. The nutrition prescription, instead of being rigid, was to be based on an assessment of lifestyle changes that assist the individual in achieving and maintaining therapeutic goals and changes that he or she is willing and able to make. For example, if an individual with type 2 diabetes has been eating 3000 kcal, it is unlikely that the individual would adhere for long to a 1200 kcal weight-reduction diet. A more realistic approach would be to negotiate manageable lifestyle changes that lower energy intake and that are of the individual's choosing. This approach has continued with subsequent ADA recommendations.

The ADA and the Academy of Nutrition and Dietetics publish updated nutrition recommendations and interventions [7, 8] that are similar. Research supports medical nutrition therapy (MNT) as a very effective therapy in reaching treatment goals [9]. Randomized controlled trials and observational studies of diabetes MNT provided by registered dietitians (RDs) have demonstrated decreases in hemoglobin A1c (A1C) of approximately 1–2% (for example, from 8.9 to 7%) depending on the type and duration of diabetes [6]. MNT outcomes are similar to those from antidiabetic medications. Although MNT has been shown to be effective at any time in the disease process, it appears to have its greatest impact at diagnosis of diabetes. Outcomes of MNT interventions are evident by 6 weeks to 3 months and at that time it should be determined if additional MNT encounters or medication changes, such as the addition of antidiabetic medications or insulin therapy in type 2 diabetes or changes in insulin regimens in type 1 or type 2 diabetes, are needed.

Central to MNT interventions are multiple encounters to provide education and counseling initially and on a continued basis. Although attempts are often made to identify one approach to diabetes

Table 9.1 Effectiveness of medical nutrition therapy

Endpoint	Expected outcome	When to evaluate
Glycemic control		
A1C	1–2% decrease (e.g., from 8 to 6–7%)	
Plasma fasting glucose	50 mg/dL (2.78 mmol/L) decrease	
Lipids		
Total cholesterol	24–32 mg/dL (0.62–0.82 mmol/L)	6 week; if goals are not achieved, intensify medical nutrition therapy and evaluate again in 6 week
LDL cholesterol	19–25 mg/dL (0.46–0.65 mmol/L)	
Triglycerides	15–17 mg/dL (0.17–0.19 mmol/L)	
HDL cholesterol		
With no exercise	3 mg/dL (0.08 mmol/L)	
With exercise	No decrease	
Blood pressure (in hypertensive patients)	Decrease of 5 mmHg in systolic and 2 mmHg in diastolic	Measured at every medical visit

Source: Reprinted from [6] with permission

Table 9.2 Glucose, lipids, and blood pressure recommendations for adults with diabetes

Glycemic control	
A1C	<7.0%[a]
Preprandial plasma glucose	90–130 mg/dL (5.0–7.2 mmol/L)
Postprandial plasma glucose	180 mg/dL (<10.0 mmol/L)
Blood pressure	<130/80 mmHg
Lipids	
LDL cholesterol	<100 mg/dL (<2.6 mmol/L)
Triglycerides	<150 mg/dL (<1.7 mmol/L)
HDL cholesterol	>40 mg/dL (>1.1 mmol/L)[b]

Source: from [10]

[a]Referenced to a nondiabetic range of 4.0–6.0% using a DCCT-based assay

[b]For women, it has been suggested that the HDL goal be increased by 10 mg/dL

MNT, a single approach does not exist, just as there is no one medication or insulin regimen that applies to all persons with diabetes. A variety of interventions, such as reduced energy/fat intake, carbohydrate counting, simplified meal plan, healthy food choices, individualized meal-planning strategies, exchange lists, insulin-to-carbohydrate ratios, physical activity, and behavioral strategies, were implemented in the 16 studies reviewed by the Academy of Nutrition and Dietetics [8]. Table 9.1 is a summary of the mean expected metabolic outcomes from MNT on glucose, lipids, and blood pressure [6].

Prioritizing Nutrition Interventions for Type 1 and Type 2 Diabetes

Improving health through food choices and physical activity is the basis of all nutrition therapy recommendations for diabetes. However, a primary goal of MNT is to attain and maintain blood glucose levels in the normal range or as close to normal as is safely possible. Because changes in lifestyle can have an immediate impact on glycemia, this is often the first focus of MNT. But MNT must also focus on the effect of lifestyle modifications on lipid and lipoprotein profiles and blood pressure so as to prevent and treat the cardiovascular complications associated with diabetes. Table 9.2 lists the ADA goals for glucose, lipids, and blood pressure [10].

Type 1 Diabetes Nutrition Interventions

Identify a Usual or Convenient Schedule of Food/Meals and Physical Activity

The first priority for persons requiring insulin therapy is to integrate an insulin regimen into the patient's lifestyle. The food/meal plan is developed first and is based on the individual's appetite, preferred foods, and usual schedule of meals and physical activity. After the RD, working with the patient, develops a food plan, this information is shared with the professional determining the insulin regimen.

Integrate Insulin Therapy into the Patient's Lifestyle

The preferred type of insulin regimen duplicates the normal physiological responses of insulin. Generally, this consists of a basal insulin, such as glargine or detemir, and a mealtime bolus insulin, such as a rapid-acting insulin (lispro, aspart, or aprida) or insulin pump therapy. These types of therapy provide increased flexibility in timing and frequency of meals, amounts of carbohydrate eaten at meals, and timing of physical activity [11].

Determine Insulin-to-Carbohydrate Ratios

Insulin-to-carbohydrate ratios are used to adjust the bolus insulin doses based on the planned carbohydrate content of the meals. Insulin-to-carbohydrate ratios can be determined by either having the individual (1) eat a consistent amount of carbohydrate in a meal, adjust the bolus insulin to obtain postmeal glucose goals, and then determine the ratio, or (2) start with an estimated ratio (often 1 unit of rapid-acting insulin for every planned 15 g carbohydrate intake) and adjust it based on resulting postmeal glucose results [12]. The insulin-to-carbohydrate ratio can also be determined by a statistically established formula: 500 divided by the daily total insulin dose [11]. For example, an individual taking 50 units of insulin per day would have an insulin-to-carbohydrate ratio of 10 (1 unit of insulin per 10 g carbohydrate). Usually the insulin-to-carbohydrate ratio is the same for all meals but may be slightly higher at breakfast.

Calculate Insulin Correction Factor

Individuals with type 1 diabetes also need a correction bolus algorithm to correct out-of-range glucose values [11]. The insulin correction or insulin sensitivity factor is defined as the estimated number of mg/dL (mmol/L) that one unit of a rapid-acting insulin will lower blood glucose over 3–5 h. To determine the correction factor 1700 is divided by the daily total insulin dose. For example, an individual taking 50 units of insulin per day would have a correction factor of 35 (1700 divided by 50 = 35). In this case, one unit of insulin lowers the patient's blood glucose by approximately 35 mg/dL (2 mmol/L). The correction factor is added to the premeal bolus dose to optimize postmeal glucose levels. Because of overlapping dosing effects, at least 4 h should elapse between correction factor doses.

Review Goals

For most people, a target premeal glucose is often 80–130 mg/dL (4.4–7.2 mmol/L). However, individuals prone to hypoglycemia may have a higher target of 90–150 mg/dL (5.0–8.3 mmol/L), and pregnant women may have a lower target of 60–99 mg/dL (3.3–5.4 mmol/L) [10]. And although

carbohydrate counting is emphasized, total energy intake cannot be ignored. Weight gain is common as treatment intensifies; therefore, individuals must also be knowledgeable about the protein, fat, and calorie content of foods.

Type 2 Diabetes Nutrition Interventions

Focus on Metabolic Control

Type 2 diabetes is characterized by insulin resistance and paradoxical insulin hypersecretion in early stages that leads to insulin deficiency (dependence upon exogenous insulin) in later stages. In most individuals, insulin resistance begins and progresses many years before the development of diabetes. However, as long as the beta cells produce adequate insulin to overcome the resistance, the blood glucose level remains normal. Impaired beta-cell function must be present before hyperglycemia develops. By the time diabetes develops as much as 50% of beta-cell function has been lost [13]. Therefore, it is essential that effective therapy lowers elevated blood glucose concentrations as early as possible to slow beta-cell exhaustion and to prevent the deleterious effects of hyperglycemia. As a consequence of the progressive loss of beta-cell secretory function, persons with diabetes usually require more medication(s) over time to maintain the same level of glycemic control and eventually exogenous insulin will be required. MNT continues to be an important component of diabetes management but changes over the natural progression of the disease.

One of the goals for the prevention of diabetes is weight loss, whereas for treatment, the goals of nutrition therapy shift to control of glucose, lipid, and blood pressure. Interventions, including weight loss, physical activity, and MNT, provide benefits in reducing risks of cardiovascular disease. In overweight and obese patients, a sustained weight loss of at least 5–7% (optimal) has also been shown to improve blood glucose control and to reduce the need for hypoglycemic agents [14–16]. Compared with conventional weight loss, bariatric surgery is more effective in improving glycemia and inducing diabetes remission, especially in obese patients, with remission of diabetes occurring in 40–80% of those undergoing surgery [17–19]. Improvement in glycemia from weight loss is most likely to be achieved in the early stage of diabetes when patients have a relatively preserved insulin secretion capacity [10, 20, 21]. However, for some it may be too late to dramatically improve hyperglycemia through weight loss alone [5, 22, 23]. Furthermore, it is noteworthy that not all individuals with type 2 diabetes are overweight or obese. As medications—including insulin—need to be combined with nutrition therapy, weight gain often occurs and thus preventing this weight gain becomes important. However, glycemic control must still take precedence over concern about weight.

Implement Nutrition Interventions for Glucose Control

Teaching individuals how to make appropriate food choices (often by means of carbohydrate counting) and using data from blood glucose monitoring to evaluate short-term effectiveness are important components of successful MNT for type 2 diabetes. Many individuals with the disease also have dyslipidemia and hypertension, so decreasing intakes of saturated and trans fatty acids, cholesterol, and sodium should also be a priority.

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). For purposes of carbohydrate counting, foods are placed into three groups: carbohydrate, meat and meat substitutes, and fat. The carbohydrate list is composed of starches, fruits, milk, and sweets; one serving is the amount of food that contains 15 g of carbohydrate. Table 9.3 lists some examples of a carbohydrate serving.

Table 9.3 Carbohydrate servings[a]

Starch	*Milk*
1 slice of bread (1 oz)	1 cup skim/reduced-fat milk
1/3 cup cooked rice or pasta	2/3 cup fat-free fruited yogurt sweetened with nonnutritive sweetener (6 oz)
3/4 cup dry cereal	
4–6 crackers	
½ large baked potato with skin (3 oz)	
¾ oz pretzels, potato, or tortilla chips	
Fruit	*Sweets and Desserts*
1 small fresh fruit (4 oz)	2 small cookies
½ cup fruit juice	1 tablespoon jam, honey, syrup
¼ cup dried fruit	½ cup ice cream, frozen yogurt, or sherbet

[a]One serving contains 15 g of carbohydrate

Carbohydrate counting does not mean that meat and fat portions can be ignored. Individuals with diabetes must also know the approximate number of meat and fat servings they should select for meals and snacks. Weight control is important as is the maintenance of a healthy balance of food choices.

The first decision for food and meal planning is the total number of carbohydrate servings the person with diabetes chooses to eat at meals or for snacks. Women with type 2 diabetes often do well with three or four carbohydrate servings per meal, with or without one to two carbohydrate-containing snacks. Men with type 2 diabetes may need four to five carbohydrate servings per meal, with or without one to two for a snack.

Learning how to use Nutrition Facts on food labels is also useful. First, individuals should take note of the serving size and the total amount (grams) of carbohydrate. The total grams of carbohydrate are then divided by 15 to determine the number of carbohydrate servings in the serving size.

When insulin is required, consistency in timing of meals and of their carbohydrate content becomes important. The administration of basal insulin once or twice a day may suffice for persons with type 2 diabetes who still have significant endogenous insulin. Once-daily glargine, detemir, or NPH at bedtime or premixed insulin before the evening meals is commonly used regimens [24]. The rationale is that supplementing with overnight insulin will control fasting hyperglycemia. However, a concern with evening NPH is nocturnal hypoglycemia. Oral agents may be continued during the day to prevent worsening of daytime glycemia. Many individuals with type 2 diabetes will eventually require an insulin regimen that better mimics the release of endogenous insulin in response to food intake in persons without diabetes.

Encourage Physical Activity

Low cardiorespiratory fitness and physical inactivity are independent predictors of all-cause mortality in type 2 diabetes, regardless of weight [25]. Indeed, it was reported that increased body mass index and body fatness did not increase mortality risk in fit men with type 2 diabetes [26]. This highlights the importance of clinicians giving greater attention to counseling for increasing physical activity and improving fitness in persons with diabetes, primarily for the benefits associated with enhanced cardiorespiratory fitness that are independent of weight.

At least 150 min/week of moderate-intensity aerobic physical activity is recommended [27]. In the absence of contraindications, performing resistance training three times per week is also encouraged [10]. In patients who were unable to achieve 150 min/week, a small amount of exercise still provides substantial benefits in diabetes management. Reducing sedentary time should also be encouraged [27].

Monitor Outcomes: Glucose, Lipids, and Blood Pressure

Outcomes must be identified and the effectiveness of nutrition therapy measured. Individuals with diabetes need to have identified target goals. Blood glucose monitoring is done to determine if progress is being made or achieved toward these goals. The A1C is evaluated at least twice a year in patients who are meeting treatment goals and quarterly in patients whose therapy has changed or who are not meeting glycemic goals [10]. Lipids are generally measured annually and blood pressure at every routine diabetes visit. If goals are not being achieved, medications may need to be added or adjusted.

Support and Continuing Education

Successful self-management of diabetes by the patient is an ongoing process of problem-solving, adjustment, and readjustment. Individuals must be able to anticipate and deal with the wide variety of decisions they face on a daily basis. And just as support from family and friends is important, continuing education and support from professionals is also essential. Structured programs with consistent follow-up contacts assist individuals to achieve lifestyle goals and to maintain what are often challenging lifestyle changes [28]. Technology is being used for education and diabetes management. Some apps provide data logging functions and food databases. These help patients validate the successful achievement of their nutrition and activity goals. There are hundreds of apps available for download, some free and some requiring a small fee. The quality of information and functionality is variable but there are reviews to help guide the user [29]. Apps have been found to provide tangible benefits when used appropriately in randomized controlled trial settings [30].

Macro- and Micronutrients

Carbohydrate

Carbohydrates are addressed first as it is the balance between carbohydrate intake and available insulin that determines postprandial glucose response and because carbohydrate is the major determinant of mealtime insulin doses. Foods containing carbohydrate—grains, fruits, vegetables, legumes, low-fat/skim milk—are important components of a healthful diet and should be included in the food/meal plan of persons with diabetes. This recommendation reflects the concern that low-carbohydrate diets eliminate many foods that are important for all persons to eat as part of a healthy lifestyle.

Amount and Type of Carbohydrate

There is strong evidence to suggest that in regard to the effects of carbohydrate on glucose concentrations, the total amount of carbohydrate in meals (or snacks) is more important than the source (starch or sugar) or the type (low or high glycemic index, GI). Numerous 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 [8, 31].

Research does not support any ideal percentage of energy from macronutrients for persons with diabetes [8] and it is unlikely that one such combination of macronutrients exists [5]. Macronutrient intake should be based on the Dietary Reference Intakes (DRI) for healthy adults.

Glycemic Index

Although different carbohydrates do 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. Benefits of a low-GI diet are complicated by differing definitions of "high-GI" or "low-GI" foods or diets, and short-term studies comparing high- versus low-GI diets report mixed effects on A1C [8]. However, Wolever et al. [32] conducted a multicenter, 12-month, randomized controlled trial comparing the effects of (1) a high-GI diet, (2) a low-GI diet, or (3) a low-carbohydrate, high-monounsaturated fat diet in subjects with type 2 diabetes managed by nutrition therapy. At study end, A1C, lipids, and body weight did not differ significantly between diets. Previous meta-analyses of studies showing benefit were based primarily on studies lasting less than 3 months. The Wolever study also found a temporary reduction in A1C with the low-GI diet which was not sustained long term.

The GI test has poor reliability with interindividual variability and intraindividual reproducibility of concern [33]. For example, in subjects who completed three tests (n = 14), the GI of white bread was 78 ± 39 (CV of 50%) with values ranging from 44 to 132 [34].

Furthermore, GI measures the incremental area under the curve (AUC) for blood glucose response over a 2 h period, not how rapidly blood glucose levels increase as emphasized in diet books promoting the use of low-GI foods. Peak glucose responses for single foods or meals occur at similar times whether they are high or low GI.

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, 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% [8]. Therefore, foods containing 25–30 g/day of fiber, with special emphasis on soluble fiber sources, (7–13 g), are to be encouraged.

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 [8, 31]. 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.

In persons with diabetic nephropathy, a protein intake of 1 g or less per kg body weight per day is recommended. It is interesting to note that in persons with diabetes and nephropathy, diets with <1 g protein/kg/day have been shown to improve albuminuria but have not been shown to have significant effects on glomerular filtration rates [8]. For persons with late-stage diabetic nephropathy, a protein intake of ~0.7 g/kg/day has been associated with hypoalbuminemia (an indicator of malnutrition). Therefore, hypoalbuminemia and energy intake must be monitored and changes in protein and energy intake made to correct deficits.

Protein is probably the most misunderstood nutrient with inaccurate advice frequently given to persons with diabetes. Although patients 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 [35]. It is often suggested to patients that adding protein to a meal or snack will slow the absorption of carbohydrate but several studies show that this is not the case. If differing amounts of protein are added to meals or snacks, the peak glucose response is not affected by the addition of protein. There is also no evidence that adding protein to bedtime snacks is helpful or will assist in the immediate treatment of hypoglycemia or prevent blood glucose levels from dropping again after the initial treatment.

Dietary Fat

Cardioprotective nutrition interventions recommended by the "Standards of Medical Care in Diabetes 2016" for patients with diabetes include reduction in saturated and trans fatty acids, as well as increase in plant sterols/stanols and $n-3$ fatty acids [21]. A previous recommendation to limit cholesterol intake to 300 mg/day was not included in the 2015 Dietary Guideline for Americans due to inadequate evidence for a specific limit. However, it is still important to be aware that foods high in cholesterol tend to have a higher saturated fat content [36].

This topic is discussed in more detail in Chap. 11. Nutrition goals for persons with diabetes are the same as for persons with pre-existing cardiovascular disease, as the two groups have equivalent cardiovascular risk. Thus, saturated fats <7% of total energy, minimal intake of trans fatty acids, and cholesterol intake <200 mg/day are recommended [5]. However, the association between saturated fat intake and risk of cardiovascular disease remains controversial. Replacing polyunsaturated fat with saturated or refined carbohydrate has been shown to provide cardioprotective benefits [37]. Consumption of $n-3$ fatty acids from fish or from supplements has been shown to reduce adverse cardiovascular outcomes [5]. Therefore, two or more servings of fish (with the exception of commercially fried fish fillets) are recommended. In persons with type 2 diabetes, 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 [31]. 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 multi-vitamin 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 [31].

Alcohol

Recommendations for alcohol intake are similar to those for the general public. This topic is discussed in Chap. 22. 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 [10]. 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. For individuals using insulin or insulin secretagogues, if alcohol is consumed, it should be consumed with food to prevent hypoglycemia.

Observational studies suggest a U- or J-shaped association with moderate consumption of alcohol (~15–30 g/day). Moderate alcohol consumption is associated with a decreased incidence of heart disease in persons with diabetes [38]. 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.

Summary

There have been major changes in nutrition recommendations and therapy for diabetes over the past decade. Medical nutrition therapy (MNT) is essential for effective management of diabetes, but to be successful it involves an ongoing process. Monitoring of glucose, A1C, lipids, and blood pressure is essential in order to assess the outcomes of nutrition therapy interventions and/or to determine if changes in medication(s) are necessary. It is important that all health-care providers understand nutrition issues and guide the individual's efforts by promoting and reinforcing the importance of lifestyle modifications, and by providing support for the lifestyle intervention process.

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Suggested Further Reading

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Chapter 10
Lifestyle Interventions to Stem the Tide of Type 2 Diabetes

Marion J. Franz, Zhuoshi Zhang, and Bernard Joseph Venn

Key Points

- Prevention of obesity is one of the most important steps for diabetes prevention.
- For persons with prediabetes, encourage a moderate and maintainable weight loss and provide individuals with support for behavioral changes. Also recommend a cardioprotective, energy-restricted diet and 150 min/week of physical activity.
- Consume whole grain foods, whole fruit, vegetables, nuts and berries, and pay heed to the type of fat in favor of foods containing monounsaturated fatty acids.
- For persons at very high risk for diabetes, in combination with lifestyle interventions, pharmacotherapy may be considered.

Keywords Type 2 diabetes • Prevention of diabetes • Lifestyle interventions • Glycemic index

Introduction

Worldwide, the number of persons with diabetes and those who are at risk for diabetes is increasing at an alarming rate, largely driven by the rising prevalence of obesity and inactivity. Of concern in the United States are the approximately 86 million people who have prediabetes and one in three people with metabolic syndrome [1]. These individuals are at high risk for conversion to type 2 diabetes and for cardiovascular disease if lifestyle prevention strategies are not implemented. After years of rises in the incidence of diabetes, one positive finding has been the reporting of a leveling off in the prevalence from 2009 to 2014 in the 45–64 years age group, although an upward trend is still evident in older age groups [2].

M.J. Franz, M.S., R.D.N. C.D.E. (✉)
Nutrition Concepts by Franz, Inc., 6635 Limerick Drive, Minneapolis, MN 55439, USA
e-mail: MarionFranz@aol.com

Z. Zhang, R.D. • B.J. Venn, Ph.D.
Department of Human Nutrition, University of Otago, PO Box 56, Dunedin, Otago 9054, New Zealand
e-mail: zhazh902@student.otago.ac.nz; bernard.venn@otago.ac.nz

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Preventing obesity is a high priority for the prevention of type 2 diabetes as many individuals are overweight or obese at the onset. However, the disease can also be diagnosed in nonobese individuals, while many obese people never develop it. Therefore, it is likely that genetic predisposition and lifestyle choices are important factors in the development of type 2 diabetes. Cereal fiber and magnesium, both components of whole grains, and fruit and green leafy vegetable intakes are consistently associated with lower risk of developing type 2 diabetes [3–5] with a possible protective role for low-fat dairy foods [6]. Remaining physically active is important as sedentary time is associated with an increased risk of developing type 2 diabetes [7]. These 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. However, elevated plasma free fatty acids (lipotoxicity) may also be a common denominator and this is generally associated with obesity and, in particular, intra-abdominal obesity. Measurement of waist circumference may help identify individuals at risk. Large clinical trials have demonstrated the role of nutrition therapy including both modest weight loss and increased physical activity in the prevention or delay of type 2 diabetes [8–11].

Diagnosis of Prediabetes

Hyperglycemia that is not sufficient to meet the diagnostic criteria for diabetes is classified as impaired fasting glucose (IFG). Impaired glucose tolerance (IGT) is another valuable measure and is determined from a glucose tolerance test. Both IFG and IGT have been officially termed "prediabetes" [12]. The following are criteria used for diagnosis:

- IFG = fasting plasma glucose (FPG) between 100 mg/dL (5.6 mmol/L) and 125 mg/dL (6.9 mmol/L)
- IGT = 2-h plasma glucose between 140 mg/dL (7.8 mmol/L) and 199 mg/dL (11.0 mmol/L)
- HbA1C = 5.7–6.4%

Prevention Trials

Based on evidence from earlier epidemiological and intervention studies suggesting the benefits of lifestyle interventions for the prevention of type 2 diabetes, four larger and well-designed trials were undertaken—the Finnish Diabetes Prevention Study [8], the Diabetes Prevention Program (DPP) [9], the Indian Diabetes Prevention Programme [11], and a Japanese study [10].

In the Finnish study, subjects in the control group were given general information on diet and exercise, whereas subjects in the intervention group received detailed counseling by dietitians on how to reduce weight, as well as total intake of fat and saturated fat, and how to increase intake of fiber and physical activity. After 3.2 years of follow-up, the lifestyle intervention was associated with a significant reduction in weight (−4.2 kg vs. –0.8 kg) and waist circumference (−4.4 cm vs. –1.3 cm) compared to the control group, and a significant reduction in 2-h plasma glucose and serum insulin, triglycerides, and blood pressure. The risk of developing diabetes was reduced by 58% in the intervention group [8]. At 7-year follow-up, participants in the intervention group still had a 43% lower diabetes risk [13]. Despite these positive findings relating to the reduced risk of diabetes, 10-year total mortality and cardiovascular mortality rates did not differ between the control and intervention groups [14]. However, caution should be taken in the interpretation of these findings as there were only 16 deaths among the cohort (3%) and the rate was low compared with another Finnish cohort that had received no intervention (11%). Overall, an intensive lifestyle program in people with prediabetes resulted in

continued lifestyle changes and reduced risk of developing diabetes, a benefit which remained even after the individual lifestyle counseling had stopped.

In the Diabetes Prevention Program (DPP), conducted in 27 centers around the United States, subjects were randomly assigned to one of three groups: (1) an intensive lifestyle change emphasizing a 7% weight loss and 150 min/week of physical activity, (2) metformin (850 mg/day for 1 month, increasing to 850 mg bid), or (3) a placebo group. After 2.8 years of follow-up, average weight loss was 5.6, 2.1, and 0.1 kg in the lifestyle, metformin, and placebo groups, respectively, and 58% of the participants in the lifestyle arm were exercising 150 min/week. Compared with placebo, the incidence of diabetes was reduced by 58% by lifestyle and 31% by metformin [9]. The lifestyle intervention also resulted in improvements in hypertension, triglycerides, and HDL cholesterol. The cumulative reduction in incidence of diabetes persisted for 10 years [15].

Six randomized controlled trials have examined the effects of pharmacological agents on the prevention of type 2 diabetes [16]. Metformin, as noted above, reduced the incidence of diabetes by 31%, acarbose by 25%, troglitazone by 55%, xenical by 37%, and rosiglitazone by 60%. The American Diabetes Association recommendations state that in addition to lifestyle counseling, metformin may be considered in those who are at very high risk (combined impaired fasting glucose and impaired glucose tolerance) and who are obese and under 60 years of age [12]. The American Association of Clinical Endocrinologists recommends that for persons with prediabetes at particularly high risk, pharmacologic glycemic treatment (metformin and acarbose) may be considered in addition to lifestyle strategies. They note that thiazolidinediones also reduce risk but safety concerns include congestive heart failure and fractures [17]. Table 10.1 summarizes therapies proven to be effective in diabetes prevention trials [16].

Table 10.1 Diabetes prevention trials: interventions and effectiveness

Study	Total *n* randomized	Population	Duration (year)	Intervention (daily dose)	Relative risk
Finnish Diabetes Prevention Study	522	IGT, BMI ≥ 25 kg/m^2	3.2	Individual diet/exercise	0.42
Diabetes Prevention Program	2161	IGT, BMI ≥ 24, FPG > 95 mg/dL (5.3 mmol/L)	3	Individual diet/exercise	0.42
Chinese Da Qing Study	577	IGT	6	Group diet/exercise	0.62
Japanese Trial	458	IGT (men), BMI = 24	4	Individual diet/exercise	0.33
Indian Diabetes Prevention Programme	531	IGT	2.5	Individual diet/exercise	0.71
Diabetes Prevention Program	2161	IGT, BMI ≥ 24, FPG > 95 mg/dL (5.3 mmol/L)	2.8	Metformin (1700 mg)	0.69
Indian Diabetes Prevention Programme	531	IGT	2.5	Metformin (500 mg)	0.74
STOP NIDDM: study to prevent non-insulin-dependent diabetes	1429	IGT, FPG > 100 mg/dL (5.6 mmol/L)	3.2	Acarbose (300 mg)	0.75
XENDOS: Xenical in the Prevention of Diabetes in Obese Subjects	3305	BMI > 30	4	Orlistat (360 mg)	0.63
DREAM	5269	IGT or IFG	3	Rosiglitazone (8 mg)	0.40
ACT NOW: Pioglitazone for Diabetes Prevention	602	IGT	2.4	Pioglitazone + dietary instruction (45 mg)	0.28

IGT impaired glucose tolerance, *FFG* fasting plasma glucose, *BMI* body mass index, *GDM* gestational diabetes mellitus
Source: Adapted from [16]

Lifestyle Intervention Recommendations

Three lifestyle interventions are consistently associated with decreased risk of type 2 diabetes in the prevention trials: moderate weight loss, regular physical activity, and frequent participant contact. Observational studies provide support for reduced dietary fat and an increase in whole grain and dietary fiber. The role of the glycemic index/glycemic load and alcohol is unclear.

Encourage a Moderate and Maintainable Weight Loss and Provide Participant Support

In the past, achieving an ideal body mass index (BMI) was often recommended for participants in weight-loss programs. But it has become clear that clinical improvements begin to appear with relatively small amounts of weight loss (approximately 5–7%), suggesting the importance of emphasizing weight loss for health benefits rather than for cosmetic reasons [18].

To answer the question about expected weight loss from weight-loss interventions, a systematic review of randomized clinical weight-loss trials with a minimum duration of 1 year was performed [19]. A mean weight loss of 5–8.5 kg (5–9%) was observed during the first 6 months from interventions involving a reduced-energy diet (and exercise) and/or weight-loss medications, with weight plateaus at approximately 6 months. In studies extending to 48 months, a mean 3–6 kg (3–6%) of weight loss was maintained with none of the interventions experiencing weight regain to baseline [19]. In contrast, advice-only and exercise alone intervention groups experienced minimal weight loss at any time point. Study participants in the clinical trials appeared to benefit from the continued professional support they received.

Changes in body weight in the DPP were similar to the weight-loss/maintenance outcomes reported above. Participants in the intensive lifestyle group experienced a mean weight loss of 7 kg at 6–12 months followed by gradual weight regain over 5 years; the lifestyle and metformin groups maintained a modest 2–2.5 kg lower mean body weight compared with their weights 10 years earlier [15]. Considerable support from well-trained staff was needed to achieve this weight-loss outcome.

Follow a Cardioprotective, Energy-Restricted Diet

The primary diet intervention in the diabetes prevention trials was a lower-energy, lower-fat diet. A cardioprotective diet such as that recommended by the American Heart Association is consistent with the diets found to be effective at reducing diabetes risk [20]. Basic behavioral strategies that are core and are used in nearly all weight-loss interventions include self-monitoring, goal setting, stimulus control, reinforcement, and cognitive change. Other behavioral strategies shown to be beneficial are problem-solving, relapse prevention, and stress management. Social support from partners, family, friends, or others, along with the support of health professionals, has also been shown to be helpful.

An area of controversy has been the macronutrient content of the energy-reduced diet although evidence from robustly conducted randomized controlled trials indicates that long-term weight loss is independent of the macronutrient composition of the diet [21]. Adopting a dietary pattern can provide metabolic benefits. A 2-year weight-loss trial reported a mean weight loss of 3.3, 4.6, and 5.5 kg in completers of a low-fat, Mediterranean, or low-carbohydrate diets, respectively [22]. Of interest was the more favorable effect on plasma glucose and insulin levels in subjects assigned to the Mediterranean

Table 10.2 Food recommendations for the prevention of diabetes

- Encourage a food pattern that includes fruits, vegetables, whole grain high-fiber foods, legumes, nuts, and low-fat/skim milk for good health
- Limit saturated fat to <7% of total calories, trans unsaturated fatty acids to <1%; substitute unsaturated fat from vegetables, fish, nuts, and legumes
- Recommend two or more servings of fatty fish per week (with the exception of commercially fried fish filets) for $n-3$ polyunsaturated fatty acids
- Limit sodium intake to 2300 mg/day by choosing foods low in sodium and limiting the amount of salt added to food
- Minimize intake of beverages and foods with added sugars
- Limit alcohol to no more than 2 drinks/day (men) and 1 drink/day (women) in those who choose to drink alcohol

diet. Providing observational support for a Mediterranean-style diet (use of unsaturated oils such as olive oil, fruits, nuts, legumes, and fish with relatively low consumption of meat and dairy) is a study that followed 13,380 adults for an average of 4.4 years [23, 24]. Those with the highest adherence to a Mediterranean diet were 83% less likely to be among those who developed diabetes. It is likely that other lifestyle factors contributed to the observations because in a randomized controlled trial, the risk of developing the metabolic syndrome was not different between Mediterranean diets and a low-fat control diet; although in people with the metabolic syndrome at baseline, the reversion rate to normal status was better for the Mediterranean diets [25]. Table 10.2 summarizes nutrition recommendations in accordance with evidence-based sources [26–28] consistent with advice from the American Diabetes Association [29, 30].

It is unlikely that one diet is optimal for all overweight/obese persons. Recommendations should be individualized to allow for specific food preferences and individual approaches to reducing energy intake. Two important considerations are: Can the diet be followed long term? and Does it encourage healthful eating habits and regular physical activity?

Recommend 150 min/week of Physical Activity

Regular physical activity and aerobic fitness improve insulin sensitivity, independent of weight loss [31], and reduce the risk of developing diabetes [32]. The activity does not need to be intensive, with 15 min of strolling after meals producing a noticeable lowering of postprandial glycemia in people with type 2 diabetes compared with being sedentary [33]. Walking after meals may be a valuable strategy for people unwilling or unable to commit to structured exercise programs. To assist with weight loss and maintenance and reduce risk of cardiovascular disease, at least 150 min of moderate-intensity aerobic physical activity or at least 90 min of vigorous aerobic exercise per week is recommended. The physical activity should be divided over at least 3 day/week, with no more than two consecutive days without physical activity. For long-term maintenance of major weight loss, a larger amount of exercise (7 h/week of moderate or vigorous aerobic physical activity) may be helpful. In the absence of contraindications, individuals should be encouraged to perform resistance training three times per week [12]. Combining recommended dietary and physical activity regimens reduces risk of developing type 2 diabetes and improves cardio-metabolic risk factors [34]. Table 10.3 summarizes physical activity recommendations.

In previously inactive patients, an initial exercise session should be of short duration (e.g., 10 min/day) of activity and gradually increase to 30 min/day of low-intensity activity. Intensity can be increased as the patient's strength and fitness improves [18].

Table 10.3 Physical activity recommendations

- For substantial health benefits, adults should do at least 150 min/week of moderate-intensity, or 75 min/week of vigorous-intensity aerobic physical activity, or an equivalent combination of moderate- and vigorous-intensity aerobic activity
- For additional and more extensive health benefits, adults should increase their aerobic physical activity to 300 min a week of moderate-intensity, or 150 min/week of vigorous-intensity aerobic physical activity, or an equivalent combination of moderate- and vigorous-intensity activity
- The first step in achieving or maintaining a healthy weight is to meet the minimum level of physical activity in the Guidelines while not exceeding caloric intake requirements
- People who are at a healthy body weight but slowly gaining weight can either gradually increase the level of physical activity (toward the equivalent of 300 min/week of moderate-intensity aerobic activity), or reduce caloric intake, or both, until their weight is stable
- Muscle-strengthening activities help maintain muscle mass during a program of weight loss

Source: Adapted from [35]

Other Nutrition-Related Factors

Carbohydrate/Fats

There is no evidence that a high-carbohydrate diet contributes to insulin resistance; indeed, it may be beneficial for insulin sensitivity [36, 37]. This is a difficult issue to resolve because as carbohydrate in the diet increases, fat, especially saturated fats, decreases. High-fat intakes, especially of saturated and trans fatty acids, are associated with a decline in insulin sensitivity [38]. Therefore, it is unclear if the improvement in insulin sensitivity is because of the increase in carbohydrate or the decrease in fat. In a review of high- compared to low-carbohydrate diets, insulin sensitivity tended either to increase or to be unaffected by the amount of carbohydrate in the diet [37].

The type of fat in the diet influences metabolic risk factors for diabetes, with overweight individuals found to be more susceptible to developing insulin resistance when consuming food rich in saturated compared with monounsaturated fatty acids [39]. In a long-term trial, Mediterranean-style diets rich in monounsaturated fatty acids from olive oil or nuts were associated with lower diabetes incidence compared with a low-fat control diet [40]. Hence, rather than simply considering dietary fat as a homogenous macronutrient, the American Diabetes Association recommends that the type or quality of fat be considered [41]. Nevertheless, it should be remembered that excess energy intake, regardless of the energy source, and positive energy balance contribute to insulin resistance by way of weight gain.

Whole Grains and Dietary Fiber

From observational data, cereal fiber is consistently associated with reduced risk of type 2 diabetes [42]. Furthermore, increasing fiber intake in people with type 2 diabetes has been found to reduce fasting blood glucose and glycated hemoglobin [43]. The mechanisms may involve insulin sensitivity, secretion of gut hormones, and effects on metabolic and inflammatory markers [44]. Indeed, increased intake of foods containing whole grains is associated with improved insulin sensitivity, independent of body weight [45]. Modest weight loss, regular physical activity, and dietary factors, including choosing whole grain foods high in cereal fiber, are primary components of an intensive lifestyle intervention.

Glycemic Index/Glycemic Load

The relationship between glycemic index (GI) and glycemic load (GL) and type 2 diabetes risk is unclear. Several large observational studies have been undertaken with mixed findings. A modest increase in risk per 5 units of dietary GI of 1.08 and of 20 units of GL of 1.03 was found in a

meta-analysis of some of these studies with high heterogeneity reported [46]. Some of the heterogeneity in outcomes may be due to methodology as there is only a predictive formula rather than a directly validated tool for assessing the GI or GL of a whole diet. Using this formula, the predictability of the GI of even a single meal is fraught with problems [47]. Interestingly, in three studies, fiber was positively associated with insulin sensitivity whereas GI/GL was not [48–50].

Despite many popular diet books promoting the use of a low-GI diet for weight loss, there is minimal evidence in support of its effectiveness. Studies supporting the role of a low-GI diet for weight loss are <6 months in duration and conducted primarily in adolescents. Longer-term clinical trials in adults have not found a benefit of using low-GI diets for weight loss [51, 52]. In a meta-analysis of long-term intervention trials, there was no effect of manipulating dietary GI on weight, waist circumference, fasting blood lipids, fasting glucose, or HbA1c [53]. Parameters found to be influenced by dietary GI were C-reactive protein and fasting insulin favoring the low-GI diet, and retention of fat-free mass favoring the high-GI diet. There was evidence of publication bias related to the fasting insulin data. Potentially, the lower C-reactive protein could be beneficial although the lower fat-free mass associated with weight loss on the lower GI diet could be detrimental. Although it is often suggested there is no harm in recommending low-GI foods even if there is no evidence of benefit, this is not necessarily true. The GI may not be the best indicator of healthful food choices. Although many healthful foods have a moderate or low GI (e.g., whole grains, fruits, vegetables, legumes, dairy products), many foods of questionable value also have low or moderate GIs. For example, Coca-Cola has a moderate GI of 58, Snickers Bar a GI of 55, premium ice cream a low GI of 37, and fructose a low GI of 19 [54]. If a food company wishes to produce a food with a low GI, they have only to sweeten it with more fructose or sucrose or add fat. Furthermore, whole wheat bread, brown rice, and brown spaghetti have the same GI value as their refined white versions. Fruits often have a low GI, but whole fruits and juice have the same GI. Health Canada did not support labeling of food with GI, suggesting that it would be misleading and would not assist consumers in making healthier food choices [55].

Alcohol

Observational studies suggest a U- or J-shaped association between moderate consumption of alcohol (1–3 drinks/day [15–45 g alcohol]) and decreased risk of diabetes [56, 57]. A meta-analysis based on 32 studies found that compared to no alcohol use moderate amounts of alcohol were associated with a 33–56% lower incidence of diabetes for the general population. In contrast, a heavy/chronic amount of alcohol (greater than 3 drinks/day) was associated with a 43% increase in incidence [56]. Small clinical trials and observational studies have shown light to moderate amounts of alcohol improve insulin sensitivity and raise HDL cholesterol levels. The type of alcoholic beverage does not make a difference.

Summary

Well-designed randomized controlled trials clearly document that diabetes can be prevented or delayed with moderate reductions in weight of 5–7% and 150 min/week of physical activity. However, well-trained staff providing continued support was needed to achieve these results. Pharmacologic therapy also significantly lowers the incidence of diabetes as does bariatric surgery [58]. The American Diabetes Association recommends the following for the prevention of diabetes [41, 59]:

- Individuals at high risk for developing type 2 diabetes need structured programs that emphasize lifestyle changes that include moderate weight loss (7% body weight) and regular physical activity (150 min/week).
- Dietary strategies to reduce caloric intake, to raise whole grain and fiber intake, to consume whole fruit, vegetables, nuts and berries, and to pay heed to the type of fat in favor of foods containing monounsaturated fatty acids.

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Suggested Further Reading

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Chapter 11
Coronary Heart Disease: Nutritional Interventions for Prevention and Therapy

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

Key Points

- Coronary heart disease (CHD) is a major cause of morbidity and mortality in the Western world.
- Diets high in trans fats, processed meat, and added sugar can increase CHD risk.
- Evidence suggests that increased consumption of fatty fish and of $n-3$ polyunsaturated fatty acids ($n-3$ PUFA) is likely to reduce CHD risk.
- While supplementation with antioxidants is unlikely to reduce CHD risk, diets rich in these micronutrients (e.g., diets rich in fruits, vegetables, and whole grain cereals) are associated with lower CHD risk.
- Adhering to a Mediterranean diet has been shown to reduce CHD risk in both the primary and secondary prevention settings.
- Maintaining a healthy weight and being physically active have each been shown to reduce CHD risk factors and CHD incidence.

Keywords Cardiovascular risk factors • Coronary heart disease • Prevention

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 CHD are increasing 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 is one where total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) are elevated and high-density lipoprotein (HDL-C) is relatively low [1]. A 1% reduction in circulating LDL-C is associated with a reduction in CHD risk of about 1% [2]. Research in recent years has added C-reactive protein (CRP), a biomarker of inflammation, to the list of risk factors.

D. Schliemann, B.Sc. • J.V. Woodside, Ph.D. (✉) • C.T. McEvoy, Ph.D.
Centre for Public Health, Queen's University Belfast, Belfast, Northern Ireland BT12 6BJ, UK
e-mail: j.woodside@qub.ac.uk

N.J. Temple, Ph.D.
Centre for Science, Athabasca University, Athabasca, AB, Canada

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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. (Epidemiological studies refer mainly to prospective cohort studies and case–control studies). Dietary factors that have been proposed to affect the risk of CHD include saturated fatty acids (SFA), trans fatty acids (TFA), polyunsaturated fatty acids (both *n*−6 and *n*−3 PUFA), non-milk extrinsic sugars, dietary fiber, antioxidant vitamins, and vitamin D. This chapter examines how each of these food components, as well as whole dietary patterns, affects CHD risk. Obesity and exercise are also considered. 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

Much attention has been paid to the question of the total intake of dietary fat and the link with CHD. A major reason for this is that increased intake of fat can lead to a positive energy balance and contribute to obesity. However, the relationship between the quantity of fat intake and the risk of CHD is much weaker. There is no strong evidence that low-fat diets reduce mortality rates from CHD. Low-fat diets (10–20% of total energy) reduce circulating LDL-C but this benefit can be cancelled out by the simultaneous reduction in HDL-C level and increase in triglyceride (TG) level, largely through the replacement of dietary fat by carbohydrate. Additionally, compliance with low-fat diets is often difficult.

The critical aspect of fat intake with regard to 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 risk of CHD [3].

Public health strategies over the past two decades emphasized the reduction of total fat in the diet. The most common recommendation was that fat intake should be "less than 30%" of energy intake. In recent years, this recommendation has shifted to a more liberal 20–35%. Common dietary recommendations for fat intake are shown in Table 10.1.

Table 10.1 Dietary fat recommendations for modification of blood lipids for the prevention of CHD

Dietary fat	Recommendation[a]	Major dietary sources
Total fat	20–35% energy intake	As below
Saturated fatty acids (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 fatty acids (TFA)	<1% energy intake	Stick margarine, cakes, pastry products, cookies, chips, many fast foods (the amounts present in food have been much reduced in recent years)
Cholesterol	<200 mg/day	Liver, kidney, egg yolk, shellfish
Polyunsaturated fatty acids (PUFA)	4–10% energy intake	Soft margarines, vegetable oils (corn, safflower, soybean, sunflower)
Monounsaturated fatty acids (MUFA)	<20% energy intake	Olive oil, canola oil, peanut oil, avocados, olives, almonds, cashews, peanuts
n−3 PUFA	0.5–2% energy intake	Sardines, herring, pilchards, salmon, tuna Walnuts, flaxseed oil, canola oil

[a]The recommendations shown are not necessarily ideal for minimizing risk of CHD but are the most common ones currently given

Saturated Fat and Dietary Cholesterol

Many studies over the past 30 years have established that SFA is consistently positively correlated with TC and LDL-C levels. Dietary cholesterol also increases TC 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%. Although the literature suggests reducing SFA intake has no effect on CHD mortality, it may reduce the risk of CHD events [4], but the literature is conflicting. A cohort study including 5209 participants suggests that the dietary source of SFA may be more important, i.e., SFA from meat are associated with an increased risk for cardiovascular disease (CVD) whereas no risk was found for dairy or plant-based SFA [5].

Trans Fatty Acids

Like SFA, TFA also raises TC and LDL-C levels. However, whereas SFA tends to increase HDL-C, TFA lowers it. A recent meta-analysis reported TFA intake is associated with an increase in CHD risk of 16%, when comparing the top and bottom thirds of intake [3]. These findings reinforce the importance of recent public health initiatives directed at minimizing dietary intake of TFA.

n–*6 PUFA and MUFA*

PUFA and MUFA are the major unsaturated fats. PUFA are divided into *n*−6 PUFA, also known as linoleic acid (LA), and *n*−3 PUFA, also known as alpha linolenic acid (ALA). *n*−6 PUFA are found in abundance in vegetable oils, while olive oil and canola oil are rich sources of MUFA. PUFA lower TC and LDL-C levels whereas MUFA tend to have a neutral effect. An analysis of 11 pooled prospective cohort studies also suggested that PUFA may be preferable to carbohydrates as a replacement for SFA as they do not induce a fall in HDL-C or rise in TG [6]. A recent Cochrane review also concluded that substituting SFA with PUFA can reduce CVD events by 27% [4]. However, the review did not distinguish between *n*−6 and *n*−3 PUFA. To date, there is strong evidence supporting the substitution of SFA with *n*−3 PUFA, but the evidence around *n*−6 PUFA is less clear.

n–*3 PUFA*

Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are long-chain *n*−3 PUFA that are found in fatty fish (Table 10.1). ALA is a plant-derived *n*−3 PUFA with a slightly shorter chain and is found in some 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. They improve endothelial function and reduce the risk of inflammation and arrhythmias, and significantly reduce rates of sudden death [7]. The benefits of dietary ALA are not as well researched but a recent meta-analysis suggests a moderate risk reduction of fatal CHD incidence [8].

Most prospective cohort studies have demonstrated inverse associations between fish consumption and risk of CHD. These studies indicate that eating fish between once and five times per week reduces risk of CHD (especially death) by around 40%. However, results are not completely consistent.

The same story has emerged from the results of RCTs. In these the effects of fish oil have been studied in patients with CHD. Most of those studies have reported reductions in fatal MI and overall mortality in subjects given fish oil [7]. The protection afforded by *n*−3 PUFA against CHD appears to extend to ALA: several epidemiological studies have reported a strong inverse relationship between intake of ALA and risk of CHD. However, the encouraging findings on *n*−3 PUFA still require further confirmation, and particularly whether increased food sources are more beneficial than supplemental sources. Current recommendations for *n*−3 PUFA are shown in Table 10.1.

We can summarize the above findings as follows: replacing SFA and TFA with *n*−3 PUFA and MUFA reduces TC and LDL-C and is likely to be protective against CHD. In general, diet change induces a greater fall in TC and LDL-C in persons with hypercholesterolemia.

Red and Processed Meat

Dietary guidelines recommend reducing intake of red and processed meat. The benefits of a diet low in these meats were primarily believed to be related to the reduced consumption of SFA. However, evidence from cohort studies suggests that intake of processed meat is associated with a 42% higher risk of developing CHD, whereas no association could be found with unprocessed meat [9]. This may be explained by the considerable amounts of preservatives used in meat processing including large amounts of sodium. A more recent meta-analysis suggests a 15% increased risk for cardiovascular mortality per serving of processed and red meat for women [10], whereas a number of studies suggest that moderate intake of unprocessed, lean red meat does not exert unfavorable effects on the blood lipid profile [11, 12].

Plant Sterols and Stanols

Phytosterols or plant sterols are structurally similar to cholesterol. Stanols are closely related substances. Plant sterols and stanols reduce the absorption of cholesterol (which comes from both the diet and from bile), and thereby lower the blood level of TC and LDL-C [13]. An intake of 2 g/day of plant sterols or stanols lowers LDL-C by around 10%. Consumption of sterols or stanols may result in reduced absorption of fat-soluble vitamins, such as vitamin E and β-carotene, but this should not be a problem, provided a nutritious diet is consumed. Products containing added sterols or stanols include specific brands of orange juice, cereal bars, salad dressings, and fat spreads. Such products are classed as functional foods.

Vitamin D

Vitamin D is a type of fat-soluble vitamin which is required for calcium and phosphate absorption. The body can generate vitamin D from skin exposure to sunlight. Small concentrations of vitamin D are also found in some foods (see Table 10.1). Vitamin status is measured as 25-hydroxyvitamin D (25[OH]D) in the blood. Low serum 25[OH]D is strongly associated with increased risk of CHD [14]. The findings from a multiethnic cohort study suggest that low vitamin D status is a greater risk factor for white and Chinese individuals than for black or Hispanic [14]. To meet optimum vitamin D status, particularly in winter months, it is recommended to take a supplement. Safe limits lie between 400 and 4000 IU per day. However, more research is required, including RCTs to determine the effect of vitamin D supplementation on cardiovascular endpoints.

Antioxidants

Many observational studies have demonstrated an association between intake of antioxidant vitamins and risk of CHD. The association is strongest for vitamin E but less consistent for other vitamins [12]. Many researchers were quick to jump to the conclusion that the epidemiological evidence means that supplements of vitamins C and E will prevent CHD. In the case of vitamin E a plausible biochemical explanation was available, namely that vitamin E prevents the oxidation of LDL particles and thereby slows the progression of atherosclerosis.

Based on the above reasoning, several large RCTs have been conducted. However, the results of the RCTs on antioxidant vitamins have been mostly negative with regard to reducing the risk of CHD.

The most important finding from these RCTs is the effect of antioxidant vitamins on all-cause mortality. A recent meta-analysis was carried out on 78 primary and secondary prevention RCTs to examine the effect of antioxidant supplements (beta-carotene, vitamin A, vitamin C, vitamin E, and selenium) versus placebo or no intervention on all-cause mortality. This review found no evidence to support antioxidant supplements for prevention of mortality [15]. Furthermore, the analysis concluded that supplementing with beta-carotene or vitamin E leads to an *increase* of about 2–5% in all-cause mortality.

These results compel the conclusion that these vitamin supplements should not be recommended in any class of patient. Instead, a diet naturally high in antioxidants (i.e., through the consumption of fruits and nuts) is recommended.

The story of antioxidants and the prevention of CHD holds a valuable lesson for many people with an interest in diet and disease. While epidemiology is a tremendously valuable research tool, it is prone to generating spurious associations. This can lead to people making claims that particular dietary components are either causative or preventive of particular diseases. Such claims should be viewed cautiously until such time as they are verified by well-conducted RCTs.

Non-milk Extrinsic Sugars

Non-milk extrinsic sugars refer to sugars that are added to foods and drinks in the food production process and do not occur naturally. A good example is sugar-sweetened beverages. A recent meta-analysis of ten prospective studies and one RCT described significant associations between sugar-sweetened beverage intake and vascular risk factors, particularly hypertension, although the data were less consistent for vascular events [16]. Data from the National Health and Examination Survey in the USA have suggested that a high calorie intake from added sugars (17–21% of total energy intake) is associated with a 38% higher CVD mortality risk compared to those consuming 8% of their total daily energy from added sugars [17].

Salt

There is a well-established link between salt and hypertension (see Chap. 12). As 49% of CHD events are attributable to hypertension, a reduction in salt/sodium intake is strongly recommended. Cohort studies that included 177,000 people showed that higher salt intake is associated with significantly greater incidence of strokes and total cardiovascular events; there is a dose-dependent association [18].

Alcohol

Consistent evidence from cohort studies suggests an inverse relationship between daily consumption of alcohol and risk of CHD [19]. Moderate consumption (1–2 units/day) reduces risk by 20% or more. The major mechanism by which alcohol achieves this effect is by reducing chronic inflammation, and increasing vasodilation, insulin sensitivity, and HDL-C. In addition, alcohol has an antithrombotic action [19].

There has been much speculation that wine, especially red wine, is more potent than other forms of alcoholic beverages. The origin of this belief is the low rates of CHD in France compared to certain other countries, such as the UK. This has been referred to as the "French paradox." These differences cannot be easily explained by looking at the "usual suspects," particularly smoking and intake of SFA. Many people found it attractive to assume that red wine deserved the credit. However, when the epidemiological evidence is looked at as a whole, especially cohort studies, then a different story emerges: all forms of alcoholic beverages—beer, spirits, and wine, both red and white—are similarly protective [19]. This saga serves as a valuable reminder of the golden rule in this type of research: epidemiology shows association, not causation. What is undisputed is that larger amounts of alcohol can be damaging; regular consumption of 30 g of alcohol or more per day has been associated with an increased disease risk [19].

Recommendations for the general public regarding intake of alcoholic beverages are discussed in Chap. 22.

Dietary Fiber

Dietary fiber was discussed in Chap. 23. Fiber represents a diverse group of substances which can be divided into two main groups: soluble fiber (or viscous fiber) and insoluble fiber. Major food sources of soluble fiber are fruit, oats, and beans. Sources of soluble fiber that can be added to the diet as a supplement include oat bran and psyllium. An appropriate dose is around 10–15 g/day. Insoluble fiber is present in abundance in most types of whole grain cereals. Fiber consumption, in particular from cereal and fruit sources, has been significantly inversely associated with CHD risk in a dose-dependent manner [20]. Furthermore, soluble and insoluble fiber seem to have a similar negative association with CHD risk [20]. To date, there are no RCTs to examine the effect of fiber intake on hard CHD clinical endpoints. However, dietary fiber may reduce established CVD risk factors via a number of potential mechanistic pathways, including reduction in total cholesterol, oxidized LDL-C, inflammation, and blood pressure.

Whole Diet Approaches to CHD Risk Reduction

A number of studies have moved beyond food components and have investigated whether whole foods are protective against CHD. Some studies have explored the efficacy of a whole diet approach for CHD prevention and therapy [21].

Fruit, Vegetables, and Whole Grain Cereals

Fruits and vegetables are complex foods and contain many bioactive components, including folate, potassium, magnesium, hundreds of phytochemicals, and dietary fiber, while also having a negligible amount of fat. Epidemiological studies and RCTs have repeatedly shown that consumption of fruit

and vegetables has a strong protective association with risk of CHD [12]. This is not surprising when we consider the various healthful effects of these foods. 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. These foods have also been used as part of the DASH diet, a dietary strategy to lower blood pressure (Chap. 12). Potatoes, especially French fries, are generally excluded from recommendations to eat more vegetables.

Epidemiological studies have also generated strong evidence that intake of whole grains is strongly and negatively associated with risk of CHD [22]. These foods are likely to be protective against CHD for much the same reasons as fruit and vegetables. Their content of fiber may be especially important.

The Mediterranean Diet

The Mediterranean diet is a dietary pattern characterized by a high intake of plant foods (i.e., fruit, vegetables, cereals, legumes, nuts, and seeds) and olive oil consumption; moderate intake of fish, poultry, low-fat dairy products, and wine; and a low intake of red and processed meat. This diet is associated with a higher antioxidant intake and is high in PUFA and MUFA. Meta-analyses have consistently reported significant inverse associations between adherence to the Mediterranean diet and CHD risk [23, 24]. Furthermore, a large RCT (PREDIMED), involving 7447 adults, reported a significant reduction in coronary events in those consuming a Mediterranean diet supplemented with either olive oil or nuts, compared to those consuming a low-fat control diet [25]. PREDIMED demonstrates that changes in diet quality consistent with a Mediterranean diet and independent of weight loss can prevent CHD.

Obesity

Obesity is strongly associated with risk of CHD, but this association becomes weaker after age 65. Much of the association between obesity and CHD, possibly all of it, can be accounted for by the frequent presence of established CHD risk factors in obese people, notably hypertension, hyperlipidemia, and insulin resistance (including glucose intolerance and diabetes) [26].

BMI is the most widely used index of obesity. However, the distribution of body fat appears to be important when assessing disease risk. Excess abdominal visceral body fat seems to be a risk factor, irrespective of BMI. For that reason, 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 health-care 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 >94 cm (>37 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 United States.

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 prevention [27]. Indeed, a sedentary lifestyle is now recognized as one of the big four risk factors, alongside elevated LDL-C, 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, at least 5 day/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/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

Compelling evidence exists that diet and lifestyle changes can substantially reduce the risk of CHD. Based on the strongest evidence presently available, we can state, with a high degree of confidence, that diets low in trans fatty acids (TFA), and with generous amounts of fruit, vegetables, whole grains, and foods that supply $n-3$ PUFA, are highly protective against CHD. This dietary pattern has much in common with that found in the traditional Mediterranean diet. The diet should also be low in refined grains (so as to make room for whole grains).

It has been demonstrated that simply lowering the percentage of energy from total fat will be unlikely to reduce total cholesterol (TC) and LDL-C or reduce CHD incidence. Different fats have very different effects on blood lipid levels and this is the key mechanism that explains how fat affects risk of CHD.

Maintaining a healthy body weight and engaging in a regular program of exercise will also reduce CHD risk. Therefore, public health policies encouraging consumption of a healthy diet (as outlined above), maintenance of a healthy weight, physical activity, and smoking avoidance have the potential to substantially reduce the burden of CHD.

The focus of this chapter has been CHD. We can conclude with some comments on other cardiovascular diseases, most notably stroke. 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 cardiovascular disease.

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Chapter 12
Diet and Blood Pressure: The High and Low of it

David W. Harsha and George A. Bray

Key Points

- Hypertension poses significant risks for stroke and heart disease.
- Weight gain and obesity increase blood pressure (BP); weight loss can reverse it.
- Diets high in fruits and vegetables and low-fat dairy products and low in red meat and sugar-containing foods (DASH Diet) can significantly lower BP.
- Dietary sodium has an important impact on BP in some people, and lowering sodium intake can lower BP.
- Alcohol intake increases BP.

Keywords Hypertension • Stroke • Sodium • Blood pressure • Antihypertensive therapy

Introduction

Hypertension is a global public health problem. Roughly one billion people worldwide are estimated to have clinically significant elevations in blood pressure (BP) with about 50 million of them in the United States [1]. Hypertension, in turn, is the most important of 67 risk factors for worldwide risk of coronary heart disease (CHD), stroke, renal disease, and all-cause mortality [2]. BP is significantly affected by nutrition which is the subject of this chapter.

The public health burden of hypertension is clearly enormous. Although perhaps impossible to tease out due to associations with other risk factors, including overweight, hypertension is a major contributor to most categories of chronic disease [3]. Diseases of the heart and cerebrovascular diseases are the first and third leading causes of mortality in the United States, accounting for more than one-third of all deaths. Hypertension is a major risk factor for both of these diseases. Therefore, reduction in hypertension constitutes a major health goal [3].

D.W. Harsha, Ph.D. (✉) • G.A. Bray, M.D.
Pennington Biomedical Research Center, Louisiana State University, Baton Rouge, LA 70808, USA
e-mail: davidharsha100@gmail.com

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In clinical trials, antihypertensive therapy can result in reductions of incidence of stroke, myocardial infarction, and heart failure [4]. In this meta-analysis, a 10 mmHg reduction in systolic BP (SBP) reduced risk of major cardiovascular disease by 20%, coronary heart disease by 17%, stroke 27%, and heart failure 28%, which, in the populations studied, led to a significant 13% reduction in all-cause mortality.

Definitions of Hypertension

The JNC (Joint National Committee) VIII [5] report divides BP into several categories and proposes primarily pharmacological treatment regimens for each. In brief, they propose contrasting drug therapies for those:

1. In the general population >60 years with a goal of reducing SBP <150 mmHg and diastolic BP (DBP) <90 mmHg.
2. In the general population <60 years with a goal of reducing DBP <90 mm.
3. In the general population <60 years with a goal of reducing SBP <140 mm.
4. In the population aged ≥18 years with chronic kidney disease (CKD) a goal of reducing SBP <140 mm and DBP <90 mm.
5. In the population aged ≥18 years with diabetes with a goal of reducing SBP <140 mm and DBP <90 mm.
6. In the general nonblack population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic, calcium channel blocker (CCB), angiotensin-converting enzyme inhibitor (ACEI), or angiotensin receptor blocker (ARB).
7. In the general black population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic or CCB.
8. In the population aged ≥18 years with CKD, initial (or add-on) antihypertensive treatment should include an ACEI or ARB to improve kidney outcomes. This applies to all CKD patients with hypertension regardless of race or diabetes status.
9. In the general population, a more detailed pharmacologic approach to treating resistant elevated BP.

JNC VIII guidelines focus primarily on pharmacological treatment of BP. They support the general population definition of HBP as >140/>90 mm.

Overweight is an increasingly prevalent condition throughout the world. In the United States, recent data indicate that 37.7% of the adult population is obese and 7.7% have a BMI > 40 kg/m^2 [6].

There is a positive relationship between overweight or obesity, on the one hand, and BP and risk for hypertension, on the other. The Framingham Study found that in both sexes hypertension is about twice as prevalent in the obese as the nonobese. Stamler and colleagues [5] noted an odds ratio for hypertension of obese relative to nonobese (BMI of <25) of 2.4 for younger adults and 1.5 for older ones. The Nurses' Health Study compared women with BMIs of <22 with those >29 and found a two- to sixfold greater prevalence of hypertension among the obese. More recent data from the Framingham Study add further support to this relationship. Divided into BMI quintiles, Framingham participants of both sexes demonstrated increasing BPs with increased overweight. In this instance, those in the highest BMI quintile exhibited 16 mmHg higher SBP and 9 mm higher DBP than those in the lowest BMI quintile. For SBP, this translated into an increase of 4 mm for each 4.5 kg of increased weight. In younger Canadian adults, there is a fivefold greater prevalence of hypertension in individuals of both sexes with BMIs of >30 relative to those <20.

Consistent with the above findings numerous clinical interventions have reported that weight loss is associated with a decrease in BP [7]. In a meta-analysis of 25 studies, Neter et al. [8] concluded that

a 1 kg loss of body weight is associated with an approximate 1 mm drop in BP. This was achieved without the necessity of also attaining normal weight status. The Trial of Hypertension Prevention, one of the largest of these studies, included a weight-loss intervention arm. In this trial, a 2 kg loss in weight over a 6-month period resulted in a decline of 3.7 mm in SBP and 2.7 mm in DBP. There was also a 42% decline in the prevalence of hypertension [9].

The SPRINT (Systolic Blood Pressure Intervention Trial) study is the most recent randomized clinical trial comparing an intensive-treatment goal of SBP <120 versus usual care with a goal of SBP <140. The primary end-point was a composite of myocardial infarction, non-myocardial infarction, acute coronary syndrome, stroke, acute decompensated heart failure, and death from cardiovascular disease. Antihypertensive medications, including thiazide-type diuretics, calcium channel blockers, and angiotensin-converting enzyme inhibitors or angiotensin receptor blocks, were used with an average of 2.8 medications in the intensive group versus 1.8 in the usual care group. The SBP in the intensively treated group was 122 versus 135 mm and resulted in a 25% reduction in numbers of participants reaching the primary outcome measure relative to the standard treatment group [10, 11]. A meta-analysis by Xie et al. [12] also showed the benefits of more intensive treatment of hypertension.

Increased physical activity (PA) has also been proposed as a means for BP reduction. Recent research indicates BP reductions of between 1 and 5 mm systolic among adults engaging in regular bouts of PA [13]. These impacts appear to require fairly intense PA sessions several times per week, with less rigorous approaches yielding more modest reductions in BP.

Diet and BP

Dietary Sodium

The jury of scientific opinion is still out on the degree to which weight loss or sodium restriction make independent contributions to BP reduction. An early study found that sodium restriction in low-calorie diets was thought to be the primary cause of BP reduction. Several more recent studies have sided with weight loss as having an independent effect on BP reduction [9].

Chief among perceived dietary influences on BP is sodium consumption. A large body of literature supports the notion that decreasing sodium consumption below that typical in Western society will result in a decline in BP [14]. Numerous epidemiological studies have demonstrated this relationship [9]. Reductions in sodium intake to around 75 mmol/day (0.18 g/day) are associated with a decline in BP of about 1.9 mm SBP and 1.1 mm DBP. The previously described Trial of Hypertension Prevention (TOHP) found that a decrease of 44 mmol/day (0.10 g/day) of sodium leads to a 38% reduction in the prevalence of hypertension in one of its treatment arms. The Dietary Alterations to Stop Hypertension Study-Sodium Study (DASH-Na) observed in persons with elevated BP who were eating a typical American diet that an approximate 100 mmol/day (0.23 g/day) reduction in sodium intake leads to a maximum reduction in SBP and DBP of about 6.7 and 3.5 mm, respectively. When the reduction in sodium consumption was only half as much (approximately 50 mmol/day or 0.12 g/day), there was much less decline in SBP and DBP (2.1 and 1.1 mm, respectively) [15]. These findings were produced in the absence of weight loss.

The results of the various studies looked at above support the recommendations of the Dietary Guidelines for Americans and the American Heart Association for a heart-healthy diet. Both recommend that people choose and prepare foods with little salt (less than 2300 mg of sodium per day or approximately one teaspoon of salt). It is important to note that reductions can be accomplished both through individual alterations in voluntary intake and through alterations in sodium content of processed foods [16].

Potassium and BP

Potassium has the opposite effect to sodium and meta-analysis shows that adding potassium to the diet and lowering the urinary sodium-to-potassium ratio generally has a mild impact on BP reduction [17, 18].

Dietary Patterns and BP

Manipulation of dietary patterns can have an important effect on lowering BP [7, 19]. The motivation for this line of research was the recognition of the inconsistent effects of micronutrient supplementation. In the DASH (Dietary Approaches to Stop Hypertension) Trial, a diet high in fruit, vegetables, and low-fat dairy servings reduced SBP and DBP by 5.3 and 3.0 mm, respectively, in the absence of either weight loss or sodium restriction [20]. A meta-analysis of 20 studies showed that the DASH diet significantly reduced SBP by 6.7 mm (95% CI: −8.2, −5.2) and DBP by 3.5 mm (95% CI: −4.3, −2.8) [19]. Similar reductions are seen when lean pork is substituted for chicken and fish [21] and when whole fat dairy products are used instead of low-fat dairy products [22].

The Mediterranean Diet [17] and vegetarian diets are widely associated with lower BP levels.

In contrast to the beneficial effect of fruits and vegetables, the opposite is seen with sugar. Increased consumption of sugar and the fructose which it contains can increase both weight and fat mass and increase BP [23].

Dietary Fat

Increased BP and dyslipidemia are both risk factors for cardiovascular disease. Whether dietary fat modifies BP in subjects with higher BP in the metabolic syndrome is unknown. This was investigated in a randomized European multicenter clinical trial lasting 12 weeks. A total of 486 subjects were assigned to one of four diets with different quantities and types of dietary fat. There were two high-fat diets, one of which was rich in saturated fat and the other in monounsaturated fat. There were two low-fat, high-complex carbohydrate diets; one was supplemented with 1.2 g/day of very long-chain n-3 PUFA while the other had no supplementation. Overall, there were no differences in SBP, DBP, or pulse pressure (PP) between the dietary groups after the intervention. The high-fat diet rich in saturated fat had minor unfavorable effects on SBP and PP in males [24].

Dietary Protein

A number of short-term controlled and randomized clinical trials have shown a BP lowering effect of increased dietary protein intake, but longer term trials show inconsistent results. Because carbohydrates were exchanged for proteins, the question remains whether there is a potential benefit from high-protein diets or whether the effect is due to decreased carbohydrate intake. There are no clear differences between plant and animal sources of protein in observational studies, and clinical trials comparing plant versus animal protein are lacking [25, 26].

Alcohol Intake

Alcohol intake is positively associated with BP in most studies in men, and a recent study has shown that this applies to women as well [27]. (Viewing the data in the larger perspective, it is recommended that alcohol consumption be limited to two drinks per day for men and one drink per day for women.)

Summary

Numerous dietary manipulations have a significant impact on BP. The array of dietary patterns and of macro- and micronutrients implicated in control of BP and hypertension is impressive and growing over time. Much further research is still necessary, particularly in the areas of micronutrient interactions and in elucidating the roles of dietary fat and protein in BP management. Findings resulting from such investigations will ultimately help fine-tune dietary approaches to the management of BP and the control hypertension.

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Suggested Further Reading

http://www.nhlbi.nih.gov/hbp The National Heart Lung and Blood Institute provides information for preventing and controlling high blood pressure.

http://www.nhlbi.nih.gov/health/public/heart/hbp/dash Access the DASH Eating Plan—"Lowering Your Blood Pressure with DASH." Click on the brochure for the full report.

Chapter 13
Role of Nutrition in Understanding Common Gastrointestinal Disorders

Michael Camilleri and Alice N. Brako

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.

Keywords Gastroesophageal reflux disease (GERD) • Peptic ulcers • Food allergy • Constipation • Diverticulosis • Inflammatory bowel disease • Colon cancer

Introduction

"Nutrition" is the term used in this chapter to characterize how food nourishes the body and influences health. Nutrition encompasses how food is consumed, digested, absorbed, and, also, how the waste products of digestion are eliminated. The gastrointestinal (GI) system receives food and extracts nutrients through complex mechanical and chemical processes involving several organs. Nutrients are substances in foods that are necessary for providing the body with energy and building blocks to support its structure and for regulating metabolism. 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. GI diseases are commonly encountered in primary care, and the prevalence of some diseases, including celiac disease, is increasing. Of the top ten high-cost physical health conditions affecting people in the United States, GI disorders rank second [1].

M. Camilleri, M.D. (✉)
Division of Gastroenterology and Hepatology, Mayo Clinic School of Medicine,
200 First Street SW, Rochester, MN, USA
e-mail: camilleri.michael@mayo.edu

A.N. Brako, B.V.M., M.P.H., C.H.E.S.
Department of Physiology, School of Medical Sciences, University of Cape Coast, Cape Coast, Ghana

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Gastroesophageal reflux disease (GERD) and peptic ulcers are common problems that affect the upper GI tract. These conditions are characterized by excessive acid production or reflux that cause frequent discomfort and tissue damage in the form of inflammation, ulceration, or even stricture formation. In addition, there is a strong association of peptic ulcer disease with *Helicobacter pylori* infection; therefore, eradication of the *Helicobacter pylori* infection is required when it is detected. Disorders of the middle and lower GI tract that have relationship with nutrition include food allergy and celiac disease, constipation, diarrhea, diverticulosis and diverticulitis, inflammatory bowel disease, and colorectal cancer.

Celiac disease is associated with genetic predisposition that is characterized by an abnormal immune response to proteins (e.g., gluten) in wheat, barley, and rye. A food allergy is a hypersensitivity reaction of the immune system to a particular food substance, usually a protein; eosinophilic esophagitis is associated with allergic responses to food and may respond to avoidance of allergens. Constipation is characterized by infrequent bowel movements, altered stool consistency or straining, that is difficulty with passage of bowel movements. Diarrhea is associated with passage of frequent stools of watery to loose consistency. Diverticulosis refers to the presence of pouches in the intestinal wall, most commonly affecting the colon; it can lead to diverticulitis if the pouches are inflamed. Inflammatory bowel diseases are chronic conditions associated with extensive damage to intestinal tissue which causes serious complications to the GI tract including bleeding, diarrhea, stricture or fistula formation, and cancer. The inflammatory bowel diseases include Crohn's disease and ulcerative colitis. Colorectal cancer is the third most frequently diagnosed malignant neoplasm in the United States.

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 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. The cellular, molecular, and genetic bases are increasingly understood [2] with involvement of an eotoxin produced by infiltrating eosinophils and inflammatory interleukins (e.g., IL-5).

Early recognition and treatment with an allergen-avoidance diet and topical steroids are key to treatment; an elemental diet is rarely required. The most common dietary allergens are cow's milk, wheat, eggs, seafood, soy, and peanuts.

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. Effective treatment is essential to prevent long-term complications such as formation of strictures.

Gastroesophageal Reflux Disease

Gastroesophageal reflux disease (GERD) is a painful condition of the upper GI tract characterized by heartburn that occurs more than twice a week. About 19 million people in the United States experience GERD each year, making it one of the most prevalent GI disorders [4]. The main cause of GERD is a transient relaxation or weakening of the lower esophageal sphincter (LES) which allows regurgitation of gastric acid and other gastric contents, including bile, back into the esophagus, thereby

causing substernal discomfort and heartburn. 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 [4].

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 [5].

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).

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 in. to allow gravity to keep stomach contents down. 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.

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 10 Americans develops a peptic ulcer at some time in his or her life [4].

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 [4].

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 [6].

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 [7], and attention to hydration and nutrition are essential for proper management of patients. The mainstays of treatment are dietary change (low fat, low nondigestible residue [fiber], small particle size supplement), prokinetics, and antiemetics. A randomized controlled trial demonstrated symptomatic benefit of a small size particle diet [8]. Other management strategies for gastroparesis and diabetic gastroparesis are detailed elsewhere [9, 10].

Bariatric Surgery

Bariatric surgery, such as Roux-en-Y gastric bypass (RYGB), sleeve gastrectomy, and the less frequently performed biliopancreatic diversion with duodenal switch, is 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. Preoperative nutritional assessment and correction of vitamin and micronutrient deficiencies, as well as long-term postoperative nutritional follow-up, are required. Bone mineral density, vitamin and micronutrient deficiencies (including thiamine, vitamins A, B_{12}, and D, calcium, copper, etc.) need to be monitored in the long term [11].

Operations, such as RYGB (especially with a long Roux limb) and biliopancreatic diversion, may result in significant steatorrhea and lead to enteric hyperoxaluria (as in Crohn's disease); this may be prevented by reduction of dietary oxalate (e.g., tea, spinach). Patients who have undergone such bariatric surgery may therefore show characteristic 24-h urine changes including low urine volume, low urinary pH, hypocitraturia, hyperoxaluria, and hyperuricosuria. Potassium citrate raises urinary pH, enhances the activity of stone inhibitors, reduces the supersaturation of calcium oxalate, corrects hypokalemia, and is useful in treating patients who develop renal calculi after bariatric surgery [12].

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 [13].

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. 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. Specific allergen immunotherapy has been introduced. It is fundamental to prevent food allergy, especially in high-risk subjects [14].

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 though the prevalence differs by ethnic group [15]. 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 [16]. 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 [17]. The only effective treatment for celiac disease is a gluten-free diet [18]. 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 hard to pass and infrequent bowel movements. 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 (<12g/day) 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. Other nutrition-related causes of constipation include use of aluminum-containing antacids and iron and calcium supplements [19]. Paradoxically, these substances are often used to treat other GI disorders or are a part of standard vitamin/mineral supplementation regimens. 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-h 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.

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 intake may be helpful in replacing commensal gut flora; and increasing soluble dietary fiber intake may be helpful with chronic diarrhea; however, these suggestions are based more on belief than evidence [20].

Irritable Bowel Syndrome

In addition to the symptoms of chronic constipation or diarrhea, the association of altered bowel function and abdominal pain is commonly recognized as irritable bowel syndrome (IBS). This is sometimes associated with abdominal bloating and passage of gas. 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.

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 [21]. 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.

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 [22].

The pattern of ulcerations in Crohn's disease is patchy, with normal tissue separated by diseased regions. Patients with Crohn's disease may require surgical resection to remove affected areas, but new regions often become ulcerated.

The main consequence of Crohn's disease is malnutrition resulting from intestinal resections as well as from impaired digestion and absorption. Reduced nutrient intake and eventual weight loss are common due to poor absorption of bile salts as a result of the interruption of the enterohepatic circulation. Thus, if the ileum is involved, bile acids may become depleted because of the loss of the active transport site for bile acids; this may cause malabsorption of fat, fat-soluble vitamins, calcium, magnesium, and zinc. Additionally, vitamin B_{12} deficiency can occur with ileal involvement, resulting in anemia.

The rectum is always 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.

Dietary treatment for both Crohn's disease and ulcerative colitis should aim at preventing symptoms associated with the diseases, correcting malnutrition, promoting healing of affected tissue, and enhancing normal growth and development in children. 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 [23]. Nutritional supplements may be recommended, especially for children whose growth has been retarded. Special high-calorie liquid formulas are sometimes used for this purpose. A small number of patients may require periods of parenteral feeding to provide extra nutrition, allow the intestines to rest and hopefully heal, or to bypass the intestines for individuals whose guts cannot absorb enough nutrition from ingested food. 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 [24].

Prebiotics are nondigestible dietary oligosaccharides that affect the host by selectively stimulating growth, activity, or both of selective intestinal (probiotic) commensal bacteria. These bacteria may provide protection, stimulate local immune responses to combat infectious organisms, or suppress inflammation caused by antigens [25]. 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 [26]. There is evidence to support the use of probiotics 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 [27].

There has been an explosion of these 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. The role of omega–3 fatty acids in the management of IBD is not clear. Results from some studies show they may have the potential to alleviate intestinal inflammation [28], but findings from other investigations do not support this anti-inflammatory role [29].

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 1 in 21 (4.7%) for men and 1 in 23 (4.4%) for women [30].

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 [31]. 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 [32]. 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 [33]. 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. Intriguingly, colorectal cancer mortality was found to be inversely proportional to serum vitamin D levels [34]. In summary, though quite often recommended, the role for many supplements, including omega–3 fats, vitamin D, folate, and vitamin B_6, remains unproven. Only calcium and vitamin D supplementation appear to add a modest benefit, particularly in those with a low intake [35].

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 and fat, as well as 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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Chapter 14
Nutrition in Patients with Diseases of the Liver and Pancreas

Roman E. Perri

Key Points

- Malnutrition is common in patients with cirrhosis. The assessment of this can be challenging but recognition and prompt treatment are essential to improving patient prognosis.
- Dietary protein intake of 1.2–1.5 g/kg/day is recommended for patients with advanced liver disease. Protein restriction should be avoided in cirrhotic patients, even those with hepatic encephalopathy.
- Severe acute pancreatitis can result in significant malnutrition and high rates of mortality. Nutritional support through enteral nutrition is the preferred method of maintaining adequate nutrition.
- Supplemental pancreatic enzymes are of central importance in managing the exocrine insufficiency associated with chronic pancreatitis.

Keywords Protein-calorie malnutrition • Hepatic encephalopathy • Ascites • Pancreatic exocrine function • Steatorrhea

Patients with Liver Disease

The end-stage liver disease of cirrhosis is a serious medical condition with high rates of mortality. The average life expectancy of a patient when diagnosed with cirrhosis is 10 years. Complications of liver disease including ascites, hepatic encephalopathy, or gastroesophageal variceal hemorrhage portend a grim prognosis with a 2-year mortality rate of 50% without liver transplantation [1]. These complications herald the onset of significant portal venous hypertension, where the degree of fibrosis within the cirrhotic liver significantly disrupts blood flow through the splanchnic vasculature. There were 36,400 deaths due to cirrhosis and chronic liver disease in the United States in 2013, with a mortality rate of 11.5 per 100,000 population [2].

R.E. Perri, M.D. (✉)
Gastroenterology, Hepatology and Nutrition, Vanderbilt University School of Medicine,
1660 TVC, Nashville, TN 37205, USA
e-mail: roman.perri@gmail.com; roman.peri@vanderbilt.edu

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Malnutrition is commonly seen in patients with cirrhosis. The appropriate medical management of patients with cirrhosis must therefore include a focus on nutritional aspects of this disease. The liver's role in metabolic homeostasis has long been recognized and with significant compromise of the liver's function, derangements of metabolism will result. In fact, the prevalence of protein-calorie malnutrition (PCM) has been recognized in up to 90% of patients with cirrhosis [3]. Typically, patients with alcoholic liver disease exhibit the most severe degrees of PCM but other causes of liver disease, including cholestatic liver disease and viral liver disease (i.e., hepatitis) are also complicated by significant rates of PCM. The presence of malnutrition in patients with cirrhosis has been recognized to be a predictor of mortality [4, 5]. The recognition of malnutrition in the patient with cirrhosis, with both an assessment of degrees of malnutrition and interventions designed to lessen its severity, are therefore of paramount importance.

The causes of malnutrition in patients with cirrhosis are multifactorial and include poor appetite, early satiety, nausea, and alterations of metabolism. In addition, cholestasis and small intestinal bacterial overgrowth can result in malabsorption of ingested nutrients [3]. The assessment of nutritional risk must therefore take these factors into account.

The clinical appraisal of malnutrition in the setting of cirrhosis can be difficult. A clinical history can disclose important information about dietary intake although in patients with even preclinical encephalopathy, patient recall may be inaccurate. A physical examination plays an important role in the assessment of malnutrition in the cirrhotic patient although these assessments can also be challenging. Measurements such as body mass index or waist circumference can be skewed due to the presence of ascites and edema. Fluid retention can obscure the loss of adipose tissue in the viscera as well as extremities. Nonetheless, a physical examination can disclose the presence of temporal muscle wasting as well as loss of proximal musculature in the arms and legs; areas that may be less susceptible to fluid retention. Indeed, subjective descriptions of proximal muscle weakness are common in patients with cirrhosis, and body protein stores have been noted to be significantly decreased in patients with cirrhosis [6].

Biochemical evidence of malnutrition by measurements of proteins such as albumin and transthyretin (prealbumin) are imperfect measurements of nutritional status as these levels are affected by the presence of inflammation. Nonetheless, serum levels of albumin have been shown to predict survival in patients with decompensated cirrhosis as a component of the Child-Turcotte-Pugh score [1]. Due to the limitations of individual markers of nutritional status, it is imperative to utilize multiple clinical tools including clinical history, physical examination, and laboratory assessments to gain as thorough an understanding as possible regarding the presence of malnutrition in the cirrhotic patient.

Nutritional support in cirrhotic patients requires that attention be paid to multiple considerations. Recommendations regarding dietary intakes in these patients should consider dry weight of the patient, discounting ascites and edema; an assessment that can be challenging in the setting of significant fluid retention. The total calorie needs of patients should be assessed; it is recommended that an intake of 25–35 kcal/kg/day should be administered to patients with well-compensated cirrhosis. Those patients with more severe illness, including decompensated liver disease and hospitalization, require higher daily caloric intake of up to 30–40 kcal/kg/day in order to combat the development of a catabolic state [7]. Protein intake is of paramount importance in the cirrhotic patient. Prior recommendations that patients with decompensated liver disease should restrict dietary protein intake in order to prevent complications of hepatic encephalopathy have not been supported by clinical studies, and have had the effect of exacerbating malnutrition in cirrhotic patients. Dietary protein intake for patients with cirrhosis should be in the range of 1.2–1.5 g/kg/day to minimize the muscle breakdown that is common in patients with decompensated liver disease [8]. Even in patients who are hospitalized with hepatic encephalopathy, immediate protein restriction has not been found to be clinically useful; a hospital diet that provides 1.2–1.5 g/kg/day of protein should continue to be administered [9].

In order to maintain an adequate daily calorie and protein intake, as well as to compensate for a poor appetite, early satiety, and hepatic synthetic dysfunction, some modifications to the daily diet

often must be considered. Cirrhotic patients should eat more frequent (4–6), smaller meals daily, including a nocturnal snack that is enriched in protein to help maintain the recommended intake of both calories and protein in the setting of their physiological derangements [3].

An alteration of the ratios of aromatic and branched-chain amino acids may play a role in the pathogenesis of hepatic encephalopathy. Dietary supplementation with branched-chain amino acids (BCAA) is well tolerated by cirrhotic patients. BCAAs are a reasonable supplement, in lieu of other protein sources, in the patient with refractory hepatic encephalopathy. Supplementation with BCAAs may offer additional benefits to cirrhotic patients including improved prognosis [10]. The regular administration of these supplements in the form of "hepatic" enteral supplements has not been demonstrated to be beneficial in routine use.

Vitamin needs should be considered in patients with end-stage liver disease. Fat-soluble vitamins are commonly found to be deficient in cirrhotic patients due to both poor oral intake and malabsorption. Vitamin D deficiency should be assessed regularly with measurement of 25-OH vitamin D levels. Supplementation should be provided to prevent the development of osteomalacia. Vitamin A deficiency can lead to night blindness. Vitamin K deficiency can lead to increased risks of bleeding in the setting of a prolonged prothrombin time. Supplementation of these vitamins is commonly required in cirrhotic patients. A lack of improvement of prothrombin time despite the administration of supplemental vitamin K implies that decreased hepatic synthetic function is responsible for the observed coagulopathy. Thiamine deficiency is commonly seen in patients with alcoholic liver disease and can precipitate neurological consequences such as Wernicke's encephalopathy. Prompt administration of supplemental parenteral thiamine should be performed in patients hospitalized with complications of alcoholic liver disease and maintenance with oral thiamine supplements should be provided thereafter.

Overnutrition and obesity have emerged as among the leading causes of liver disease. Nonalcoholic fatty liver disease (NAFLD) is the hepatic manifestation of insulin resistance. This condition is increasing in prevalence and is the leading cause of cryptogenic cirrhosis [11]. Paradoxically, the presence of protein-calorie malnutrition (PCM) can coexist with cirrhosis due to overnutrition. Clinically useful medications have not yet emerged for NAFLD although clinical trials are ongoing. At present, the mainstay of therapy for NAFLD is gradual weight loss achieved through lifestyle modification. Various diets, including low-calorie diets as well as ketogenic low-carbohydrate diets, have been studied; an optimal diet for the treatment of NAFLD has not been defined. Some studies have suggested that restriction of simple carbohydrates, or modulating certain types of fatty acids in the diet may have an effect on improving hepatic histology but convincing evidence that would allow firm recommendations continues to be lacking [12].

Ascites is the most common of the major complications of cirrhosis and, as mentioned, heralds a 2-year mortality of 50%. The presence of ascites can result in decreased gastric accommodation and resultant early satiety leading to malnutrition. The etiology of ascites is retention of sodium, not water. The fluid that accumulates in ascites and edema is passively associated with retained sodium. The initial therapy of ascites is to decrease dietary sodium intake thereby inducing a negative sodium balance. This can often be accomplished with sodium restriction to 2000 mg/day, a level of intake that is still consistent with a palatable diet. When dietary interventions fail, diuretic therapy with spironolactone as well as furosemide may be required to increase urinary sodium excretion.

Nutritional support for patients who cannot utilize their intestines, either temporarily due to medical or surgical issues or permanently due to gut failure, is by total parenteral nutrition (TPN). While this intervention has been helpful in the maintenance of the patient's nutrition, well-defined hepatic complications of TPN include the development of cholestasis and even of end-stage liver disease in 15% of those receiving long-term TPN [13]. It is unclear what the best treatment options are for liver disease associated with TPN. Recent studies have focused on the potential use of omega-3 fatty acid infusions during TPN administration although a lack of high-quality data prevent firm recommendations from being made [14].

The utility of herbal supplements in patients with cirrhosis is poorly defined. Milk thistle (silymarin) has been used medicinally for centuries and purportedly has beneficial effects on the liver. Despite the fact that milk thistle has been tested in human trials and the general acceptance of the herb's safety, a clinical benefit for its use of has not been established. In the absence of evidence of utility of other herbal remedies, the use of herbal dietary supplements for the treatment of chronic liver disease is not recommended. The potential hepatoxicity of herbal remedies has been long recognized [15] and without clear evidence of safety, the use of these supplements is not recommended in patients with chronic liver disease.

Patients with Pancreatic Disease

Acute pancreatitis is characterized by marked abdominal pain with nausea and vomiting and associated elevations of serum levels of amylase and lipase. Abdominal imaging with computed tomography can also be used to secure a diagnosis. Typically, abdominal pain is exacerbated by eating which has been attributed to stimulation of the inflamed pancreas that occurs during the digestion process. Acute pancreatitis is characterized as mild when edema of the pancreas is noted on abdominal imaging. Discontinuation of eating is typically one of the first measures taken in a bout of acute pancreatitis along with administration of intravenous fluids and analgesics. In cases of mild acute pancreatitis, abdominal pain typically abates over a few days. Upon improvement of pain, oral intake can be resumed. As oral intake is only delayed by a few days, it is not felt that bouts of mild acute pancreatitis pose a significant nutritional risk to patients.

Severe acute pancreatitis is associated with the development of the systemic inflammatory response system that can result in a high risk of morbidity and mortality. Pancreatic necrosis can result from organ failure; resultant infected pancreatic necrosis can entail mortality rates as high as 30% [16]. Mortality rates are high when adequate nutritional support is lacking because of the marked negative nitrogen balance, hypermetabolism, and catabolism that are characteristic of severe acute pancreatitis. The standard management of patients with severe acute pancreatitis was, for many years, to avoid oral intake so as to prevent further stimulation of the inflamed pancreas. When nutritional support was necessary, this was typically provided by TPN. This approach, however, was found to be associated with high rates of infectious complications due to bacterial overgrowth and translocation of bacteria via the intestines [17]. The use of enteral nutritional support has resulted in improved outcomes from severe acute pancreatitis. It is necessary to initiate nutritional support within 48 h of admission for pancreatitis in order to combat the metabolic distress of the condition [16]. Enteral nutrition improves the structural integrity of the intestinal mucosa, preventing bacterial translocation and infectious complications.

Nutritional support is best administered via a nasojejunal feeding tube, which has the advantage of delivering nutrition distal to the pancreas thereby avoiding further stimulation of the pancreas. Interestingly, studies have demonstrated that there is no significant difference in outcomes between nasojejunal and nasogastric feedings [18]. Therefore, enteral nutrition should not be delayed if deep intestinal intubation is not obtained with a feeding tube. There is no convincing evidence that any particular type of enteral tube feeding is superior [19]. There is no evidence that the administration of probiotics yields any improvement in clinical outcomes and clinical trials have actually yielded contradictory data as to whether mortality rates may be affected by the administration of probiotics [19]. Until clear evidence emerges, no recommendations about specific enteral formulations can be made, other than that enteral nutritional support is superior to parenteral nutrition, as well as superior to no nutrition at all.

Chronic pancreatitis is the condition where progressive inflammatory changes in the pancreas result in structural changes of the pancreatic duct as well as fibrosis and calcification of the pancreatic body. Over time, both endocrine and exocrine functions of the pancreas become compromised. The most common cause of chronic pancreatitis is long-standing abuse of alcohol, which may be

accompanied by nutritional deficits irrespective of associated pancreatic disease. Chronic pancreatitis is a cause of pain that can lead to anorexia and resultant malnutrition. Maldigestion of food results from deficient pancreatic exocrine function. When the functional mass of the pancreas declines to the point that pancreatic enzymes including lipase and trypsin are reduced to less than 10% of baseline, steatorrhea indicative of poor fat digestion can occur [20].

Maintaining adequate caloric intake is the nutritional goal of patients with chronic pancreatitis but can be limited by chronic pain. Multiple modalities often need to be utilized to treat the chronic pain. There is some evidence that elemental diets, fat avoidance, supplemental pancreatic enzymes, and lifestyle modification including alcohol avoidance and tobacco cessation may improve symptoms of pain in chronic pancreatitis [21]. In addition to conservative measures to improve the pain, the judicious use of analgesics, as well as surgical and endoscopic therapies may improve pain and anorexia in selected patients [21].

While avoidance of dietary fat will result in improvement of steatorrhea, this intervention can result in an inadequate intake of fat-soluble vitamins. Therefore, the use of supplemental pancreatic enzymes (SPE) along with a normal fat diet is the preferred means of treatment of steatorrhea [22]. The administration of 25,000–75,000 IU of pancreatic lipase ingested concurrently with meals allows for the proper digestion of dietary fat and amelioration of steatorrhea [20]. As the effect is greatest if the enzymes properly mix with ingested food, it is therefore important that the SPE be taken during the meal and not before or after it. SPE should be taken with all ingested foods though the amount taken can be reduced for snacks. Some types of SPE are susceptible to inactivation by gastric acid; medical control of gastric acidity may therefore be required for full effectiveness. Fat-soluble vitamin supplementation (A, D, E, and K) should be offered to all patients with chronic pancreatitis in whom maldigestion or steatorrhea is seen.

In the rare patient in whom weight loss and steatorrhea persist despite the use of SPE, medium-chain triglycerides can be used as a dietary supplement [20]. They are absorbed by the intestine in a lipase-independent manner and can provide adequate fat-derived calories despite the lack of sufficient pancreatic function. The use of TPN is generally not required in patients with chronic pancreatitis though rare indications may be discovered.

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Chapter 15
Medical Nutrition Therapy for Kidney-Related Disorders

Desirée de Waal

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.
- A referral to a dietitian with expertise in CKD should be recommended upon diagnosis of CKD.

Keywords Chronic kidney disease (CKD) • Acute kidney injury (AKI) • End-stage kidney disease (ESRD) • Acidosis • Hemodialysis • Peritoneal dialysis • Kidney stones

Introduction

Chronic kidney disease (CKD) is a global problem with lifetime risks increasing [1–3]. The Centers for Disease Control and Prevention (CDC) estimates that kidney diseases are the ninth leading cause of death in the United States with more that 10% of the adult population being affected [4]. 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 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. 15.1 with colors showing which groups of patients are at

D. de Waal, M.S., R.D., C.D., F.A.N.D. (✉)
Department of Nephrology, University of Vermont Medical Center,
1 South Prospect Street, Burlington, VT 05401, USA
e-mail: Desiree.deWaal@UVMHealth.org

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higher risk for major health outcomes [5, 6]. One of the major goals for CKD is a reduction in new cases of kidney disease and its complications, disability, death, and economic cost [7].

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 [8]. 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. Patients with kidney disease are often prescribed diets that are low in potassium due to hyperkalemia; they are given handouts that focus on limiting fruits and vegetables. Patients become confused and frustrated as this recommendation is at odds with diets widely recommended for the prevention of other diseases, such as diabetes and heart disease (e.g., the Mediterranean and DASH diets); those diets emphasize fruits, vegetables, and whole grains. Evolving evidence of a link between the gut and kidney health [9] 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. The presence of kidney disease increases the risk for cardiovascular disease, including heart attacks and strokes. Fluid retention may lead to edema, severe hypertension, pulmonary edema, pericarditis, and heart failure. Other common health-related consequences in CKD include anemia, metabolic acidosis, hyperkalemia, and bone and mineral disorders [10].

CURRENT CHRONIC KIDNEY DISEASE (CKD) NOMENCLATURE USED BY KDIGO

CKD is defined as abnormalities of kidney structure or function, present for > 3 months, with implications for health and CKD is classified based on cause, GFR category, and albuminuia category (CGA).

Prognosis of CKD by GFR and albuminuria category

Prognosis of CKD by GFR and Albuminuria categories: KDIGO 2012				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildy increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmal	30-300 mg/g 3-30 mg/mmal	>300 mg/g >30 mg/mmal
GFR categories (ml/min/ 1.73 m²) Description and range	G1	Normal or high	≥90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD): Yellow: moderately increased risk; Orange: high risk; red,very high risk.

Fig. 15.1 Prognosis of CKD by GFR and albuminuria category. Reproduced from: Kidney Disease: Improving Global Outcomes (KDIGO) CKD Working Group. KDIGO 2012, Ref. [6], with permission

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 [4]. 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. 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 [11]. 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 [12]. The findings from studies that investigated dietary acid load and the incidence of CKD suggest a potential avenue for reducing CKD risk through diet [13]. 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 also demonstrated some preservation of kidney function [14, 15], contrary to the goals presented in much of the aforementioned dietary modification literature provided for CKD patients.

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. Poorly controlled diabetes is the most common cause of hyperkalemia in advanced CKD. Certain medications (some blood pressure medications, NSAIDS) and severe constipation may also cause hyperkalemia. 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. 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. 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 [14, 15].

The management of hyperkalemia requires a review of 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 often used. A high-fiber diet which includes fruits and vegetables will also help manage constipation which also may cause hyperkalemia.

Bone and Mineral Disorders

CKD affects calcium and phosphorus balance resulting in a renal bone disease. As CKD progresses, vitamin D levels decline and parathyroid hormone levels rise [16]. High serum phosphorus levels are not usually seen until the later stages of kidney disease, but a diet high in phosphorus may be contributing to the changing bone patterns as CKD progresses. As kidney function decreases, one of the most challenging areas for patients is the control of their phosphorus levels through their choices of food and beverages. Long-term high phosphorus intake contributes to disequilibrium in bone minerals causing increased levels of intact parathyroid hormone (iPTH); this indicates secondary hyperparathyroidism which is common in advancing CKD. A high iPTH level also poses an increased risk for vascular calcification. The control of phosphorus intake and the use of phosphorus binders taken with meals help decrease the absorption of phosphorus. The RD/RDN with expertise in kidney disease is able to recommend the best therapy to help manage secondary hyperparathyroidism. Treatment may include supplementation with vitamin D, especially if vitamin D levels are low.

Evidence shows that a diet high in phosphorus contributes to adverse kidney disease outcomes including vascular calcification, an additional cardiovascular risk in CKD [17]. 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 [18].

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 [9]. 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 [19]. 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 [20]. 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.

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, an RD/RDN who specializes in kidney disease has more training in how foods affect kidney function, bones, and the heart. Unfortunately, MNT provided by an 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 [21, 22]. 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 an 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 28 provides detailed information on food guides as well as for dietary choices in general. The DASH diet (Dietary Approaches to Stop Hypertension) is 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 an 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.

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.

In hemodialysis, the choice is in-center (HD), home hemodialysis (HHD), or nocturnal home dialysis (NHD). The diet for HD and HHD are 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.

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 icodextran 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.

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 iPTH 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, fluid balance, and assist the patient with their nutritional goals.

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; diets low in oxalate is a thing of the past [23]. 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., cystine stones). The major promoters of kidney stones include a low intake of fluid or of fruits 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 an 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.

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 [24]. Patients should be educated on diet and lifestyle triggers for gout. Food triggers include large servings or animal protein, high-fat foods, alcohol, and foods high in processed sugars. Drastic weight loss measures such as fasting, low-calorie, 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.

Acute Kidney Injury

Acute kidney injury (AKI) is a sudden and usually reversible decline in eGFR. Table 15.1 shows staging for acute kidney injury [6, 25, 26]. 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 preexisting 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, 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.

Nephrotic Syndrome

Nephrotic syndrome is caused by a variety of disorders that damage the kidneys leading to proteinuria. The most common symptoms include proteinuria, edema, foamy appearance of the urine, fluid accumulation, and hyperlipidemia. MNT goals for nephrotic syndrome are similar to CKD with a focus on a healthy eating pattern.

Table 15.1 Staging of AKI

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

Adapted from KDIGO Clinical Practice Guideline for Acute Kidney Injury, Refs [25, 26]

Summary

MNT facilitated by an 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 Reading

GFR Calculator. https://www.kidney.org/professionals/KDOQI/gfr_calculator.
Kidney Health Australia. http://www.kidney.org.au.
National Institute of Diabetes and Digestive and Kidney Diseases. http://www.niddk.nih.gov.
National Kidney Federation, UK. http://www.kidney.org.uk/.
National Kidney Foundation. www.kidney.org.
The Kidney Foundation of Canada. http://www.kidney.ca.

Chapter 16
Inherited Metabolic Disorders and Nutritional Genomics: Choosing the Wrong Parents

Asima R. Anwar and Scott P. Segal

Key Points

- Inherited metabolic disorders are categorized to better aid in diagnosis.
- Inherited metabolic disorders can be classified into three categories: disorders presenting as intoxication or encephalopathy; disorders of energy metabolism; and disorders involving complex molecules.
- General guiding principles for the nutritional management of inherited metabolic disorders are given.
- Specific approaches to nutritional therapy are discussed for the most common diseases in this group, such as medium-chain acyl-CoA dehydrogenase deficiency, maple syrup urine disease (MSUD), phenylketonuria (PKU), homocystinuria, and galactosemia.

Keywords Inherited metabolic disorders • Nutritional management • Medium-chain acyl-CoA dehydrogenase deficiency • Maple syrup urine disease • Phenylketonuria • Homocystinuria • Galactosemia

Introduction

Many countries, including the United States, Canada, along with those in the EU, have established screening services in place for the detection of inherited metabolic disorders (IMD) in newborns. These disorders are not individually common within the population. However, in aggregation they are relatively common among genetic disorders, and they are a significant cause of morbidity in infants, affecting one in 1500 to one in 5000 live births [1]. Many inherited metabolic disorders (IMD) have severe symptoms, which may lead to significant disability and mortality, if not rapidly diagnosed and treated shortly after birth. IMD primarily result from toxic accumulation of precursors or end products

A.R. Anwar, B.Sc.
Recreation and Parks Department, Mississauga, ON, Canada

S.P. Segal, Ph.D. (✉)
Department of Biology, Winona State University, Pasteur Hall 240, 175 W. Mark St, Winona, MN, USA
e-mail: ssegal@winona.edu

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of metabolism. Specific disorders are difficult to diagnose due to the fact that many IMD show similar symptom profiles. Thus, rapid testing after birth is required to determine the exact disorder afflicting the patient to determine the correct course of treatment.

IMD Diagnostic Classifications

IMD can be divided into three categories according to their clinical presentation [2].

Disorders Presenting as Intoxication or Encephalopathy

Syndromes of intoxication or encephalopathy may be caused by an accumulation of toxic metabolites due to a metabolic block of an essential product or a defective transport process. This group includes inborn errors of intermediary metabolism, such as aminoacidopathies, organic acidurias, urea cycle disorders, sugar intolerances, metal disorders, and porphyrias. Clinically, infants with these disorders appear normal at birth and are symptom free for hours or days. Lethargy, poor feeding, vomiting, increased muscle tone, seizures, liver failure, and coma ensue, often quite rapidly. Some newborns have respiratory symptoms, such as apnea or hyperventilation, the latter being more likely if the disorder causes metabolic acidosis. Neurologic findings, such as hyper- or hypotonia, opisthotonus, pedaling, coarse tremors, and myoclonic jerking, are typical of the disorders presenting as intoxication or encephalopathy.

Disorders of Energy Metabolism

Hypoglycemia is a consistent symptom of disorders of energy metabolism including disorders of fatty acid oxidation. Other clinical features are lactic acidosis, hypotonia, and cardiac involvement (cardiomyopathy, arrhythmias, conduction disturbances, and congestive heart failure), but lethargy and coma rarely occur.

Disorders Involving Complex Molecules

These disorders affect either the synthesis or catabolism of complex molecules. These disorders involve cellular organelles, such as the lysosomes and peroxisomes. Symptoms of these disorders are generally present immediately after birth and include facial dysmorphia (facial deformities) and severe neurologic dysfunction.

Newborn Testing for Inherited Metabolic Disorders

Rapid newborn of newborns screening is critical for early detection of IMD in order to prevent morbidity and mortality and represents one of the major advances in newborn health within the last century. Newborn screening originated with the work of Robert Guthrie in the 1960s to identify and treat

prevalent IMD in infants, such as PKU, and in which the symptoms could be controlled [2]. In theory, using newborn screening for genetic diseases such as IMD is a noble idea. However, according to Wilson and Junger, its path to implementation is fairly difficult, as there are offsets in providing treatment to those with previously undetected IMD, while on the other hand not causing harm to those not in need of treatment [3].

Development of Screening Criteria

In 1968, Wilson and Junger proposed a series of criteria for newborn screening that were adopted by the World Health Organization (WHO) and are mainly still the standard today [4]. The Wilson-Junger Criteria cover aspects of screening that include identification of a health problem, education of the patient, as well as cost of testing and treatment. Based on the Wilson-Junger Criteria, a modern set of criteria for whether to screen for inborn errors of metabolism, as well as other genetic disorders, were developed, along with a set of criteria for the actual screening tests [4]. Three main criteria for whether to screen for these disorders are used [4]:

1. Incidence of the disorder
2. Clinically identifiable signs and symptoms within the first 24 h
3. Burden of the disease if not initially treated

For the actual screening test, the following seven criteria should apply [4]:

1. Availability of a test for the specific disorder
2. Ability to test blood spots, an alternative specimen or by some other simple, in-nursery procedure
3. The test is based on a platform that offers high throughput capability
4. The cost of the test is less than $1 per infant screened
5. Multiple analytes relevant to one condition can be detected in a single run
6. Other conditions (secondary targets) can be identified by the same analytes
7. Multiple conditions can be detected by the same test.

Screening for IMD by Tandem Mass Spectrometry

Tandem mass spectrometry (MS/MS) allows for a complete metabolite profile and detection of either reduced or increased levels above a normal baseline [5, 6]. It allows for a more accurate and rapid detection of IMD, and only requires a single blood spot taken after birth. The method generates a complete acylcarnitine and amino acid profile on a blood specimen. It is being used in an increasing number of countries to screen for organic acid and fatty acid oxidation and amino acid disorders, including maple syrup urine disease (MSUD), homocystinuria, phenylketonuria (PKU), and hereditary tyrosinemia [7]. Most of these diseases respond well to dietary manipulations, but, unfortunately, a large number of patients suffer irreversible damage before any warning symptoms appear. Currently, MS/MS is best suited for identification of acidemias, both amino and organic, such as maple syrup urine disease and phenylketonuria, as well as fatty acid oxidation disorders, such as MCAD [5, 6].

Nutritional Management of Inherited Metabolic Disorders: The General Approach

One common goal that is central to nutritional management of all inherited metabolic disorders is to provide sufficient energy, amino acids, and nitrogen to support and maintain normal growth and development. Shils et al. [8] have suggested 12 general approaches to therapy for this group of diseases which may be used sequentially or simultaneously:

1. Enhancing anabolism and depressing catabolism
2. Correcting the primary metabolic imbalance by using both the dietary restrictions to reduce substrate accumulation as well as provision of products that may be deficient
3. Enhancing excretion of accumulated substrate. The kidney may aid as a dialysis organ while maintaining the equilibrium between diuresis and hydration
4. Providing alternative metabolic pathways to decrease accumulated toxic precursors in blocked reaction sequences
5. Using metabolic inhibitors to lower overproduced products
6. Supplying products of blocked secondary pathways
7. Stabilizing altered enzymes
8. Replacing deficient coenzymes
9. Artificially inducing enzyme production
10. Replacing enzymes
11. Transplanting organs
12. Correcting the underlying defects in DNA so that the body can manufacture its own functionally normal enzymes

Nutritional Management of Inherited Metabolic Disorders: Disease-Specific Approach

Although more than 300 genetic disorders have been reported, only the primary examples of the more debilitating or common IMD are considered in this chapter. Until improved methods of providing patient gene therapy are developed, treatment must generally focus on nutritional management and palliative therapy.

Medium-Chain Acyl-CoA Dehydrogenase Deficiency (MCAD Deficiency)

The autosomal recessive disorder, medium-chain acyl-CoA dehydrogenase deficiency, is the most common abnormality of fatty acid metabolism seen in the population. Caucasians of Northern European descent exhibit the highest frequency of this disorder [9], with an incidence of one in 15,000. Common symptoms of MCAD disorder include recurrent hypoglycemia (when fasting for more than 10–12 h), vomiting, lethargy, encephalopathy, respiratory arrest, hepatomegaly, seizures, apnea, cardiac arrest, coma, and sudden death. Long-term outcomes may include developmental and behavioral disability, chronic muscle weakness, failure to thrive, cerebral palsy, and attention deficit disorder. Mutations in MCAD gene result in the autosomal recessive MCAD deficiency, which results in production of an abnormal MCAD enzyme.

Nutritional management focuses mainly on restricting dietary fat intake to 20% [10] or 30% or less [11] of total caloric intake. Due to decreased fat intake, caloric intake from carbohydrates as well as from night feeding (or extra snack before bed) should be increased to prevent lipolysis and hypoglycemia. For instance, children at 8 month of age (when pancreatic enzymes become fully functional) should be started on a diet of uncooked corn starch [12], with dosing initially at 1.0–1.5 g/kg and gradually increased to 1.75 g/kg by the second year of age [13]. This will allow for the necessary sustained release of glucose. Carnitine supplementation may also be used during prolonged unavoidable fasting, such as for surgery as well as other medical testing. Medium-chain triglyceride oils, flaxseed, canola, walnut, or safflower oils are used for alternate fat form and to avoid essential fatty acid deficiency [14]. Daily multivitamin and mineral supplements that include all fat soluble vitamins are also recommended.

Although no specific commercial dietary formulas are available to meet the complex needs of patients with fatty acid oxidation disorders, a combination of different formulas to provide a diet high in complex carbohydrate, low in fat, and adequate in vitamins and minerals [11] are usually prescribed.

Maple Syrup Urine Disease

This is a rare IMD in which the patient has a deficiency of the 2-keto acid dehydrogenase enzyme. This results in the inability to effectively metabolize branched-chain amino acids, such as isoleucine and leucine. Internationally, it has an incidence of one in 185,000 newborns; however, it has a much higher incidence of one in 176 in Mennonite populations. The excess buildup of branched-chain amino acids in these patients will cause the urine to have a sweet smell similar to maple syrup. Clinical symptoms of MSUD include neurotoxicity, including opisthotonos, seizures, blindness, mental retardation, and coma, which are due to elevated plasma levels of branched-chain amino acids [15]. Without proper treatment, individuals with this disorder will die at a very early age.

Dietary therapy for MSUD requires lifelong restriction of branched-chain amino acid intake, to control the plasma levels of these amino acids, particularly leucine. It is important to control the levels of branched-chain amino acids without impairing growth and intellectual development of the patient. Recommendations include the measurement of plasma amino acid levels at appropriate intervals for the first 6–12 months of life. In addition to dietary therapy, thiamine (10–1000 mg/day) should be administered, irrespective of clinical phenotype [16]. This high dose has become common practice by pediatricians due to the fact that excess thiamine poses no harm and is excreted in the urine [16].

Phenylketonuria

PKU is caused by amino acid substitutions in the phenylalanine hydroxylase enzyme, which impair its ability to sufficiently metabolize the amino acid phenylalanine. One in 14,000 Caucasian newborns and one in 132,000 African-American newborns are affected by PKU. Symptoms include mental retardation, seizures, hyperactivity, and muscular hypertonicity. Untreated maternal PKU during pregnancy has extremely harmful effects on fetal development, including mental retardation, microcephaly, maternal phenylketonuric syndrome, congenital heart disease, and intrauterine growth retardation [2, 8, 17–19].

Therapy for PKU consists of a diet with a low content of phenylalanine. This includes a diet of fruits, vegetables, regular/special low-protein breads, pastas, and cereals, which are low in phenylalanine.

Foods that contain large amounts of phenylalanine, such as milk, dairy products, meat, fish, chicken, eggs, beans, and nuts, must be eliminated. Since these foods are also high in protein, adequate protein intake is achieved by adding special phenylalanine-free formulas, and therefore, most of the patient's nutrient intake will be through phenylalanine-free formulas. Although phenylalanine intake should be restricted in individuals with PKU, it should not be outright eliminated, especially during the critical period of brain development early in infancy. Plasma phenylalanine levels maintained above 1–2 mg/100 mL were consistent with better growth and levels up to 7 mg/100 mL allowed for good mental development [20].

Individuals with PKU should also show caution with respect their use of artificial sweeteners. Aspartame (Equol®) contains phenyalanine and is a common ingredient in many reduced- or low calorie foods and beverages [21]. Suggested alternative phenylalanine-free artificial sweeteners such as sucralose (Splenda®) or saccharin (Sweet'n Low®) may be suggested.

Homocystinuria

Homocystinuria is an autosomal recessive disorder caused by deficiency of the enzyme cystathionine beta-synthase. This renders the patient unable to properly metabolize homocysteine, which is an intermediate in the metabolism of the amino acid methionine. Newborn screening in 13 countries found only one case in 334,000 infants but the frequency is much higher in infants of Irish descent: one in 58,000 [22]. Common symptoms of include dislocated lenses, intravascular thrombosis, skeletal changes, osteoporosis, and mental retardation.

Patients with homocystinuria should be given a methionine-restricted diet, which is supplemented with betaine and l-cysteine [8]. Some examples of commercially available methionine-free medical foods are HOM-2 (Milupa), Hominex-2 (Abbott), HCY-1 and HCY-2 (enfamil), and XMET Maxamaid (Nutricia). Additionally, some patients may respond well to supplements of vitamin B_6 and folic acid [8]. Nutritional support should be followed throughout adulthood, as termination of nutrition support in adulthood may increase the risk to thromboembolisms and lens dislocation [23, 24].

Galactosemia

Galactosemia is an autosomal recessive disorder caused by a deficiency of the galactose-1-phosphate uridyltransferase (GALT) enzyme (Type I), the galactokinase 1 (Type II), or UDP-galactose-4-epimerase (Type III) [25]. Type I galactosemia is by far the most common in the population and has two variants, the Classic and the Duarte variants, with the Duarte patients still retaining 14–25% GALT activity [26]. The GALT enzyme is necessary for the breakdown of the monosaccharide galactose and thus deficiencies of galactose-1-phosphate will manifest as hyperglycemia. The incidence of all three types of galactosemia is 1 in 30,000–60,000 births [25]. Symptoms of galactosemia include acute hepatotoxicity and prolonged jaundice may appear with the start of human milk or infant formulas containing lactose (a disaccharide that is digested to galactose and glucose). Other complications include delayed speech development, severe mental retardation, irregular menstrual cycles, and decreased ovarian function and ovarian failure. The condition is irreversible and requires abstinence from milk, milk products, and galactose-containing foods for life [8].

Generally, patients with galactosemia should have a diet of foods that contain neither galactose nor lactose. Patients retaining a small amount of GALT activity may be able to tolerate small amounts of galactose found in muscle meat, fruits, and vegetables [8]. Due to the dairy

restrictions these patients must endure, calcium supplements are recommended to offset the lack of dietary calcium intake. Infants with this disorder also should not be fed milk, instead they can be fed with soy formula, meat-based formula, Nutramigen (a protein hydrolysate formula), or other lactose-free formula [26].

Coverage for Treatment of IMD

Treatment of IMD is expensive and must be strictly adhered to throughout the life of the patient. Depending on the disorder, treatment requires the use of modified low-protein foods, supplements, feeding supplies, or medical foods. According to the FDA, medical foods are those which are taken under supervision of a physician, and which are intended for specific dietary management of a disease for which distinctive nutritional requirements are established through medical evaluation [27]. The cost of using medical foods can be anywhere from 10 to 20 times their unmodified counterparts, whereas using modified low-protein foods can cost between 2 and 8 times their unmodified counterparts [28]. Although many patients or their families carry insurance that covers the use of medical foods, coverage is oftentimes incomplete, requiring significant out-of-pocket expenses [28].

Conclusions

Many of the inherited metabolic disorders are now included in routine neonatal screening. Diagnosis of these disorders at birth through MS/MS may facilitate early intervention, prior to further confirmation from follow-up tests. The main course of treatment is nutritional management, which prevents severe pathologic complications by reducing the overproduction and accumulation of toxic metabolites. Treatment is by nutritional management which also provides the necessary nutritional constituents that are deficient, allowing support and maintenance of sufficient growth and development throughout the life span. However, treatment is lifelong and comes at a significant expense. More complete insurance coverage is needed for medical foods.

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Suggested Further Reading

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Children living with inherited metabolic diseases. Crewe: The National Information Centre for Metabolic Diseases. http://www.climb.org.uk. Website offers support to parents and family members with children suffering from inherited metabolic disorders.

Chapter 17
Food Allergy and Intolerance: Diagnosis and Nutritional Management

Janetta Harbron

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 challenge.
- Nutritional management of food allergy involves avoidance of exposure to the allergen and establishing through oral food challenges (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.

Keywords Food allergy • Food intolerance • Non-allergic hypersensitivity • IgE tests • Oral food challenge • Elimination diet

Introduction

Adverse reactions to food may develop at any age and to any food [1]. They are classified as non-toxic (food hypersensitivity [FHS]), toxic (e.g., food poisoning), or psychologically based (food aversion) [1]. This chapter focuses on non-toxic 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. 17.1) [1–4].

J. Harbron, Ph.D., M.Sc., B.Sc., R.D. (✉)
Division of Human Nutrition, Department of Human Biology, Faculty of Health Sciences, University of Cape Town, Anzio Road, Observatory, Cape Town 7925, South Africa
e-mail: janetta.harbron@uct.ac.za

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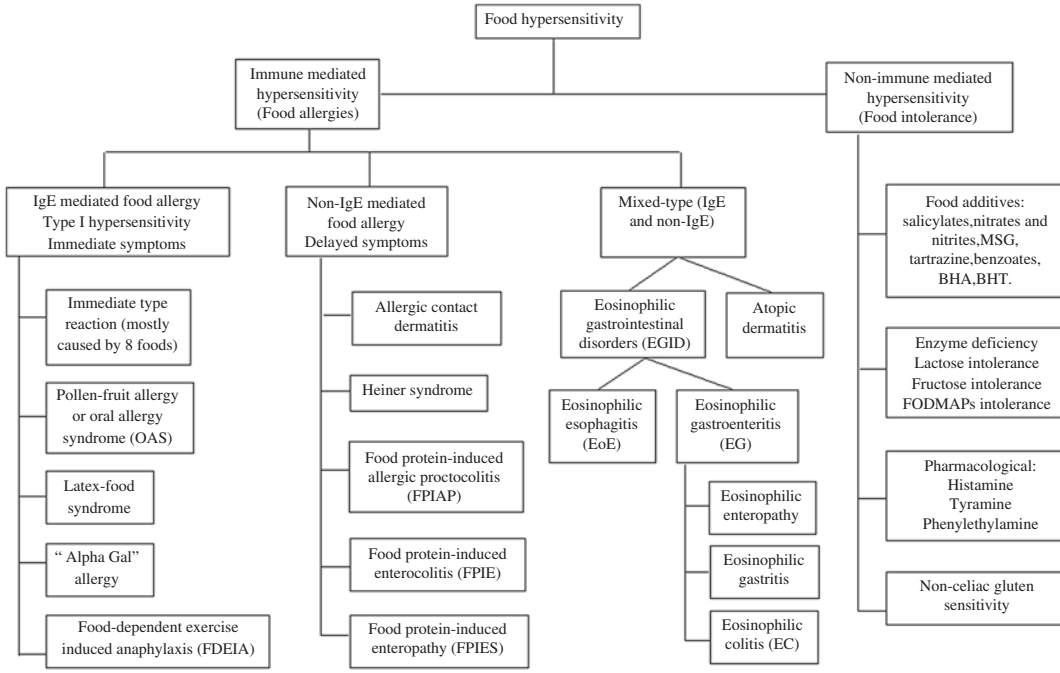

Fig. 17.1 Classification of food allergy and intolerances

The prevalence of FA and food intolerances has substantially increased over the past two decades and are a growing public health concern worldwide. In the United States (US), the prevalence of FA almost doubled in children from 1997 to 2011 [5]. It is estimated that 8% of children and 4% of adults in the US have FA [5]. The prevalence of FA in pre-school children in developed countries is estimated to be around 10% [6], while the prevalence of food intolerance ranges between 15% and 20% [7].

While elimination diets of causative food can be successful in managing these conditions, it can be cumbersome and lead to 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 or allergy specialist when necessary.

Food Allergy

FA develop due to an adverse immune response towards one or more proteins or other molecules (allergens) in food and are 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]. The distinct symptoms of each are illustrated in Table 17.1. The symptoms may range from mild to severe and involve one or several organ systems [2].

Table 17.1 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 multi-system manifestations • Symptoms recur every time when exposed to food • Severity of symptoms may change over time	Immediate to delayed onset (see Tables 17.2 and 17.3)	• 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 lip, mouth and throat. Immediate urticarial, 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. [1–4, 7–9, 11–13]

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, 8]. In infants, the most common allergies are to CM and egg. Allergies to peanuts, tree nuts, seafood, CM, and eggs are usually observed in older children, while

adults are more prone to peanuts, tree nuts, seafood, and pollen allergies causing cross-reactive FA [1]. 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 [1]. The consequent 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 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 [1].

Oral allergy syndrome (OAS) is an allergic reaction to certain fruit, vegetables, and nuts that develops due to cross-reactivity (e.g., the same IgE antibody recognizes distinct antigens found in common pollens, or house dust mite and in fruit, vegetables and nuts). Almost all patients with OAS first develop IgE sensitization to the aeroallergen; this often presents as seasonal rhinitis if pollen is the aeroallergen. The subsequent ingestion of fruit or vegetables that have proteins with homologue epitopes to the aeroallergen results in an immune reaction and allergy symptoms. Examples of common overlapping antigens in OAS include [1, 4]:

- Birch pollen with apple, peach, plum, cherry, apricot, almond, carrot, celery, parsley, 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 that develop in more than half of individuals with latex allergies due to cross-reactivity. The food involved include avocado, kiwi fruit, chestnut, papaya, banana, mango, papaya, passion fruit, tomato, and potato [1].

Food-dependent exercise-induced anaphylaxis (FDEIA) refers to the presence of signs and symptoms of anaphylaxis during or soon after exercise and within 2–4 h after ingestion of a food allergen. Symptoms should be absent when the food is consumed without exercise or when vigorous exercise is performed alone. IgE sensitization to the food should be evident through skin prick testing (SPT) or serum immunoglobulin E (sIgE testing) [2].

Non-IgE-Mediated and Mixed-Type FA

The underlying mechanisms involved in non-IgE-mediated FA are not well-understood [1]. They occur mostly in children and are usually outgrown. The classification of these FA is illustrated in Fig. 17.1 and the main symptoms, diagnostic procedures, and treatment recommendations for some of these are briefly summarized in Tables 17.2 and 17.3.

Diagnosis

The diagnosis of FA requires evidence of immune system sensitization as well as reproducible symptoms after exposure to the allergen. The first-line diagnostic approach is a thorough clinical examination and history of the patient's experiences with the suspected food [3]. If the clinical history suggests FA, further tests are necessary to confirm sensitization. The second-line approach involves either *in vivo* (SPT) or *in vitro* food-specific sIgE testing of the suspected food(s) identified through the clinical history [3]. The third-line approach is to carry out elimination diets and oral food challenges (OFC) to establish clinical relevance of SPT or sIgE results, if necessary to confirm the diagnosis or to establish tolerability levels [1].

Table 17.2 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
Symptoms 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 diarrhoea, steatorrhea, failure to thrive
	Other: irritability, anemia, abdominal distention, failure-to-thrive	Stools may be more frequent but diarrhoea 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, 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, 2, 4, 8]

Clinical History and Examination

The clinical history aims to identify the possible presence of FA, trigger food, and the underlying immunological mechanism (e.g., IgE, non-IgE, or mixed). It is recommended that structured questions be used to obtain information on [2, 3, 8]:

Table 17.3 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, diarrhoea, 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 or 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 Often poor response to anti-reflux drugs	Some resolve before age 5 years In many patients, EG is persistent at 5 years follow-up	AD usually resolves during childhood; however, if peanut or tree nut FA is the cause, it is more likely to be persistent

Source: [1, 2, 4, 8]

1. Causative food: type (probe regarding the eight major food allergens or certain fruit and vegetables if suspecting oral allergy syndrome (OAS)), amount ingested that cause a reaction and form of food (processed, raw, baked, heated, dried), route of exposure (oral, inhalation, skin).
2. Symptoms: reaction type, duration and severity of symptoms, reproducibility of symptoms, frequency of symptoms, time frame involved from exposure to symptom onset, age when symptoms started.

3. Co-factors that may augment FA reaction: alcohol, exercise, NSAID, fever, and acute infection.
4. Socio-demographic factors: age, geographic location, and ethnic dietary habits of the patient; these may all give clues regarding trigger food.
5. Other factors: known risk factors (exposure at school, work, home), family history of allergies, any other coexisting medical problems or allergic diseases (e.g., asthma, allergic rhinitis, atopic dermatitis); if a child, the duration of breastfeeding.
6. Treatment: details on how symptoms were treated.

The clinical examination may reveal acute or chronic signs of asthma, allergic rhinitis, or atopic dermatitis, although this is not necessarily important for FA diagnostic purposes [8].

A dietary history, preferably performed by a dietitian, should include evaluation of nutritional status, including growth monitoring in children and dietary intake. A review of food labels and detailed food diaries may assist in identifying possible causative food, hidden ingredients, or pattern of reactions [3].

Diagnostic Test for IgE Sensitization

Both SPT and sIgE tests (Table 17.4) are reliable and validated to detect IgE-mediated sensitization to food allergens, but cannot be used as the sole tests for clinical allergy diagnosis [9]. One reason for this is false positives. This refers to positive SPT or sIgE test results, but where there are no symptoms or signs of FA when exposed to the specific food allergen. Such individuals do not have FA and it is therefore recommended that the clinical history should always guide diagnostic testing. Testing for large panels of food allergens should be discouraged as false positive SPT or sIgE results may lead to unnecessary dietary elimination and nutritional inadequacies [2, 3]. False negative results are another problem. Accordingly, negative SPT or sIgE results combined with a strong clinical history suggesting FA should be interpreted with caution and warrant further investigation [8]. False negative SPT or sIgE results may, for instance, be possible due to the commercial test extract not containing the relevant allergen found in the raw food [8]. SPT tests are often preferred over sIgE tests due to their lower costs and near instant results [8]. SIgE testing should be used when SPT is contraindicated or ineffective [3].

Promising Diagnostic Tests

Technological advancement in tests, such as component-resolved diagnosis (CRD), make it possible to detect IgE sensitization in specific proteins or protein components instead of the whole food extract, which results in a low misclassification rate and a high sensitivity and specificity [1, 2]. The basophil activation test (BAT) has been used to effectively discriminate between sensitization to some allergens and clinical allergy [3, 8, 9]. However, further research is necessary before these tests can be used for routine diagnosis of FA [3, 8, 9].

Elimination Diets

Elimination diets cannot confirm FA diagnosis on their own, but can help to identify causative food in IgE and non-IgE-mediated FA [3]. These diets are also effective in reversing the clinical severity of mixed-type FA such as eosinophilic gastrointestinal disorders (EGIDs) [2]. The clinical history, allergy-focused diet history, and SPT or sIgE testing should guide which food should be eliminated [8]. There are several different types of elimination diets that can be used including the allergy-directed diet

Table 17.4 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) • High sensitivity (>90%) • 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	• No risk of anaphylaxis • Order from physician's office without specialist referral • 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 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

(continued)

Table 17.4 (continued)

	Skin prick testing (SPT)	sIgE
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 cut-offs have been defined for egg, milk, and peanut FA in children [9]	• Food-specific diagnostic cut-offs 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. [1–3, 8, 9]

(elimination of specific food(s)), the oligo-antigenic diet, the extensively-hydrolyzed or amino acid-based elemental diet, the six-food group elimination diet, the four-food group elimination diet, the gluten-free diet, and the milk-elimination diet [2, 3]. 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 [8]. The elimination phase is then followed by a well-planned reintroduction phase of eliminated allergens according to specified guidelines [8].

Oral Food Challenges (OFC)

The double-blind placebo-controlled oral food challenge is the gold standard procedure for objective diagnosis of FA [2, 3, 9]. As this test is expensive, labor intensive, and time-consuming [3, 8], open or single-blinded OFC are often used in clinical practice [10]. When open or single-blinded OFC cause an objective unequivocal reaction, it is deemed sufficient to diagnose a FA [8], while the double-blind challenge is recommended when symptoms are subjective.

Food challenges are usually performed in a specialist practice where emergency treatment is available for severe allergic reactions [8, 9]. Protocols for performing OFC exist and involve re-introduction to one food allergen at a time, in specific dosages that increase in a stepwise manner over several hours while monitoring reactions [2, 8].

Alternative Tests

Alternative tests are often used by the public, but should not be advised or used for the diagnosis of FA or food intolerances as they lack evidence to support their use in clinical practice [1, 8, 11]. Examples are as follows:

- Electrodermal tests
- Hair analyses
- Applied kinesiology
- IgG and food-specific IgG4 levels
- Iridology
- Lymphocyte stimulation
- Facial thermography
- Gastric juice analyses
- Endoscopic allergen provocation
- Cytotoxicity assays
- Mediator relapse test
- Pulse test

Furthermore, intradermal testing to food and atopy patch tests are not validated and standardized and thus not routinely recommended for investigating FA [3].

Monitoring for Tolerance

As about 70–80% of children outgrow FA to egg, CM, wheat, and soy by adolescence, regular monitoring is important to identify when tolerance has been reached in order to avoid unnecessary dietary eliminations. Peanut and tree-nut allergies most often continue into adulthood [12]. Favorable factors associated with outgrowing FA include younger age, type of allergy (e.g., CM, egg, soy, wheat), 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 [10]. It is recommended that diagnostic tests (SPT or sIgE) be repeated every 12–18 months in children <5 year old and every 2–4 years in those >5 year old to establish change in sensitization [10]. An OFC is the gold standard procedure to confirm that FA is no longer present [10].

Nutritional Management

General Dietary Recommendations for FA

Dietary elimination of the food allergen(s) is key in the management of FA [8]. However, exposure to the food allergen may occur through the skin, the lungs, or by oral intake. Oral intake may result in mild to severe reactions when ingesting a very small amount of the allergenic food, by ingesting food that is cross-contaminated with the allergen, or due to cross-reactivity [10]. Self-elimination of food or food groups can cause nutritional deficiencies, significant stress, poor quality of life, and impact negatively on family life. It is therefore important that referral to a dietitian is made to ensure effective dietary management of FA. During dietetic consultations, education and practical advice on any of the following (applicable to the patient or caregiver) can be provided [13]:

- Diet sheet indicating food allowed and restricted/eliminated as well as alternatives for these.
- Well-planned nutritionally balanced avoidance diet [8].
- Supplementation if necessary.
- Reading labels and examples of terms used in the ingredient list that refer to the causative allergen (by law in most countries food labels must indicate if the food contains the eight major food allergens).
- 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 or yoghurt not made from CM).
- 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, ethnic restaurants, bakeries (peanut, egg, CM, and tree nuts), and buffets (all food) [10].
- Eating in restaurants: order plain food, be careful of fried food, sauces, condiments, pastries, bakery items, desserts.
- Tips for travelling abroad as this can be particularly challenging. Translated information may be necessary on food products and emergency treatment [14].
- 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.
- Importance of education for all caregivers: teachers, grandparents, friends' parents.
- Cross-reactive food. Cross-reactivity often occurs between the following food and exclusion of the other food in the same group may be necessary [1]:
  - Peanuts with other tree nuts and sesame
  - CM with goat's milk
  - 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.
- Breastfeeding. Although food allergens are detected in breastmilk, breastfeeding remains the first choice milk for infants with FA. In rare cases, however, it might be necessary for the mother to follow an allergen-elimination diet [1, 8].
- Milk choice for infants with cow's milk protein allergy (CMPA) that are formula fed [1, 8]:
  - Partially hydrolyzed formula milk is inappropriate for CMPA and should not be recommended.
  - 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.
  - Goat, sheep, and other mammalian milks are not suitable due to high cross-reactivity (e.g., 95% of children with CMPA react to goat's milk).
- Food reintroduction and "milk ladder" [15].
- Tolerance to baked CM and egg (see below).

Managing Oral Allergy Syndrome

Patients with OAS must avoid the raw trigger fruit and vegetables [1]. 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 [1, 2]. 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

Results from various studies indicate that about 69–83% or 63–84% of children with CM or egg allergy, respectively, can tolerate baked CM or egg as the extensive heating modifies certain CM or egg 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 quality of life, variety of food choices, and nutritional content. Furthermore, children who regularly consumed the baked forms were more likely to outgrow their CM or egg allergy compared to those who never or infrequently consumed baked CM or egg. It is therefore recommended that tolerance to baked egg and CM should be established and those who can tolerate the baked forms should regularly consume these [16].

Although most studies indicate that higher sIgE and SPT levels are associated with intolerance to baked egg or CM, no definite cut-points have been defined. Therefore, to diagnose tolerance to baked CM or egg, physician-led OFCs according to standardized protocols are recommended as anaphylaxis to baked CM or egg have been reported. Those tolerant to baked egg or CM should still eliminate all fresh CM, other dairy products, raw egg and eggs that are not extensively heated for a long duration such as stove-top egg preparations [17].

Peanut Allergy

Some individuals are highly sensitive to peanut allergens and may react to an environment or mucosa that has been contaminated with peanuts. The peanut antigen has been detected 110 days after peanut butter was smeared onto a table [1]. While normal dishwashing liquid is not sufficient to remove the antigen from cutlery, a disinfectant wipe can be used to clean surfaces to eliminate the allergen [1].

The severity of symptoms that develop due to accidental peanut exposure may change over time, e.g., a child may initially only present with hives to peanut exposure, but in subsequent exposures may develop anaphylaxis. It is thus important that care-givers do not become at ease to exposure of small amounts of the allergen if reactions are initially mild [10]. Furthermore, FA and eczema in early life (<2 years of age) may progress into asthma and allergic rhinitis, known as the atopic march [18].

Compared to other FA, a lower percentage of children (20–25%) outgrow peanut and tree nut allergies [4, 19]. SPT and sIgE cut-points that predict persistence of peanut allergy after age 4 years have been published [19]. However, children who outgrow peanut allergy can at a later stage re-acquire the allergy, especially if peanuts have been avoided [4]. Recently, the results of the Learning Early About Peanut Allergy (LEAP) randomized controlled trial indicated that "high risk" infants who were introduced to peanuts early in life (between 4 and 11 months of age) and consumed 6 g peanut protein (equal to 24 g peanuts or three teaspoons peanut butter) per week for 5 years had a relative risk reduction of 80% for development of peanut allergy by age 5 years compared to the group who avoided peanut consumption during the first 5 years of life [20]. Consequently, various allergy associations have published an interim guideline that recommends the early introduction of peanuts in the diets of "high-risk" infants [21]. It is suggested that infants with severe early onset eczema or egg allergy in the first 4–6 months of life be referred to an allergist to perform SPT and possibly peanut OFC (if SPT is <4 mm) and to provide a recommendation regarding the implementation of these guidelines. The recommendation for infants or children with a SPT wheal diameter >5 mm to peanuts is to avoid peanuts and follow-up SPTs should be done on an annual basis [21]. Further research is necessary to establish the effect of sporadic peanut intake, alternative peanut dosages, early discontinuation of peanut intake, and minimum time necessary to induce risk reduction [21].

Prevention

The avoidance of major allergenic food during pregnancy, breastfeeding, and infancy is not recommended for allergy prevention. Exclusive breastfeeding for the first 6 months of life is widely recommended for various health benefits, but whether it protects against FA is unclear due to conflicting results from various studies [22].

In the past decade, several studies have indicated that the delayed introduction of the major allergenic food is not protective against the development of FA [22]. Early introduction and regular consumption of peanuts have actually been associated with FA prevention [20]. However, it is unknown whether early introduction of the other major allergenic food prevents FA; research in this regard is ongoing [22]. Detailed practical guidelines on the introduction of complementary food, including the

major allergenic food, from 4 to 6 months of age are outlined elsewhere [22]. Once allergenic food have been introduced and shown to be well-tolerated, regular consumption is advised so as to maintain tolerance, although the appropriate amount and frequency is not known [22].

Food Intolerance

Food intolerance is a non-allergic reaction to food with the immune system not being involved (Fig. 17.1) [1]. The differences and similarities in symptoms between FA and food intolerance are summarized in Table 17.1.

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 contain substances collectively termed FODMAPs (fermentable oligo-, di-, mono-saccharides, 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 [1, 11]. FODMAPs include lactose (disaccharide), fructose (monosaccharide), fructans and galactans (oligosaccharides), and polyols such as sorbitol, mannitol, and xylitol [11]. 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.

The enzyme lactase digests lactose in the GI tract to glucose and galactose, which can then be absorbed [7, 11]. Newborns have the highest concentration of lactase, which declines during childhood to <10% of pre-weaning levels [7]. Lactase deficiency may lead to lactose malabsorption (no symptoms) or lactose intolerance (malabsorption with symptoms). There are three types of lactase deficiencies, namely congenital, primary late onset, or secondary. The majority of lactose intolerance seen today is due to primary late-onset hypolactasia, i.e., a gradual decrease of lactase activity from age 2 years with symptoms manifesting from age of 5–6 years, but in the majority of cases only during adolescence or adulthood [7].

The capacity for fructose absorption in the GI tract is limited. Fructose malabsorption occurs when the absorption process is incomplete, when the total fructose intake or load is too high, or when too much "free fructose" food (that have high fructose and low glucose content) are consumed [1].

Humans lack enzymes to completely digest food with fructans (branched fructose polymers) and galactans (galactose polymers). Polyols are passively absorbed in the GI tract, but the rate of absorption may vary between individuals and consequently cause a laxative effect [1, 23].

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 [11].

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 [11].

Noncoeliac Gluten Sensitivity

Noncoeliac gluten sensitivity (NCGS) is a relatively new term that describes individuals who develop GI tract symptoms to gluten exposure, but do not have coeliac disease or wheat allergy [1, 11]. These individuals report that dietary gluten elimination results in improvement of a wide array of symptoms; however, clinical studies are inconsistent and unreliable to confirm NCGS [11]. The underlying mechanism is unclear, but it is possible that it overlaps with IBS [1].

Diagnosis

Food Exclusion, Symptom Improvement, and Food Challenge

The most reliable method for diagnosing food intolerance is exclusion or reduced intake of possible trigger food followed by symptom improvement, as well as gradual reintroduction of the food followed by symptom induction. If the diet history points to one specific food or food component (e.g., lactose), the food exclusion and challenge can be executed based on the elimination of all food that contain lactose. However, it is often difficult to identify specific trigger food or it is possible that more than one food intolerance contributes to the symptoms. It is then recommended that the low FODMAP (fermentable oligo-, di-, mono-saccharides, and polyols) diet be followed for 3–4 weeks followed by the reintroduction of food using a specific food challenge process under expert guidance to identify trigger food and individual tolerance thresholds to these food [11].

Breath Tests

Hydrogen and/or methane breath testing can be used to assess lactose or fructose malabsorption in the GI tract as these products are produced by bacterial fermentation of the undigested lactose or fructose, rapidly absorbed, and expelled through the lungs. Various protocols exist with most involving either 50 g of lactose or 25–35 g of fructose that must be ingested after an overnight fast. Breath hydrogen or methane is measured at baseline and every 15 or 30 min for 3–5 h depending on the protocol used. Malabsorption is indicated by a 10–20 ppm increase in breath hydrogen or methane above baseline on two consecutive measurements [11]. These tests should not be used alone for diagnostic purposes as the results only indicate malabsorption; many patients with a positive test may not experience any symptoms and are therefore not intolerant. Breath tests for sorbitol, mannitol, fructans, and galactans are not useful for identifying malabsorption and are therefore not recommended [11].

Other Tests

The lactose tolerance blood test, which measures change in blood glucose levels following a lactose load, is less sensitive than breath tests and is not recommended for diagnostic purposes [7]. No further objective tests currently exist that can identify food intolerance. Confocal laser endomicroscopy is a novel technique that explores the real-time effect of food antigens on the GI tract. It may be useful in future to diagnose food intolerance, but more research is necessary to validate the procedure and usefulness in clinical practice [11].

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 12–15 g (250–320 mL) of milk daily, or even higher amounts, without any symptoms [1, 7, 11]. The tolerance threshold is dependent on several factors and should be individually determined [11]. It is recommended that intakes should be spread throughout the day [11]. Fermented products such as yoghurt and buttermilk are better tolerated [11]. Lactose-free milk is also available in food stores. It is important to advise patients regarding the benefits of still including a tolerable amount of lactose in their diet as dairy food provide several essential nutrients, such as calcium and vitamin B_{12}. An additional reason for milk ingestion is to help build up tolerance to lactose. Although lactase supplements can be prescribed, this is expensive and unnecessary for the majority of patients. It is controversial whether hypolactasia causes infantile colic; lactose-free formulas are not recommended, while breastfeeding remains the preferred option [7].

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 to <3 g. Food that usually contain >3 g fructose per standard serving include dried fruit, fruit bars, two or more fresh fruits, fruit juice, fruit concentrate, fortified wines (sherry), food sweetened with HFCS, SSBs, and indulgent quantities of confectionaries. The intake of "free fructose" food should be limited [23].

Food high in fructans include wheat products, vegetables (e.g., artichoke, garlic, leeks, onion), and other food (added as fructo-oligosaccharides (FOS), inulin, oligofructose). Galactans are found in human milk, legumes, some grains, and nuts. Polyols are found naturally in higher amounts in certain fruit (apricots, peaches, cherries, apples, pears) and vegetables (mushrooms and cauliflower), but are also added as artificial sweeteners to food products. It is advised to restrict FODMAPs globally using a low FODMAP diet rather than restricting individual FODMAPs, unless only lactose or fructose intolerance is diagnosed [23].

Food additives and pharmacological agents are widely spread in food and elimination may lead to nutritional inadequacies; careful planning of such elimination diets are necessary [11].

Conclusion

The prevalence of food allergies and intolerances is increasing world-wide. 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 elimination diets.

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Suggested Further Reading

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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.
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Chapter 18
Bone Health: Sound Suggestions for Stronger Bones

Laura A.G. Armas and Corrine Hanson

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 protein.
- Most adults require additional vitamin D supplementation, especially if they have little sun exposure.
- Improvements in nutrition can make a significant difference to bone health, even if started later in life.

Keywords Bone health • Calcium • Vitamin D • Phosphorus • Magnesium • Protein

Introduction

Bone is a complicated organ made of collagen, proteins, calcium, phosphate, and cells that remodel and maintain bone. It requires many nutrients obtained from the diet 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. But remember that in food, these nutrients do not occur in isolation; they are present in nature packaged in various combinations of fat, protein, 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.

More than 40 million Americans have osteoporosis and over two million of them experience a fragility fracture due to osteoporosis every year. If a patient is being treated with medication for osteoporosis, we emphasize that these nutrients, the essential nutrients required for bone formation, are the

L.A.G. Armas, M.D., M.S. (✉)
Diabetes, Endocrinology and Metabolism, University of Nebraska Medical Center,
984130 Nebraska Medical Center, Omaha, NE 68198, USA
e-mail: laura.armas@unmc.edu

C. Hanson, Ph.D., R.D., L.M.N.T., F.A.N.D.
Medical Nutrition Education, University of Nebraska Medical Center, Omaha, NE, USA

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building blocks that the medication uses to form bone. This seems a simplistic explanation, 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 effects of the pharmacologic agents depend to some extent on these supplemental nutrients.

Calcium

For over 100 years we have been aware of calcium's effects on bone health. Of the nearly 100 clinical trials using calcium supplements or dairy foods, all but four have shown positive outcomes, i.e., greater bone mass during growth, reduced bone loss with age, and reduced fractures. Despite this knowledge, about 85% of the female population fails to get the recommended intake of calcium.

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 calcium in 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 (kidney stones), 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, depending on vitamin D status, but the mineral is also lost through gastrointestinal secretions. As a result net intestinal absorption is only 10–15%. Additionally, calcium is lost in urine and sweat [1, 2]. 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 amount of net absorption requires a daily total intake of 1000–1500 mg (the equivalent of 3–5 dairy servings). See Table 18.1.

During growth, net absorption is more efficient and bones will 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.

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, or some other disease present, 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.

Table 18.1 Dietary reference intakes (DRI) for calcium

Age group	DRI (mg)
Childhood	700–1300
Adolescence	1300
Adult 19–50 years	1000
Adult >50 years	1200

Source: Ref. [3]

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. This is especially problematic for those following a vegetarian 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 [4].

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 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. 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.

In recent years, there has been considerable controversy over the use of calcium supplements in raising cardiovascular risk. Meta-analyses of calcium supplement studies have showed either no increase in risk [5] or a small increase in risk of cardiovascular disease with calcium supplements [6], but these reports have been widely disputed by the scientific community [7].

Vitamin D

A second nutrient that has been closely linked to bone health is vitamin D. 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 (25-OHD) by the liver. 25-OHD 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 (1,25-OH_2D). Like calcium, 1,25-OH_2D is physiologically regulated and serum measurements do not reflect vitamin D status. The mechanism by which vitamin D has been implicated in cancer prevention, immune response, and cell cycle regulation has been elucidated in recent years [8–10].

Vitamin D is essential for 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 25-OHD status [12]. Reduction in risk of fracture has been reported in 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].

Vitamin D Requirements

Vitamin D intake recommendations have been a source of considerable controversy in recent years. In 2011, the Food & Nutrition Board (Institute of Medicine) revised their recommendations to 600–800 IU daily [3], but that was challenged by several groups as being too low for optimal health [17–19]. 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 and work indoors are at greater risk of deficiency. The simplest way to assess vitamin D status is by checking 25-OHD 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 [20]. 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 also fortified with a small amount of the vitamin.

Sun

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.

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 [21]. Moreover, the light source may also generate UVA rays which can cause skin aging.

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 25-OHD levels [22–24]. 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 25-OHD level. In calculating supplement dose for a normal weight person, a good rule of thumb is 100–150 IU daily will raise 25-OHD 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 D_3 dose (IU) = [Weight (kg) * desired change in 25-(OH)D * 2.5] − 10 [25]. Occasionally, patients with malabsorption or gastrointestinal surgery may require substantially more vitamin D and in this case the 25-OHD 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 daily seems to be adequate for many patients and is a good place to start without 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 25-OHD levels <200 ng/mL were not associated with toxicity and concluded that the tolerable upper limit should be 10,000 IU daily [26]. The IOM used a more conservative tolerable upper limit of 4000 IU daily [3]. We find in practice that we occasionally need to give >10,000 IU daily to particular patients who have obvious reasons for malabsorption.

Other Vitamins

There are other vitamins besides vitamin D which might contribute to healthy bones. One of these is vitamin K. This vitamin is best known for its role in blood clotting, but there is new evidence to suggest that it 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 was 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 (K_1) is found mostly in leafy green vegetables, such as spinach, broccoli, and kale. 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. Vitamin K 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 doesn't 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 anti-coagulation medications are often advised to limit their intake of these types of foods. Patients taking these types of medications should work with their healthcare providers to make sure their diet contains adequate amounts of healthy nutrients.

Protein

Bone is one of the most protein-dense tissues. When bone is remodeled and new bone is laid down, it requires additional 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 (amino acids) and through its effects on insulin-like growth factor. In the Framingham Study, age-related bone loss was inversely related to protein intake [27]. In a calcium intervention trial, only subjects with the highest protein intake and calcium supplementation gained bone [28]. In patients with hip fractures, mortality and recovery is improved if the patients have adequate protein intake (≈1 g protein/kg body weight/day) [29].

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 allowances (RDA) for protein for adults is 0.8 g of protein 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 people eating a weight-reduction diet. Another problem group is older women who eat poorly: 10% of women >60 years and 15% of women >80 years consume <70% of the RDA for phosphorus. 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 half 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.

Summary

In summary, bone requires many nutrients obtained from the diet for remodeling and maintaining the bony structure. We have emphasized calcium and vitamin D in this chapter, but protein and phosphorus are also important. A balanced variety of foods is a key factor in intake and supplements should not be relied on exclusively for meeting the needs of the skeleton.

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Suggested Further Reading

Center for Disease Control. Calcium supplement facts sheet. https://ods.od.nih.gov/factsheets/Calcium-HealthProfessional/.
International Osteoporosis Foundation. Nutrition. http://www.iofbonehealth.org/nutrition.
National Osteoporosis Foundation. Food and your bones. http://nof.org/foods.
Up-to-date calcium and vitamin D for bone health. http://www.uptodate.com/contents/calcium-and-vitamin-d-for-bone-health-beyond-the-basics.

Chapter 19
Diet, Physical Activity, and Cancer Prevention

Elaine B. Trujillo, Sharon A. Ross, and Cindy D. Davis

Key Points

- Achieve and maintain a healthy weight throughout life; this is one of the most important ways to reduce cancer risk.
- Eat mostly foods of plant origin, including at least 2–2½ cups (14–20 oz or 400–575 g) of a variety of non-starchy vegetables and fruits. Eat whole grains and/or legumes with every meal, and limit refined starchy foods.
- Limit consumption of red meat to 18 oz (510 g) per week and limit processed meat consumption.
- Limit daily alcoholic drinks to two drinks a day for men and one for women.
- Minimize sedentary behavior and engage in regular physical activity of all types, including occupational, household, transport, and recreational for cancer prevention.
- Cancer survivors should follow the recommendations for cancer prevention regarding diet, body weight, and physical activity.

Keywords Cancer • Diet and prevention • Body mass index • Phytochemicals • Meat • Alcohol

Introduction

Cancer is a leading cause of death in the USA. *Cancer* is a general term that represents more than 100 diseases, each with their own etiology. Cancer risk is influenced by both genetic and environmental factors including dietary habits. While each type of cancer has unique characteristics, all cancers share one common feature, unregulated cell division. All cancers begin when a single cell acquires multiple genetic changes and loses control of its normal growth and replication processes. The cancer process, which can occur over decades, includes fundamental, yet diverse, wide cellular processes, such as cellular differentiation, cellular proliferation/signaling, and apoptosis [1]. These processes can be influenced by diet.

E.B. Trujillo, M.S., R.D.N. (✉) • S.A. Ross, Ph.D., M.P.H.
Division of Cancer Prevention, National Cancer Institute,
National Institutes of Health, Rockville, MD 20850, USA
e-mail: trujille@mail.nih.gov

C.D. Davis, Ph.D.
Office of Dietary Supplements, National Institutes of Health, Rockville, MD, USA

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Evidence continues to mount that altering dietary habits is an effective and cost-efficient approach for both reducing cancer risk and modifying the biological behavior of tumors [2]. The importance of diet was emphasized more than a quarter century ago when Doll and Peto [3] suggested that approximately 35% (10–70%) of all cancers in the USA might be attributable to dietary factors. In 2007, similar conclusions were reached by the World Cancer Research Fund/American Institute of Cancer Research (WCRF/AICR) in the most comprehensive evidence-based report on the role of food, nutrition, and cancer prevention; the report concluded that diet and physical activity were major determinants of cancer risk [2]. On a global scale, diet and physical activity could potentially prevent over three to four million cancer cases each year [2]. The WCRF/AICR provides an ongoing update of diet, nutrition, and physical activity and cancer risk through the Continuous Update Project [4].

The American Cancer Society's (ACS) latest annual report on cancer incidence, mortality, and survival indicates a 23% drop in the cancer death rate since its peak in 1991; overall, cancer incidence is stable in women and declining by 3.1% per year in men. This trend is thought to be due to steady reductions in smoking combined with advances in cancer prevention, early detection, and treatment of some of the leading causes of cancer death [5]. Greater attention to environmental factors, such as dietary habits and smoking, holds promise to make even greater reductions in cancer rates. Cancer is no longer being viewed as an inevitable consequence of aging. Only about 5–10% of cancers can be classified as familial. The capability of utilizing smoking cessation, food and nutrition strategies, and the promotion of physical activity suggests that cancer is a largely preventable disease.

While considerable evidence points to diet as a critical factor in determining cancer risk, there are numerous inconsistencies in the literature. Much of this variation in response may relate to the genetic background of the individual which can markedly influence the response to specific foods [6]. By utilizing genetic information, we may be able to identify those individuals who must assure an adequate intake of a particular nutrient for cancer prevention. For example, dietary calcium can interact with a polymorphism in the vitamin D receptor (the *Fok 1* restriction site) to affect colon cancer risk. In this example, dietary calcium was not associated with colon cancer risk in individuals who were homozygous for the capital F genotype for the vitamin D receptor, but low dietary calcium was found to be associated with increased colon cancer risk with increased copies of the little f allele for the vitamin D receptor [6]. Selected polymorphisms may also be useful as surrogate markers for those who might be placed at risk from excessive exposures. However, the existence of about 30,000 genes and many million single nucleotide polymorphisms indicate that understanding individual responses to foods or components is extremely complicated.

Overweight and Obesity

The latest estimates from the Center for Disease Control and Prevention (CDC) show that obesity rates among adults rose to almost 38% in 2013/2014, up from 35% in 2011/2012 [7]. Excess body weight has been suggested as a risk factor for most, but not all, cancers [8]. On the other hand, overweight and obesity are protective against lung cancer, especially in current and former smokers [9]. In addition to differences in cancer etiology, the lack of an association across all cancers may reflect the imprecision in using body mass index (BMI) as a surrogate risk marker. BMI is the most common marker for overweight and obesity; overweight and obesity are defined as a BMI >25 and >30, respectively. BMI has been shown to correlate with direct body fat measures. However, in older persons or those who have muscle loss or wasting, BMI may indicate a lesser degree of body fatness than is actually the case and, conversely, BMI may reflect a higher degree of body fatness in persons with higher lean body mass.

The use of biomarkers of the metabolic syndrome holds promise for determining which shifts in body energetics are likely contributing to increased cancer risk or changes in the behavior of tumors [10]. Regardless, the WCRF/AICR panel judged the evidence as convincing that greater body fatness is a cause of cancers of the esophagus, pancreas, colorectum, postmenopausal breast, endometrium, and kidney [2, 4]. Greater body fatness is probably a cause of cancer of the gallbladder, both directly and indirectly, through the formation of gallstones [2]. Location of body fat also appears important since intra-abdominal visceral fat accumulation may be more detrimental than peripheral subcutaneous fat accumulations [8]. Hence, a high waist circumference may be especially hazardous.

Energy balance is often used to describe the complex interaction between diet, physical activity, and genetics on growth and body weight over an individual's lifetime. The influence of energy balance on cancer risk involves many potential interrelated mechanisms, including insulin resistance, altered sex hormone metabolism, and increased inflammation (Fig. 19.1).

Early in the twentieth century, research began to emerge that caloric restriction was an effective strategy for increasing longevity and decreasing cancer risk. Caloric restriction has several favorable effects on cancer processes including decreased mitogenic response, increased rates of apoptosis, reduced inflammatory response, induction of DNA repair enzymes, altered drug-metabolizing enzyme expression, and modified cell-mediated immune function [10]. At least parts of these anticancer properties associated with caloric restriction likely involve changes in the IGF-1 pathway [10]. Modalities for the treatment of the metabolic syndrome, such as bariatric surgery and metformin, also may mitigate cancer development through altering IGF-1 [11]. Attainment and maintenance of a healthy body weight throughout life may be one important way to protect against cancer and other common chronic diseases including hypertension and stroke, type 2 diabetes, and coronary heart disease.

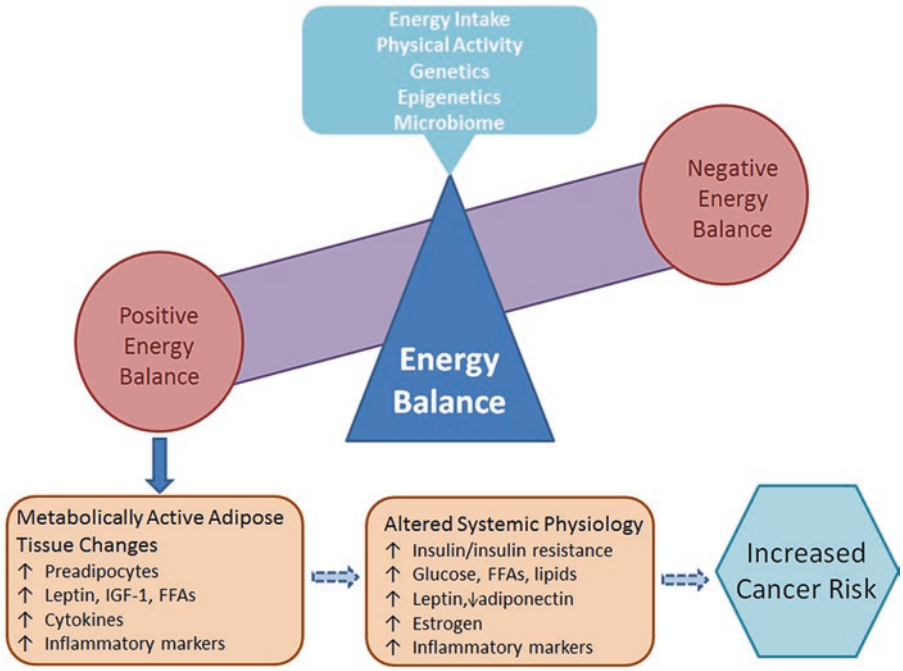

Fig. 19.1 Long-term positive energy balance due to excessive energy intake and/or low levels of energy expenditure can lead to obesity. The metabolic consequences of long-term positive energy balance and the accumulation of excessive body fat include increased IGF-1, insulin, and leptin concentrations. These effects can stimulate cellular proliferation, inhibit apoptosis, increase insulin resistance, alter steroid hormone metabolism, and stimulate inflammatory/oxidative stress processes, all of which can contribute to increased cancer risk [8]

A major challenge in understanding the complex relationship between obesity and cancer is determining which host characteristics are causative and which are associative. Recent research suggests that obesity is associated with alterations in the gut microbiome [12], but it is not yet clear whether these obesity-microbiome changes cause the increased cancer risk associated with obesity. The human gastrointestinal tract harbors trillions of microorganisms, most of which are commensal and have adapted over time to the milieu of the human colon. The mutualistic relationship between the intestinal microbiota, particularly bacteria, and their mammalian host is thought to be influenced, at least in part, by diet. Consumption of various nutrients and other food components affects the structure of the microbial community and provides substrates for microbial metabolism. Eating patterns modify microbial community structure, and microorganisms can also generate new compounds from food components. Some of these compounds are beneficial while others may be harmful. Many of the specific bacterial taxa, as well as microbially generated metabolites, may have a role in health and disease development including obesity and cancer.

Physical Activity

A key variable in the energy balance equation is energy expended via physical activity. Despite the numerous health benefits associated with physical activity, Americans are not incorporating enough physical activity into their daily routines. The CDC estimates that less than half of all adults meet the 2008 Physical Activity Guidelines and that less than three in ten high school students get at least 60 min of physical activity every day [13]. Overall, industrialization, urbanization, and mechanization have fostered a largely sedentary population in many parts of the world.

Regular, sustained physical activity protects against cancer of some sites independent of its effects on body fatness [2]. The WCRF/AICR panel found convincing evidence that physical activity protects against colon cancer [2, 4]. It probably also protects against endometrial and postmenopausal breast cancer; however, the evidence for premenopausal breast cancer is limited [2, 4]. Because physical activity promotes a healthy body weight, physical activity also likely protects against those cancers whose risk is increased by obesity.

Physical activity may influence cancer development through multiple, perhaps overlapping, biological pathways, several of which are mentioned in Fig. 19.1. Physical activity promotes regular bowel movements, which may decrease the time the colon is exposed to potential carcinogens. Additionally, physical activity causes changes in insulin resistance, metabolism, and hormone levels, which may help prevent tumor development, and alters a number of inflammatory and immune factors [14].

The WCRF/AICR recommends that individuals should be moderately physically active, equivalent to brisk walking for at least 30 min every day. As fitness improves, individuals should aim for at least 60 min of moderate activity, or 30 min of more vigorous physical activity, everyday [2].

Plant Foods

Evidence that plant foods protect against cancer comes principally from epidemiological, animal, and cell culture studies. Plant-based diets are high in nutrients and dietary fiber, low in energy density, rich in phytochemicals, vitamins, and minerals, and are associated with protection from various cancers. Phytochemicals refer to a variety of plant components that often perform important functions in the plant, such as providing color, flavor, or protection. The phytochemical composition of fruits and vegetables depends on the species and the subtype, as well as the environmental, cultivation, growing, harvesting, and storage conditions. Many of the health benefits, including cancer prevention, of diets rich in fruits and vegetables are due, in part, to the presence of multiple phytochemicals (Table 19.1).

Table 19.1 Selected dietary compounds and cancer risk

Phytochemical/nutrient	Dietary sources	Cancer effect [↑, ↓, I]	Potential cancer site[s]	Comments
Phytochemicals				
Allyl sulfur compounds	Onions, garlic, leeks, chives	↓	Stomach, CRC	Although compounds in garlic demonstrate anticancer activity, there is insufficient clinical evidence for recommending garlic supplements
Carotenoids	Citrus fruit, carrots, squash, pumpkin	↓	Mouth, pharynx, larynx, lung	
β-Carotene	Green leafy vegetables, carrots, pumpkin, sweet potatoes, squash, spinach, apricots, cantaloupe, pink grapefruit, green peppers	↓	Esophageal	
		↑	Lung	Evidence is from high-dose β-carotene supplements
Lycopene	Tomatoes, tomato products, guava, watermelon, pink grapefruit, apricots	**I**	Prostate	Epidemiological studies suggest that consuming foods containing lycopene decreases prostate cancer risk, interventional studies do not confirm the effect
Phytates, lignin, plant stanols, sterols	Whole grain and cereal products	↓	CRC, stomach	
Quercetin	Onion, red grapes, citrus fruit, broccoli	↓	Lung	
Soy isoflavones [genistein and daidzein]	Soybeans	**I**	Breast	Because of the potential to stimulate growth of estrogen-dependent human tumor cells [in animals], women on antiestrogen treatments should avoid soy isoflavone supplementation. No risk associated with soy isoflavones from food. Foods containing soy may decrease all-cause mortality in cancer survivors
Nutrients				
Calcium	Milk, cheese and other dairy products	↓	CRC	Milk [from cows] and supplemental calcium [1200 mg/day] probably decrease CRC risk; cheese may increase CRC risk
Folate	Vegetables [especially dark green leafy vegetables], fruits, and liver	↓	Pancreatic, esophageal, CRC	Folic acid is the supplemented form of folate and is added to bread and grain products to decrease occurrence of neural tube defects in newborns

(continued)

Table 19.1 (continued)

Phytochemical/nutrient	Dietary sources	Cancer effect [↑, ↓, I]	Potential cancer site[s]	Comments
n-3 Fatty acids	Fish [salmon, tuna]	**I for ↓**	CRC	Evidence refers to n-3 fatty acids from fish [DHA and EPA, not alpha-linolenic acid found in flax, soy, walnuts]
n-6 Fatty acids	Vegetable oils [corn, soybean, sunflower], salad dressings	**I for ↑**	Breast	WINS trial found that reducing dietary fat intake to 20% calories from fat with weight loss may reduce breast cancer recurrence, especially in women with ER disease
Selenium	Seafood, organ meats, muscle meats, cereals and other grains, dairy products, poultry, fish, eggs	↓	Prostate, stomach, lung, CRC	AICR CUP downgraded evidence for prostate cancer risk from strong to no conclusions
		↑	Prostate	SELECT trial found that high dose selenium supplements doubled the risk of developing high-grade cancer in men who started the trial with high selenium levels
Vitamin B6 [pyridoxine]	Fish, beef liver, organ meats, starchy vegetables, fruit [other than citrus], fortified cereals, beef, poultry	↓	Esophageal	
Vitamin C	Fruits and vegetables: citrus fruits, tomatoes and tomato juice, potatoes, red and green peppers, kiwifruit, broccoli, strawberries, Brussels sprouts, cantaloupe	↓	Esophageal	
Vitamin D	Fortified dairy products, eggs, mushrooms, fish	**I**		2014 US Preventive Services Task Force: no conclusions could be drawn regarding the benefits or harms for cancer prevention
		↓	CRC	
Vitamin E	Nuts, seeds, vegetable oils, green leafy vegetables, fortified cereals	↓	Esophageal, prostate	

(continued)

Table 19.1 (continued)

Phytochemical/nutrient	Dietary sources	Cancer effect [↑, ↓, I]	Potential cancer site[s]	Comments
Macronutrients				
Fat	Dietary fats from plant and animal foods	↑	Lung, postmenopausal breast, CRC	Total fat may increase risk of lung and postmenopausal breast; animal fat may increase risk of CRC
Fiber	Whole grains, fruits, vegetables, legumes	↓	CRC, breast	Fiber may decrease all-cause mortality for cancer survivors
Sugar	Sugar in foods [juices, milk, honey, syrups, high-fructose corn syrup], sugars added to foods [sugar-sweetened beverages, baked goods, cereals, canned products]	↑	CRC	
Specific foods/beverages				
Alcohol	Beers, wines, spirits/liquors	↑	CRC, mouth, pharynx, larynx, esophageal, postmenopausal breast, liver	
		↓	Kidney	Alcohol intakes up to 30 g/day [about two drinks]
Coffee	Coffee beverages from ground, roasted coffee beans	↓	Endometrial, liver	
Legumes	Beans, lentils, peas, peanuts	↓	Prostate, stomach	
Processed meat	Ham, bacon, hot dogs, pastrami, salami, sausages	↑	CRC, esophageal, lung, stomach, prostate	Convincing for CRC
Red and processed meat	Beef, lamb, pork, goat	↑	CRC, stomach, esophagus, lung, pancreas, endometrial	Convincing for CRC
Salt and salty foods	Added table salt, salt-preserved foods [salted meat, fish, vegetables], salty processed foods [chips, nuts, snack foods]	↑	Stomach	

↑ increased cancer risk, ↓ decreased cancer risk, *I* inconclusive effects on cancer risk, *CRC* colorectal cancer, *ER* estrogen receptor, *DHA* docosahexaenoic acid, *EPA* eicosapentaenoic acid
Source: Refs. [2, 4, 15, 16, 28–30]

Vegetables, particularly the non-starchy vegetables, and fruits may be protective for a variety of cancers, notably stomach, colorectal, mouth, pharynx, larynx, lung, esophageal, and pancreatic [2]. While these relationships are based on the epidemiologic literature, there are a number of limitations that are specific to the analysis of dietary intake of fruit and vegetables, including: most studies of consumption of dietary fruit and vegetables have been conducted in populations with relatively homogeneous diets; smokers consume less fruit and vegetables than nonsmokers; fat intake inversely correlates with fruit and vegetable intake in the United States; and studies using self-reporting tend to overreport vegetable and fruit consumption. Thus, many uncertainties exist about the relationship between plant-based diets and cancer prevention.

The magnitude of the response to vegetables and fruits and other dietary components is probably influenced by many factors, including individual genetic background and a host of environmental factors, as well as the type, quantity, and duration of consumption of these foods, and interactions among food components. The allium family, which contains about 500 food species including garlic, onion, leeks, and chives, illustrates the complexity of food. The allyl sulfur compounds within the allium family are thought to contain anticancer properties. However, these foods also contain many other potentially protective constituents, including amino acids, carbohydrates, and flavonoids. Similarly, other foods contain multitude phytochemicals that make drawing conclusions about the health benefits of a single compound in a food difficult.

Common green, yellow, red, and orange vegetables and fruits contain a variety of carotenoids, including lutein, zeaxanthin, cryptoxanthin, lycopene, β-carotene, and α-carotene. Carotenoid intake is associated with reduced risk of cancer of the mouth, pharynx, larynx, and lung [2]. Although epidemiological studies reported that high intakes of β-carotene-rich fruits and vegetables or high plasma concentrations of the β-carotene are inversely associated with lung cancer risk [2], in two randomized intervention trials, the intake of β-carotene supplements were found to have adverse effects. The α-Tocopherol β-Carotene Study (ATBC) and the β-Carotene and Retinol Efficacy Trial (CARET) showed increased lung cancer incidence in high-risk subjects (active smokers) [15, 16]. Unlike β-carotene supplements, β-carotene-rich vegetables and fruits contain many other compounds that may be protective against cancer, which may explain the variability seen in these studies. In fact, β-carotene may simply be a marker for the actual protective substances in vegetables and fruit. Alternatively, the protective effect at dietary intake amounts of carotenoids may be lost or reversed at the pharmacological levels found in supplements. The ATBC and CARET studies illustrate that consumption of supplements for cancer prevention might have unexpected adverse effects in certain populations and that definitive evidence for safety and efficacy is required before dietary supplementation guidance can be proposed.

Folate, an essential B vitamin found in dark green leafy vegetables, legumes, and fruits, serves as an example for the importance of diet–gene interactions. The mechanisms by which folate can modulate carcinogenesis are related to the sole biochemical function of folate—mediating the transfer of one-carbon moieties. In this role, folate is an important factor in DNA synthesis, stability, integrity, and repair. Evidence from cell culture, animal, and human studies indicates that folate deficiency is associated with DNA strand breaks, impaired DNA repair, and increased mutations. Folic acid, the supplement form of this vitamin, can correct some of the defects induced by folate deficiency. Epidemiologic and intervention studies support the role of folate in reducing the risk of colorectal cancer [2]. However, a common polymorphism in methylenetetrahydrofolate reductase (MTHFR) can potentially modify the effect of folate on colorectal cancer risk. Several MTHFR genes appear to influence colorectal cancer risk. MTHFR 677C>T has been studied extensively and is most strongly related to colorectal cancer risk, though not for risk of colorectal adenoma [17]. Furthermore, other MTHFR polymorphisms, combined with low plasma folate levels, may increase colorectal cancer risk [18]. Possibly 50–100 genes, either directly or indirectly, are involved with folate metabolism, which illustrates the complexity of diet–gene interactions. Not all individuals respond identically to folate

and other bioactive food components. A further understanding of the genetics of folate metabolism will clarify the optimal quantity of folate intake at a population and potentially individual level.

Whole grain intake also has been linked to a reduction in cancer risk, particularly those of the colon/rectum and stomach. Benefits attributed to whole grain consumption are observed at relatively low intakes (between two and three servings per day). However, in some Western countries, typical consumption of whole grain foods is less than one serving per day. Brown rice, bulgur, pearl barley, whole grain corn, whole oats, whole rye, and whole wheat are widely available whole grains in the USA. Unraveling the effects of grains is complicated by the fact that individuals consuming enhanced quantities of whole grains and cereal fibers have better health status, lower BMIs, lower intakes of alcohol and red meat, smoke less, and are more physically active [19]. Several compounds, including phytate, phytoestrogens such as lignan, plant stanols, and sterols, and several vitamins and minerals, present in whole grains may contribute to the observed lower risk of cancer. Additionally, the high fiber content of whole grains, and also of fruit and vegetables, is satiating and therefore helps prevent overconsumption of energy and may explain in part their anti-carcinogenic properties.

Just as individual foods are complex, containing multiple phytochemicals that may affect health and disease risk, the diet and dietary pattern is also complex and may affect disease risk. Individuals eat varying quantities, proportions, and combinations of foods and beverages at different frequencies. How various dietary patterns affect disease risk is an emerging area of nutrition research.

The Dietary Patterns Methods Project (DPMP) analyzed the association of select dietary patterns as characterized by dietary quality indices and mortality outcomes using three large cohort studies in the USA. Using four dietary indices commonly used in the USA, the Healthy Eating Index 2010, the Alternative Healthy Eating Index 2010, the alternate Mediterranean Diet score, and the Dietary Approaches to Stop Hypertension score, the DPMP found that high dietary quality scores were associated with a 19–24% and a 11–23% lower cancer mortality in men and women, respectively [20].

Several leading organizations provide public guidance on the optimal diet for cancer prevention. According to the WCRF/AICR, the ACS, and the World Health Organization, a cancer prevention diet is plant-based and includes vegetables and fruits, legumes, whole grains, and nuts [2, 21, 22]. Specifically, the guidelines include consuming 2–2½ cups (14–20 oz or 400–574 g) of a variety of non-starchy vegetables and fruits daily, and foods prepared with whole grains instead of refined grains [2, 21, 22].

Meat Intake

Meat, including all animal flesh apart from fish and seafood, can be classified as red or white. White meat is generally poultry and usually has more white than red muscle fibers. Red meat is unprocessed mammalian muscle meat, including beef, veal, pork, lamb, mutton, horse, or goat meat. Processed meat refers to meats preserved by smoking, curing, salting, or addition of chemical preservatives [2]. In 2015, the International Agency for Research on Cancer (IARC) concluded that there is sufficient evidence to conclude that processed meat is carcinogenic in humans; they classified the consumption of processed meat as a Group 1 carcinogen. These conclusions were based on the weight of evidence for colorectal cancer. A positive association was also found between the consumption of processed meat and stomach cancer. In regard to red meat consumption, the IARC found limited evidence for carcinogenicity; consumption of red meat was classified as Group 2A, probably carcinogenic to humans [23].

A range of mechanisms may account for the observed relationship between meat consumption and colorectal cancer risk. Cooking methods may foster the formation of carcinogens including polycyclic aromatic hydrocarbons (PAHs) and heterocyclic amines (HCAs) [23]. The formation of PAHs and HCAs is dependent on cooking time and temperature; the amounts of these compounds are increased

in meats that are cooked at high temperatures until well done [24]. PAHs are formed from the pyrolysis of fats that occurs when fat drips from meat onto hot coals, forming smoke that is redeposited on the meat surface. HCAs are formed during high-temperature cooking by the reaction between creatinine or creatinine, amino acids, and sugars found in muscle meats [24]. In view of the possible role of PAHs and HCAs in human carcinogenesis, minimizing exposure, such as by avoiding overheating and overcooking, seems prudent.

Nitrites and nitrates are often used as preservatives in meats and add the red-pink color to cured meats. These additives are not carcinogenic, but they can interact with dietary substances such as amines or amides to produce *N*-nitroso compounds which are carcinogenic to humans [24]. Several naturally occurring foods and their constituents, including tea, garlic, and cruciferous vegetables, may inhibit the formation of endogenous nitrosamines. This reduction in carcinogen formation may contribute to the generally protective effect of fruit and vegetables on cancer risk.

Iron deficiency is the most common and widespread nutritional deficiency in the world. Heme iron from animal sources is better absorbed than iron from plant sources, and thus animal food is important in minimizing iron deficiency. However, heme iron can act as a catalyst in the formation of *N*-nitroso compounds in the gut and may increase cell proliferation in the mucosa [24]. Environmental pollutants, such as some heavy metals, polychlorinated dibenzo-*p*-dioxins, and dibenzofurans, dioxin-like polychlorinated biphenyls, and others contained in raw or unprocessed meat, may play a role in carcinogenesis [25]. Genetic mutations and diet–gene interactions with red meat intake also may make individuals and/or populations susceptible to increased cancer risk, particularly colorectal cancer.

Meat can be a valuable source of many nutrients, including protein, iron, zinc, selenium, and vitamins B_6 and B_{12}. Therefore, consumption of red meat in moderation can be part of a healthy diet. Cancer prevention guidelines include moderate consumption of red meat, if eaten at all, and suggest limiting intake to less than 18 oz (510 g) per week. Very little, if any, processed meat is recommended [2, 21].

Alcohol

Dietary alcohol (ethanol) has been classified by the IARC as a human carcinogen [26]. It is both a source of dietary energy and a drug, and can therefore influence both mental and physical performance. The WCRF/AICR panel judged that there is convincing evidence that alcoholic drinks increase cancer of the mouth, pharynx and larynx, esophagus, colorectum (men), and breast [2, 4]. Alcoholic drinks are probably also a cause of liver and colorectal cancers in women [2, 4]. Conversely, evidence suggests that moderate alcohol intake may decrease the risk of kidney cancer [2, 4]. The type of beverage consumed does not appear to influence risk and thus total alcohol appears to be the primary agent leading to the transformation of cells to neoplastic lesions.

Acetaldehyde, the first and most toxic metabolite of alcohol metabolism, is particularly damaging to cells. It reacts with DNA in experimental animals to form cancer-promoting compounds [27]. In addition, highly reactive, oxygen-containing molecules formed during alcohol metabolism can damage DNA, thus promoting tumor development. Experimentally, chronic alcohol consumption has been reported to promote tumor proliferation via increased vascular endothelial growth factor expression and tumor angiogenesis [27]. Considerable evidence also points to the ability of alcohol to alter retinoid metabolism and thus interfere with differentiation. A change in DNA methylation may be an overarching factor accounting for changes in multiple cancer-related processes [27]. The response to alcohol may depend on multiple factors including smoking, adequacy of the diet, and genetic susceptibility. A true understanding of the effect of dietary alcohol may be clouded because of the compounds found in alcohol, which can both promote and potentially suppress tumorigenesis.

Conclusions

Accumulating evidence continues to demonstrate that food can have a profound effect on cancer risk and tumor behavior. The overall response is likely dependent on literally thousands of bioactive components that occur in food and their interactions with other environmental factors, the gut microbiota, and the consumer's genetics. These effects, which may be inhibitory or stimulatory depending on the specific bioactive food component, are mediated through diverse biological mechanisms. The identification and elucidation of the specific molecular sites for food components is critical for identifying those who will benefit maximally or be placed at risk from excess exposure. Until this information is available it remains prudent to eat a variety of foods and to maintain a healthy weight through controlling caloric intake and exercise.

Expanding knowledge about the physiological consequences of nutrigenomics—which includes nutrigenetic (genetic profiles that modulate the response to food components), nutritional transcriptomics (influence of food components on gene expression profiles), and nutritional epigenomics (influence of food components on DNA methylation and other epigenetic events and vice versa)—should help identify those who will and will not respond to particular dietary interventions. New reports are constantly surfacing that population studies are underestimating the significance of diet in overall cancer prevention and therapy and that subpopulations may be particularly sensitive to subtle changes in eating behaviors. To identify those who will benefit most from dietary change, more attention needs to be given to the identification of three types of biomarkers: (1) those reflecting exposures needed to bring about a desired response; (2) those which indicate a change in a physiologically relevant biological process which is linked to cancer; and (3) those which can be used to predict a personalized susceptibility based on nutrient–nutrient interactions and gene–nutrient interactions.

As the science of nutrition unfolds, a clearer understanding will surely emerge about how food components modulate cancer, and how the food supply might be modified through agronomic approaches and/or biotechnology. While the challenges to unraveling the relationships between diet and cancer prevention are enormous, so is the societal and health benefits that will occur because of these discoveries.

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Suggested Further Reading

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Part III
Food, the Substances in Food, and Their Effects on Health

Chapter 20
Vegetarian and Vegan Diets: Weighing the Claims

Caroline McGirr, Claire T. McEvoy, and Jayne V. Woodside

Key Points

- Between 1 and 10% of the population in developed countries are thought to be vegetarian. Women are more likely to be vegetarian than men. Vegetarian and vegan diets are heterogeneous in nature, which makes provision of dietary recommendations difficult.
- Populations following vegetarian diets have potential health benefits including reduced risk of coronary heart disease and obesity.
- Very restrictive or unbalanced vegetarian diets can result in nutrient deficiencies particularly iron, calcium, zinc, and vitamins B_{12} and D.
- Carefully planned vegetarian and vegan diets can provide adequate nutrition for all stages of life.

Keywords Vegetarian • Vegan • Nutrient status

Introduction

Vegetarian diets are becoming increasingly popular in developed countries. While no reliable prevalence data for vegetarian populations exist, results of polls and surveys have reported population prevalence of between 1 and 10% in the European Union, the United States, and Canada [1]. A recent study in the United States reported that 2.8% of respondents never ate meat, poultry, fish, or other seafood, although 4–10% would classify themselves as vegetarian [2]. Vegetarian diets are often heterogeneous in nature, involving a wide range of dietary practices. These are summarized in Table 20.1. Even within classifications of dietary practices, there can be a high level of variability depending on the individual dietary restriction(s). Vegetarian or vegan diets may be practiced for a variety of reasons, including health, cultural, philosophical, religious, and ecological beliefs, or simply because of taste preferences. This chapter will discuss vegetarian and vegan diets and their impact on human health.

C. McGirr, B.Sc. • C.T. McEvoy, Ph.D. • J.V. Woodside, Ph.D. (✉)
Institute for Global Food Security (Centre for Public Health), Queen's University Belfast, Belfast, Northern Ireland BT12 6BJ, UK
e-mail: j.woodside@qub.ac.uk

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Table 20.1 Classification of vegetarian and vegan diet

Vegetarian diet	Description
Semi- or Demi-	Excludes red meat. May exclude poultry. Fish is usually eaten
Pescetarian	Excludes red meat and poultry but eats fish and possibly shellfish
Lacto-ovo-	Excludes all meat, fish, and poultry. Milk, milk products, and eggs are usually eaten
Vegan	Consumes no food of animal origin. Eats plant food, grains, legumes, nuts, seeds, vegetable oils
Raw food	An extreme form of veganism with emphasis on organic, home-grown, or wild food in their raw or natural state. Usually comprises 80% by weight raw plants. Periods of fasting and laxative use may be practiced
Fruitarian	An extreme form of veganism which excludes all food of animal origin and also living plants. Diet is mainly raw: 70–80% fruit with small amounts of beans, bread, tofu, nuts, and seeds
Macrobiotic	This extreme diet progresses through ten levels becoming increasingly restrictive. It is based on 50–60% wholegrain, 25–30% fruit and vegetables (fruits can also be restricted), 5–10% beans and sea vegetables, and restricted beverages. Fish may be eaten initially 2–3 times per week Food may be gradually eliminated through the ten levels. At the final level, only cereal (brown rice) is eaten

Health Benefits of Vegetarian Diets

There has been renewed interest in the proposed benefit of plant-based diets in reducing the risk of chronic diseases such as cardiovascular disease (CVD), cancer, and type 2 diabetes. Mediterranean-style diets are associated with a reduced risk of CVD; this occurs through modification of known risk factors, including blood pressure, body mass index (BMI), insulin resistance, and lipid profiles. The Mediterranean diet is characterized by a moderate/low intake of red meat and an increased intake of olive oil, fresh fruit, vegetables, legumes, nuts, wholegrains, and oily fish. Balanced vegetarian diets also tend to be rich in complex carbohydrate, dietary fiber, $n-6$ fatty acids, folate, vitamins C and E, and magnesium. However, in contrast to a Mediterranean or omnivorous diet, vegetarian diets (particularly vegan diets) tend to be lower in protein, $n-3$ fatty acids, vitamin A and B_{12}, zinc, and calcium; this is due to the absence of red meat, animal protein, and/or dairy products.

Epidemiological evidence suggests that vegetarians have a relatively low mortality rate compared to the general Western population [3]. Much of this evidence comes from studies where different populations have been compared. However, we must at this point inject a note of caution. These studies have investigated health-conscious populations such as Seventh Day Adventists. Such populations not only have a high prevalence of vegetarianism, but also generally have numerous other lifestyle differences from the general population, including consuming little alcohol, having low rates of smoking, and possibly having increased levels of physical activity. These confounding factors make it difficult for epidemiologists to disentangle the role of vegetarianism from the other factors. Another line of research is prospective cohort studies, i.e., comparing vegetarians vs. omnivores within the same population and tracking the development of disease. In addition to nutritional differences, vegetarians typically have lifestyle differences from omnivores, making it extremely difficult to make definitive conclusions regarding the relationship between a vegetarian diet and risk of disease. The above problems also apply to studies on the relationship between vegetarianism and specific diseases, such as CVD and cancer.

Vegetarian Diets and Cardiovascular Disease

Systematic reviews of epidemiological studies have reported that vegetarians have a reduced risk of CVD mortality (i.e., both coronary heart disease (CHD) and stroke) when compared to omnivores [4, 5]. Generally, the lowest risk is seen in those eating fish but not meat. These findings may be explained, in part, by the observed differences in lipid profiles, blood pressure, and weight measures.

Vegetarian Diet and Serum Lipids

Vegetarians generally have lower serum levels of total cholesterol and low-density lipoprotein (LDL)-cholesterol when compared to omnivores [6]. This can be explained, to a large extent, by the fact that vegetarian diets, particularly vegan diets, tend to be lower in saturated fat and trans fat and higher in dietary fiber compared to omnivorous diets [7]. Vegetarian diets may also include many functional foods such as oats (β-glucans), psyllium, soy protein, and plant sterols, which have independent cardioprotective effects.

Nuts are consumed more frequently in vegetarian diets and they are inversely correlated with CHD risk. Nuts, especially almonds and hazelnuts, are high in monounsaturated fat and have produced appreciable reductions in LDL-cholesterol. This topic is also discussed in Chap. 11.

Vegetarian Diets and Blood Pressure

Vegetarian diets appear to reduce blood pressure, which is associated with the risk of CVD [7, 8]. Nonvegetarians, both normotensives and hypertensives, prescribed vegetarian diets demonstrate lower blood pressure. Furthermore, the prevalence of hypertension appears to be lower in vegetarian populations, especially vegans [9].

Important findings came from the Dietary Approaches to Stop Hypertension (DASH) study. The DASH diet had a significant lowering effect on blood pressure, independent of sodium intake, in both hypertensive and normotensive adults [10]. The DASH diet is largely plant-based, high in nuts, allows plenty of low-fat milk, recommends fish/chicken rather than red meat, and is low in saturated fat, cholesterol, and refined carbohydrates. The diet is therefore similar to a varied vegetarian diet.

Vegetarian Diets and Obesity

Vegetarians, and particularly vegans, have lower body weights than the general population, with a low prevalence of obesity [11, 12]. BMI is on average 1–2 kg/m^2 less in vegetarians and vegans compared with nonvegetarians [7, 11]. Actual nutrient intakes in vegetarian diets are discussed in more detail later in this chapter.

Cancer

It is widely recognized that dietary risk factors is one of the most important avoidable causes of cancer, after smoking. It has been suggested that approximately one third of cancer deaths can be avoided by changes in diet [13]. There is little scientific evidence evaluating whole dietary approaches in the prevention of cancer; therefore, limited recommendations advocating vegetarian diets can be made. However, there is some good evidence for a protective effect of some dietary components that are more likely to be consumed in greater frequency within a vegetarian diet. Fruit and vegetable intake have been found to be protective for certain cancers, particularly for mouth, esophageal, larynx, lung, gastric, and possibly prostate cancer [13, 14]. It is currently recommended that diets should include 400 g of total fruit and vegetables per day, which equates to about five servings [13, 14].

Additionally, there is a growing body of evidence demonstrating a very direct and positive relationship between red and processed meat consumption and colon cancer risk. A recent report by the International Agency for Research on Cancer [15] investigated relevant cohort and case-control

studies and concluded that there is evidence to support a carcinogenic effect of processed meat consumption, but limited evidence to support a carcinogenic effect of red meat consumption, although it is classified as 'probably carcinogenic' [15].

Type 2 Diabetes

Clinical studies investigating the impact of vegan/vegetarian diets in people with type 2 diabetes have shown significant reductions in fasting blood sugar, cholesterol, and triglyceride levels [16, 17]. Epidemiological studies have supported the hypothesis that vegetarian diets protect against type 2 diabetes [18]. Results of a cohort study with up to 433,000 participants reported that high intakes of red meat and processed meat are potential risk factors for the development of type 2 diabetes [19]. A meta-analysis, involving 442,101 participants and 28,228 incident diabetes cases, reported that daily consumption of 50 g processed red meat per day or 100 g unprocessed red meat per day was associated with a 51% and a 19% increase in the risk of type 2 diabetes, respectively [20]. Further clinical studies are, however, needed to assess the impact of vegetarian diets on outcome measurements and incidence in type 2 diabetes.

Bone Health

Adequate calcium intake is important for optimal bone mineral density. This is achievable for vegetarians consuming dairy products, but is more challenging for vegans. There is surprisingly little information regarding the long-term bone health of vegans, although there is some suggestion that bone mineral density may be reduced especially in those following macrobiotic and strict vegetarian diets. However, bone quality is also important for fracture prevention. There is a growing body of evidence suggesting that a diet high in fruit and vegetables and low in animal protein can reduce the renal acid load and therefore reduce calcium loss and bone resorption [21].

Nutrient Deficiencies in Vegetarian Diets

Carefully planned vegetarian and vegan diets can provide adequate nutrients for optimum health [22]. Evidence suggests that infants and children can be successfully reared on vegan and vegetarian diets [23, 24]. However, all dietary practices, including nonvegetarian diets, can be deleterious for health if essential nutrients are not consumed according to individual needs. Therefore, it is essential that vegetarian and vegan diets contain a balance of nutrients from a wide variety of food. If the diet becomes more restrictive, the risk of specific nutritional deficiencies increases. This is particularly the case for infants and children, and for women who are pregnant, lactating, or menstruating. Nutrients most likely to be deficient in unbalanced or very restrictive vegetarian diets are energy, protein, calcium, iron, zinc, iodine, vitamins A and B_{12}, and $n-3$ fatty acids. These are discussed in more detail below.

Energy

Energy intakes are comparable in vegetarian and nonvegetarians [25]. However, energy intake may be of concern in vegan infants and children, particularly those following macrobiotic or raw food diets. The growth rates of vegetarian children have been found to be similar to nonvegetarian

children [25]. However, vegan children can show a tendency for smaller stature when compared to a reference population; height measurements may still reside within normal limits and catch-up growth usually occurs by the age of 10 years [24]. In a UK study, vegan children, both boys and girls, were found to be slightly lighter than a reference population [23]. This may, of course, be advantageous. Failure to thrive in infants and children has been observed in extremely restrictive diets, such as fruitarian diets, and these diets are not recommended for children. Furthermore, protein-energy malnutrition and nutrient deficiencies have been reported in infants and children fed with inappropriate vegetarian diets [25]. The vegan diet is bulky, owing to an increased content of dietary fiber, which may cause early satiety in children, thereby limiting energy intake. Frequent meals and snacks, using soy protein, and alternative fat sources can be used to increase the energy density of the diet and support growth and development in vegan children. Nut and nut butters, which are calorific, can be introduced after 3 years [23].

Protein

Protein intakes tend to be lower in vegetarian and vegan adults and children [24, 25]. It is reported to be approximately 12% of energy intake, which is sufficient for nitrogen balance, *provided energy intake is adequate* [25]. Plant proteins tend to have lower biological values than animal protein and the protein is in a less utilizable form. However, when a wide range of plant protein is consumed (soy protein, textured vegetable protein, legumes, nuts, seeds, and grains), essential amino acid requirements can be adequately met. It is generally felt that there is no need for protein combining at mealtimes [24]. Protein requirements may be higher in vegan athletes, lactating or pregnant women, infants, and children. Infants should be breastfed exclusively for the first 6 months or a commercial soy-based formula used. Products such as home-prepared milks or milk from rice, nuts, or seeds should not be used to replace breast milk or commercial soy milk for infants under 1 year due to differences in macronutrient and micronutrient ratio. The weaning guidelines for vegetarian infants are the same as nonvegetarian infants [22]. Protein requirements are therefore likely to be met in vegan diets when adequate energy intake is consumed.

Calcium

Calcium intakes are adequate for lactovegetarians, but can be lower than recommended amounts in vegan adults and children [23, 24]. Good sources of calcium in vegan diets are shown in Table 20.2 [26, 27] and a general discussion on calcium and bone health can be found in Chap. 18.

When calcium intake is lower, intestinal absorption is greater; and adequate calcium intake for bone mass may therefore be achievable at a lower calcium intake. Additionally, high intake of protein, sodium, and caffeine increase body losses of calcium [28]. As vegans often have a reduced intake of these dietary components, they may therefore be able to conserve a higher proportion of dietary calcium intake than omnivores [25]. However, any advantage for calcium absorption in vegans could be offset by the high phytate and oxalate content of the vegan diet. Low oxalate green vegetables, such as cabbages, spring greens, and kale, have higher calcium bioavailability (49–61%) and should be consumed regularly by vegans [22]. For optimal calcium intake in vegetarians and vegans, the American Dietetic Association recommends a minimum of eight servings per day of bioavailable calcium foods, such as those listed in Table 20.2 [26]. This requirement may be greater in teenagers, and women who are lactating or pregnant.

Table 20.2 Main sources of nutrients in vegetarian/vegan diets [26]

Nutrient	Main vegetarian source	Amount per average serving	Notes
Calcium	Green vegetables (broccoli, cabbage, collard greens, bok choy, turnip greens, kale)	79–239 mg	Oxalate/phytate reduces bioavailability
	Fortified soy products (milk, yogurts, tofu, tempeh)	92–430 mg	Intestinal absorption increases when intake reduced
	Fortified cereals	55–315 mg	
	Dried figs (5)	137 mg	
	Almonds	88 mg	
	Sesame tahini	128 mg	
Iron	Cooked soybeans, tofu, tempeh	2.2–6.6 mg	Absorption of nonheme iron is enhanced by ascorbic acid, small amounts of alcohol, retinol, and carotenes
	Cooked legumes (lentils, chickpeas, adzuki, kidney)	2.2–3.3 mg	Absorption is inhibited by phytates, tannins/polyphenols, and soy protein
	Dried pumpkin/squash seeds, cashews, sunflower seeds, tahini	2.1–5.2 mg	
	Fortified cereal	2.1–18 mg	
	Baked potato (including skin)	2.3 mg	
Zinc	Soybeans (cooked/roasted), tofu, fortified veggie meats	1.0–4.2 mg	Phytate reduces bioavailability of zinc
	Baked beans, lentils, navy beans	1.8–2.3 mg	
	Pumpkin/squash seeds dried, cashews, sunflower seeds toasted	1.8–2.6 mg	
	Fortified cereal	0.7–15 mg	
	Wheat germ	1.8 mg	
	Cooked peas	1.0 mg	
Vitamin B_{12}	Fortified foods: cereal, yeast, soy milk	0.6–6.0 μg 1.5 μg 0.4–1.6 μg	Supplement may be required
Vitamin D	Fortified cereal	0.5–1.0 μg	Supplement may be required
	Fortified soymilk	0.5–1.5 μg	
	Vegan margarines	Variable	
n−3 fatty acids	Ground flaxseed	1.9–2.2 g	Supplement may be required
	Flaxseed oil	6.9 g [27]	
	Canola oil	1.3 g [27]	
	Cooked soy beans	0.5 g [27]	
	Walnuts	2.6 g [27]	

Iron

Iron deficiency can occur as a result of inadequate intake, but also because of poor absorption from the GI tract. An adequate intake of iron in vegetarians and vegans can easily be achieved, assuming their diet is balanced. However, plant sources of nonheme iron are less bioavailable than heme iron found in meat. Phytate, soy protein, and polyphenols/tannins within the plant-based diet can inhibit iron absorption. For that reason, it is recommended that iron intakes should be 1.8 times higher in vegetarians and vegans than in nonvegetarians [22]. Ascorbic acid, retinol, alcohol, and carotenes can enhance the absorption of nonheme iron.

The prevalence of iron deficiency anemia is no greater in vegetarians than in omnivores, although iron stores tend to be lower, especially in women [29]. Women of child-bearing age are at most risk. Dietary advice should focus on encouraging a variety of nonheme iron sources (cooked legumes, fortified breads and cereals, baked potatoes, soy proteins), encouraging high intakes of ascorbic acid with meals to aid absorption, and avoiding consumption of inhibitors, such as tea or coffee with meals. There is some tentative evidence that fermentation of soy proteins to produce miso and tempeh can reduce the phytate content and improve iron availability [22]. Additionally, iron cookware may be advocated, since significant amounts of iron dissolve in food [29].

Zinc

The majority of zinc in the Western diet comes together with animal proteins. Legumes, whole grains, nuts, and seeds are reasonable plant-substitute sources of zinc. However, the bioavailability of zinc is reduced by high levels of supplemental calcium and by phytate, which is also found in legumes, whole grains, nuts, and seeds. Vegetarians and vegans appear to have adequate zinc status, but lower serum levels than nonvegetarian counterparts [30]. Little is known regarding the effects of marginal zinc deficiency. Although adaptation to a low intake may occur over time, thanks to increased intestinal absorption [29], good plant sources of zinc, as shown in Table 20.2, should be encouraged.

Vitamin B_{12} (Cobalamin)

Vitamin B_{12} is required by the body in microgram amounts and is found only in food of animal origin. Deficiency of this vitamin is extremely rare as the human body stores several years' worth of it. Elderly and strict vegan individuals are most at risk. Deficiency of B_{12} can cause pernicious anemia and can result in megaloblastic anemia with central nervous system demyelination if not treated early. Symptoms in infants and children include irritability, failure to thrive, and feeding difficulties; prolonged deficiency can lead to permanent developmental disabilities [31, 32]. Diagnosing B_{12} deficiency prior to symptom development in vegetarians is difficult, usually due to a high folate intake masking the hematological signs of deficiency. Since folate intake is often higher in vegan diets, elevated serum methylmalonic acid, holo transcobalamin, and/or homocysteine may be more sensitive indicators of a B_{12} deficiency [32]. Purported plant-based sources (tempeh, algae extracts, and sea vegetables) have been found to contain more inactive corrinoids than true B_{12} [32] and thus they are not reliable sources of B_{12}. Risk of B_{12} deficiency in vegans is increased if their diet is not supplemented with fortified products (fortified yeast extract, fortified soy products, and some brands of breakfast cereals). It is recommended that vegans include three dietary sources of B_{12} per day. If this is not achievable, a daily supplement of 5–10 μg is recommended for adults [26]. Supplementation of 25–100 μg/day has been used to maintain vitamin B_{12} levels in older people. Unless the maternal diet is adequate in B_{12}, breastfed infants should receive 0.4 μg/day from birth to 6 months, and 0.5 μg/day after that time [23].

Vitamin D

If a person has adequate exposure to sunlight and normal liver function, the body can produce 25-hydroxyvitamin D. However, for many people, especially those in urban environments and during the winter months, dietary supplementation may be important because they do not receive adequate

exposure to sunlight. This is especially the case if living in high latitudes where there is less opportunity for sunlight exposure. Major dietary sources of vitamin D are limited to animal food. Vegans and those consuming very restrictive vegetarian diets are therefore at risk of deficiency. There have been reports of a high prevalence of rickets in children reared on macrobiotic diets [25]. Alternative dietary sources include fortified soy milks and cheeses and vegan margarines. In some cases, a vitamin D supplement may be required, particularly in children under 2 years and lactating mothers with inadequate vitamin D intake.

n–*3 Fatty Acids*

Vegetarian diets can be lower in *n*−3 fatty acids, in particular the marine fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), and higher in *n*−6 fatty acids (linoleic acid). α-Linolenic acid, the *n*−3 fatty acid found in plant foods, can be converted to EPA and DHA, but the rate of conversion is very low and can be further inhibited by a high intake of linoleic acid. These long-chain fatty acids are thought to be important for immune, cognitive, and cardiac function. Most studies show lower serum levels of EPA and DHA in vegans [33]. Good vegan sources of *n*−3 fatty acids include flaxseed and flaxseed oil, canola oil, walnuts, and/or vegan DHA supplements. For adults, intake of *n*−3 fatty acids should be 0.5–2% of total energy intake [34].

Summary

Many individuals and special interest groups claim that vegetarian diets can reduce the aging process, prolong life, and promote health and vitality. These claims are largely unsubstantiated in terms of reliable scientific evidence. However, vegetarian and vegan diets may be associated with improved health outcomes, especially for CHD and certain cancers. Vegetarian lifestyles often encompass attitudes and behaviors which can serve to improve overall health and well-being; for example, physical activity, not smoking, and limiting alcohol consumption.

It is widely recognized that over-reliance on one single food, or food group, will not provide the range of nutrients required for optimum health and well-being. This is the case for all diets—omnivorous, vegetarian, and vegan. All dietary practices should aim to meet current recommended nutrient intakes to prevent chronic diseases [34]. A diet low in fat, sugar, and salt and rich in fruit, vegetables, wholegrains, and dietary fiber is encouraged. Variety in individual diets is also important. If a particular food or food group is not consumed routinely, alternative nutrient sources should be included.

Vegetarian and vegan diets can be balanced and healthy for all stages of life, provided appropriate preparation and planning is given [22]. This is especially the case for groups at risk of nutrient deficiency including infants, small children, menstruating and lactating women, and athletes. Supplementation of vegan diets may be necessary if adequate intake of nutrients cannot be achieved.

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The Vegetarian Society provides information on vegetarianism, vegetarian books and recipes, and links to related sites. www.vegsoc.org

Chapter 21
Dietary Recommendations for Nonalcoholic Beverages

Ted Wilson and Kerrie Kaspar

Key Points

- Coffee and tea consumption imparts modest health benefits.
- Caffeine is ubiquitous for its effect on wakefulness and has a 3–6 h half-life.
- Fruit and vegetable juices can be a part of a balanced diet, if the consumer can remain mindful of their contributions to energy and possible salt intake.
- Milk consumption has slowly decreased as consumption of soft drinks has increased; health-care professionals should suggest that their clients reverse this consumption pattern.
- Nonnutritive (artificial) sweeteners may help reduce caloric intake, but their use may not be associated with improved weight loss.
- Meal replacement beverages are often used. They can be of value, especially for elderly people.
- Sports drinks can be of some value but many of their claimed benefits lack supporting scientific evidence.
- Energy drink consumption should be limited and can lead to problems with sleep, especially when large amounts of caffeine are ingested.

Keywords Beverages • Tea • Coffee • Caffeine • Milk • Fruit juices • Sports beverages • Aspartame

We Are (Mainly) What We Drink

Water represents as much as 60% of the body weight in a lean person and as little as 45% in the obese. The Dietary Recommended Intake (DRI) for water in non-exercising persons is 3.7 L/day for men and 2.7 L/day for women, with newborns and the elderly being most sensitive to dehydration. Beverages play a major role in determining hydration status and nutritional health.

T. Wilson, Ph.D. (✉)
Department of Biology, Winona State University, 232 Pasteur Hall, Winona, MN 54603, USA
e-mail: twilson@winona.edu

K. Kaspar, Ph.D.
Ocean Spray Cranberries, Inc., One Ocean Spray Drive, Lakeville-Middleboro, MA 02349, USA
e-mail: kkaspar@oceanspray.com

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Few clinical recommendations exist to help physicians guide patients in their understanding of the importance of beverages as part of nutritional health. This is surprising given that beverages provide about one-fifth of our daily caloric intake, with the greatest caloric intake occurring in 19–39-year-olds [1]. Beverages are widely variable in their nutrient content; they may contain carbohydrates, fats, and proteins, vitamins, and minerals, whose health effects are well understood, and polyphenolic compounds, whose effects on health are poorly understood. Beverages are also the main source of caffeine in the diet. The major health implications of alcohol are discussed in Chap. 22. This chapter provides a short review of the beneficial and detrimental effects of major nonalcoholic beverages, including coffee, tea, fruit juices, soft drinks, energy drinks, sports drinks, drinks for weight management, and water.

Coffee Consumption Poses No Health Risk for Most Persons

Approximately 75% of Americans aged >20 years drink coffee and they consume about 14 oz (1.8 cups or 417 mL) in an average day [2]. Low-to-moderate coffee consumption (≤3 cups/day) is safe for the typical consumer. Indeed, this level of consumption appears to be moderately protective against cognitive disorders (dementia, Alzheimer's, and cognitive decline) with the lowest risk ratio (RR) of 0.8 achieved at a daily intake of 1–2 cups [3]. Moderate coffee consumption has also been associated with neutral or moderately beneficial effects on cardiovascular disease (CVD) risk and overall mortality [4]. Recent evidence also suggests that coffee consumption may help prevent type 2 diabetes [5]. Epidemiological evidence shows that low-to-moderate levels of coffee intake impart little or no added risk for cancer and that the beverage may be mildly protective against cancer [4]. Taking the above evidence as a whole, a general guideline for coffee is a limit of 2–3 cups/day and an intake of 5 cups/day probably poses a negligible risk to health.

When estimating coffee consumption, it is important to consider the size of the container, the habit of refilling the cup, the variability of coffee drinking between different days (weekdays/weekends), and seasonal differences in intake. The method used to prepare coffee from the grounds can also influence the health effects. Drip coffee makers with paper filters represent how most coffee in the USA is prepared, although French press and espresso methods are also popular. Different brewing methods lead to slight differences in phenolic extraction, caffeine content, and taste; in this regard, non-drip methods may result in coffee that provides better cardiovascular protection than French press methods.

Coffee beans may contain 1.0–2.5% caffeine by weight; the actual caffeine content in what a consumer considers to be a "cup" is quite variable (Table 20.1). The size of the cup, mug, or container used to deliver the coffee ranges from a small one-ounce espresso cup to a mammoth 40-oz mug

Table 20.1 Typical caffeine content of commonly consumed beverages adjusted to a 8 oz (240 mL) serving sizes for uniform comparison

Drink	Caffeine content (mg)	Drink (8 oz)	Caffeine content (mg)
Filter-drip coffee	95–233	5-Hour energy	800
Instant coffee	27–173	Mountain Dew	36
Decaffeinated coffee	3–20	Diet Mountain Dew	36
Green tea	13–20	Coca-Cola Classic	23
Black tea	66	Diet Coke	31
Chai tea	50	Coke Zero	23
Lipton brisk iced tea	5	Sunkist Orange Soda	27
Arizona iced tea	15–30	Orange Crush	0
Hot chocolate	13	Monster Energy	80
Chocolate milk	5	Monster Hitman Sniper	600
Milk chocolate (28 g)	8	RockStar Energy Drink	80

popular with many long-haul truckers. Filter-drip methods remain the most popular method and tend to have shorter periods for the caffeine and phenolic substances in the coffee to be extracted. Persons seeking more caffeine may wish to use French press methods of brewing because the grounds are permitted a longer time for caffeine extraction.

Coffee is far more than caffeine: it is a complex mixture of caffeine and phenolic acids. The phenolic acids in coffee impart its color, taste, and smell, and also help explain the health effects of coffee.

The decaffeination process does not remove all the caffeine; there is much variation in the amount of residual caffeine in "decaffeinated" coffee. The decaffeination process is also associated with a reduced phenolic content and the possible introduction of compounds, such as nitric acids and formaldehyde, which are sometimes used to extract the caffeine and may impart side effects.

What's the Buzz Regarding Caffeine?

Caffeine is a stimulant of the nervous system and can improve reaction times and wakefulness. It is integral to the effects of many beverages and the content of caffeine varies widely in different beverages (Table 20.1). The estimated average consumption of caffeine in the USA is 165 mg/day for all persons and highest (225 mg/day) for persons aged 50–64 years [6]. Caffeine consumption for those aged 12–17 years is estimated to be 50 mg/day [7]. Caffeine has also been shown to improve athletic performance by postponing fatigue, increasing muscle efficiency, and improving oxygen utilization [8]. However, caffeine intoxication is medically defined as consumption over 400 mg and a lethal dose is estimated at 10 g [9].

Caffeine has a profound stimulant effect in some persons, although individual sensitivities vary widely. Caffeine is of course an integral part of coffee, tea, energy drinks, and other beverages that have been previously described in this chapter. It potentially induces its effects by acting on adenosine receptors and/or by inhibiting phosphodiesterase to increase intracellular cAMP. Surprisingly few negative health effects have associated with caffeine consumption. However, as a cautious recommendation, the elderly and pregnant women may wish to limit their intake of caffeinated beverages. Given that caffeine has a half-life of 3–6 h, it can act as a causative agent for insomnia or other sleep disorders.

Tea Consumption Is Protective and Should Be Encouraged

After water, tea is the most popular beverage in the world. The popularity of tea in the United States is increasing, possibly in response to reports of its favorable health benefits. Leaves from the tea plant *Camellia sinensis* are the source of the primary tea types (green, black, and oolong). Industrial processing of green and black teas changes their respective polyphenolic profiles. Freshly brewed green tea contains many phenolic compounds including (−)-epigallocatechin-3-gallate (EGCG), while black tea contains lower levels of these compounds. EGCG makes up more than 40% of the total polyphenolic mixture and appears to be responsible for most of the beneficial effects of green tea. Its maximal plasma concentration is achieved 1.3–2.4 h after consumption. EGCG is classified by the FDA as "generally recognized as safe" (GRAS) and is a popular food additive and nutraceutical supplement. Tea also contains caffeine though considerably less than the amount in coffee (Table 20.1).

Many epidemiological studies have reported a protective association between green tea and the risk of both cancer and CVD [10, 11]. However, this evidence is based heavily on studies in Japan and China where many people drink eight or more cups per day. Thus, one or two cups/day may have a

fairly small (though useful) effect. Black tea has also been demonstrated to be protective against CVD, possibly by helping to improve endothelial cell function and vasodilation [12]. In Western populations, the consumption of three or more cups/day of black tea has also been strongly associated with protection from coronary heart disease (CHD) [13]. As a general guideline, consumption of up to 3–4 cups/day should be recommended.

Milk Is Good for You

Milk has long been recognized as a way to enhance calcium intake and bone health, especially when it is fortified with vitamin D, a topic discussed more thoroughly in Chap. 18. Nearly all milk sold in the USA and Canada is fortified with vitamin D to obtain a standardized amount of 400 IU (15 μg) per cup (250 mL). Milk is also an excellent source of potassium, magnesium, and protein.

Surprisingly, the fat content of milk does not lead to deleterious changes in the lipoprotein profile nor does it lead to increased risk for CHD. Indeed, the DASH study demonstrated that low-fat and high-fat dairy consumption lead to similar decreases in blood pressure [14]. Milk consumption may promote improved weight control and consumption is inversely correlated with the risk of developing insulin resistance.

Milk consumption is arguably most important in younger persons who are developing bone mass. Unfortunately, in the last few decades, milk consumption has declined among this age group at the same time that soft drink consumption has increased. Recommendations for milk have seen ups and downs and ups over the last 20 years leading to a lack of clarity. Milk consumption should be promoted in persons who are not lactose intolerant. A general guideline is 2–4 cups/day.

Lack of lactase in the intestine results in lactose intolerance. This condition can be dealt with either by avoiding milk or by consuming lactose-free dairy products. This condition is most common among persons of southeast Asian decent followed by Native Americans, African-Americans, and Mediterranean peoples, and is least common among those of northern European descent. Potential food allergies to milk are discussed in Chap. 17.

Health Benefits of Fruit and Vegetable Juices

It is notable that persons in the lowest quartile of fruit and vegetable consumption are in the highest quartile for risk of CVD and cancer. The DASH study suggested that the inclusion of fruits and vegetables may also be associated with improved blood pressure [14]. For many reasons, the five-a-day program seeks to boost fruit and vegetable consumption and the American Dietetic Association recommends that juice consumption can be used to improve fruit and vegetable intake. Because of their enjoyable taste, widespread accessibility, and ease of storage, juice is a popular way to increase fruit consumption. However, patients should also be reminded that consumption of fruit juice is only a partial solution to improving intake of fruit for the following reasons:

(a) Juices are usually a poor source of fiber.
(b) They have a high content of simple sugars, and this can induce an excessive energy intake when not consumed in moderation.
(c) The vitamin C content decreases over time; products should be consumed within a week of opening.
(d) The polyphenolic profile of juices is highly related to environmental and processing conditions, and the fruit source.

(e) Total consumption recommendations are difficult to make, but should probably not exceed two 8 oz (250 mL) cups per day.
(f) Consumers should be reminded that whole fruits provide better nutritional value, although they may be more expensive or less available than frozen or pasteurized juice. Ideally, people should eat whole fruit, not fruit juice.

There are several types of pseudo fruit juices that are, in reality, nutritionally the same as cola. These include those labeled as fruit beverages, fruit nectar, fruit drink, and fruit punch. Consumers should not be fooled by pictures of fruit on the main label; it is important to read the ingredients in the small print and look for the actual percent juice in the product if this info is given.

Health Benefits of Citrus Juice Consumption

Orange juice (OJ) and grapefruit juice represent the two most commonly consumed citrus juices in the United States. OJ is the most nutrient-dense of the commonly consumed fruit juices. An 8-oz serving (1 cup or 250 mL) of OJ provides 120 kcal and 72 mg of vitamin C (120% of Daily Value). OJ is also a good source of potassium (450 mg or 13% of DV), folate (60 μg or 15% of DV), and thiamin (0.15 mg or 10% of DV). Grapefruit juice differs slightly from OJ in its nutrient profile. An 8-oz serving of grapefruit juice contains about 90 kcal and has a similar amount of vitamin C as OJ. Grapefruit juice contains lower concentrations than OJ of potassium, B vitamins, folate, thiamin, and niacin. It has a different profile of phenolic acids, some of which may be responsible for an alteration of drug metabolism, a topic discussed at greater length in Chap. 34.

Consumption of citrus juice was found to promote cognitive benefits [15, 16]. It may also help to protect against CHD by various mechanisms. Consumption of OJ may lead to a reduction in systolic blood pressure (SBP) [15] and may also help lower LDL cholesterol [17].

Health Effects of Other Types of Fruit Juice

Cranberry juice has been used in folk medicine for hundreds of years. Recent clinical studies have confirmed its usefulness for the prevention of urinary tract infections [18, 19]. The major bioactive antibacterial agents in cranberry are proanthocyanidins (PACs). These substances have been shown to prevent bacterial adhesion to the urinary tract and may also improve oral and gastric health [20, 21]. Consumption of cranberry products is associated with improved antioxidant status and lipid profile in addition to anti-inflammatory, vasodilatory, and antiplatelet aggregation properties that may make these products a viable substitute for red wine and Concord grape juice for protection from CHD [22–24]. However, there is a large range (3–100%) in the amount of cranberry juice actually present in the beverages available for sale. Based on beverages used in clinical trials, it is recommended that cranberry juice contains at least 27% cranberry v/v, a value typically found on US beverage labels. Concord and purple grape juices contain an array of polyphenolic compounds that are similar to those of red wine as discussed in Chap. 22. The biological effects of grape juice have been demonstrated to include a small improvement in plasma lipid profile, vasodilation, and antiplatelet aggregation activities.

Many fruit juices contain a high content of (natural) sugar. For instance, a cup of Concord grape juice provides an energy intake of around 140 kcal. Grape and pear juices are also used as "natural" sweeteners in blended juice products. The term "natural" often appeals to the consumer because of its

"healthful" connotation, but the consumer needs to remember that sugar calories are sugar calories, regardless of whether they come from high-fructose corn syrup, cane sugar juice, or pear juice. These considerations lead to the firm conclusion that, as with all things, moderation is best.

And Don't Forget Vegetable Juices

Tomato juice has been popular for decades. Unfortunately, the health benefits associated with its content of micronutrients and lycopene are potentially reduced by the excessive content of salt (as high as 560–660 mg sodium/cup) that is added to improve palatability. However, some brands are low in salt, which is usually prominently stated on the label. Older and hypertensive patients, in particular, should be strongly advised to "read the label" before consuming them.

Tomato and other vegetable juices typically have a low energy content (50 kcal/cup as compared to 110 kcal/cup in OJ and apple juice). It is also important to recognize that some vegetable drinks include pear, white grape, or other juices as a source of sweeteners; this improves their palatability at the cost of increased caloric content.

Many vegetable juices can be stored without refrigeration. For these reasons, these products are a convenient and affordable way for people to inject more vegetables into their diets: they can help people reach the five-a-day goal for fruit and vegetable consumption.

Health Effects of Soft Drink Consumption

The Dietary Guidelines for Americans recommend that individuals should consume less than 10% of energy from added sugars [25]. Alas, the sugar in soft drinks may contribute as much at 28% of the energy intake in the diet of adolescents. There is much evidence that soft drinks pose a significant health hazard.

Soft drinks can contribute to an increased caloric intake and their consumption is positively correlated with weight gain [26]. Part of the problem related to soft drinks and weight gain may stem from the observation that carbohydrates in a beverage do not promote satiety as efficiently as they do when present in a solid food, hence subjects may experience an increase in caloric intake [27]. Soft drink consumption is associated with several diseases, including type 2 diabetes [28], hypertension [29], and the metabolic syndrome [30]. Soft drinks are also associated with dental decay. These drinks completely lack vitamins and minerals and may therefore lead to a nutritional imbalance by displacement of more nutritious foods. In particular, consumption of milk is often displaced by soft drinks, and this leads to a reduced intake of calcium and vitamin D. This may lead to a reduction in bone density which may be a particular concern for adolescents and the elderly.

Health Effects of Nonnutritive Sweeteners

Diet soft drinks offer the advantage of helping to reduce caloric intake. They substitute what are termed noncaloric, reduced calorie, artificial, or nonnutritive sweeteners (NNS). The term "diet" on the label of a beverage implies that they are useful for controlling obesity or reducing weight; however, documentation of weight loss or control has not been demonstrated in all studies. Indeed, some studies suggest that consumption of diet soft drinks is associated with weight gain [31]. Consumption of diet beverages is probably higher for persons with weight management issues, and these persons are at higher risk for cardiovascular disease [32].

NNS include sucralose, acesulfame potassium, aspartame, and various plant-derived sweeteners such as stevia and monk fruit that are rapidly gaining popularity. Aspartame is approximately 200 times sweeter than sucrose, but it is not stable when heated which limits its use in heat-processed beverages. Sucralose (sold under the brand name Splenda©) is about 600 times sweeter than sucrose. Acesulfame potassium (Ace-K) is a heat-stable sweetener that is 200 times sweeter than sucrose. Steviol glycosides (Stevia) are extracted from the leaves of *Stevia rebaudiana*, a plant that is native to South America. Stevia is 200–400 times sweeter than sucrose and appeals to consumers partly due to its natural plant-based origin.

The average consumer probably has a poor ability to identify NNS on food labels, either as a chemical name (e.g., sucralose) or trade name (e.g., Splenda®). In a recent survey, approximately two-thirds of university students were unable to name two NNS by chemical or trade name and only 12% could name three or more NNS [28]. Hence even if patients ask about NNS, they are unlikely to know if NNS are actually in their diet.

Meal Replacement Beverages

A variety of meal replacement beverages are available (e.g., Ensure, Boost, and Glucerna). They may have a place in the regular nutrition of many persons, although consumption of whole foods is best. These beverages provide consumers with a convenient way to consume a relatively balanced nutritional intake of about 200 kcal along with a typically large protein intake, as well as minerals and vitamins. The elderly often have a high risk for malnutrition, inadequate protein intake, and poor weight maintenance. These beverages are readily available and often quite palatable. Most brands can be stored without refrigeration. For these reasons, meal replacement beverages may be useful and are commonly consumed. However, consumers should be aware that some brands contain generous amounts of fat or sugars which are added to improve palatability.

Surprisingly, older persons tend to consume more food during the meal following consumption of a meal replacement beverage, making these beverages useful for elderly persons attempting to gain weight, but detrimental for overweight persons attempting to lose weight [33]. Their effects in middle-aged persons are not clear. While meal replacement beverages may be useful for some persons, the best nutritional advice for most people is to consume a balanced diet that emphasizes a variety of foods consumed in their solid form.

Another type of meal replacement beverages are those intended to help with weight loss (e.g., Slim-Fast, Met-Rx, and Atkins Nutritionals). Supporting evidence regarding their value is not convincing.

Sports Beverages

The loss of a small amount of body water, as little as 2% of body weight, can impair physical and mental performance. These beverages have been found to be generally effective for improving hydration and electrolyte status and physical performance. They are also consumed to promote improved recovery after athletic events. However, there are few peer-reviewed studies to support claims of improving muscle mass in body builders. Part of the difficulty in performing research on sports beverages is their ever-changing formulation, although a few consistent observations can be made.

Improving hydration during an athletic event is a function of taste; if people like the taste, then they are more likely to drink more of the beverage before or during exercise, thereby leading to greater improvements in their hydration status. Many beverages include sodium and glucose; their presence permits the intestine to cotransport the two substances into the blood. In addition, as sodium and glucose maintain spheres of hydration, this also enhances the rapid absorption of water from the intestine.

If a beverage contains too much sugar (e.g., soft drinks), it actually promotes an osmotic effect in the intestine that can paradoxically lead to solvent drag of water into the intestine and dehydration.

Sports beverages can improve electrolyte status, although the effects are most significant for exercise of long duration (e.g., a half marathon or mowing a lawn on a hot summer day for 2 h). However, if a person is adequately hydrated and has a proper electrolyte balance prior to beginning their exercise, a sports beverage is unlikely to facilitate a significant improvement in physical performance.

A visit to a health food store or perusal of the advertisements in a body building magazine will demonstrate that a variety of liquid supplements are marketed with the claimed ability to improve muscle mass, appearance, or performance. While many products include some sort of claim, there is a dearth of supporting evidence coming from papers published in credible peer-reviewed journals.

A typical product comes in a powdered form that provides a rich content of protein, vitamins, and minerals, but with a small content of carbohydrate and fat. Some products may also contain creatine phosphate, caffeine, or plant-derived extracts/compounds. The inclusion of these ingredients is poorly regulated by the FDA. The price of these sports drinks varies widely from one to ten dollars per liter, and given this high cost it is a tribute to the power of marketing that they are so popular. For these reasons, the authors believe that clinicians and other health-care professionals should use their influence to counsel caution among users. However, many persons who use these beverages do not share that information.

Energy Drinks Remain Controversial Beverages

The increasing popularity of so-called "energy drinks" is an American and global phenomenon. Their gross sales are worth several billion dollars per year. They are consumed for perceived enhancements in mental acuity, wakefulness, and physical performance.

The formulation of energy drinks is highly variable. While caffeine is a primary ingredient in most brands, its content is quite variable (Table 20.1). Energy drinks generally contain a variety of other compounds with potential for altering physiological/mental activity. These often include taurine (neurotransmitter function) and various B vitamins. In addition, most brands contain sugars, although some are nearly calorie free; caloric contents range from 10 to 150 kcal per 8-oz serving.

While energy drinks are commonly believed to have significant physiological effects, documentation in this regard is relatively scant [34]. However, given the significant number of anecdotal reports that link cardiac pathologies with consumption of energy drinks, especially when consumed with alcohol, caution seems warranted. In light of these concerns, the classic energy drink Red Bull® was banned in some European countries.

Conclusions

We are mainly what we drink. Nonalcoholic beverages contain a variety of components, in addition to water, that may impact human health. In many cases, as with the micronutrients and phytochemicals in fruit and vegetable juices, these are likely to be beneficial. Coffee and tea generally have health-neutral to beneficial effects. Tea has been linked to reduced risk of CHD while coffee may be protective against type 2 diabetes. Milk has been determined to promote improved cardiovascular health and its fats may even improve weight control. But beverages can also be a major source of excessive caloric intake that may contribute to obesity and type 2 diabetes. Regarding sports drinks, energy drinks, and caffeine, caution should be an operative word; however, conclusive evidence to support health concerns regarding their consumption generally does not exist. No single beverage can replace water, that ubiquitous beverage.

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Chapter 22
What Is Best for the Patient: Abstinence or Moderate Alcohol Consumption?

Ted Wilson and Norman J. Temple

Key Points

- Moderate consumption of alcohol is generally defined as two drinks a day for a man or one for a woman.
- This is associated with significant protective effects against coronary heart disease and several other diseases and health problems.
- Below age 40 alcohol is associated with an increased risk of death.
- For people older than about 50 or 60 alcohol consumption has a J-shaped relationship with risk of mortality; the lowest risk of death is seen in moderate drinkers.
- 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.

Keywords Alcohol drinking • Alcohol-related disorders • Coronary heart disease • Mortality

Introduction

The widespread consumption of alcoholic beverages and their potentially conflicting health impacts makes a discussion of this topic vitally important for physicians. Alcohol (ethanol) consumption in large quantities is strongly linked to dramatic negative health 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 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). While the health effects of alcohol consumption is the topic of countless reviews, this chapter focuses on issues related to recommendations that physicians may give to their patients.

T. Wilson, Ph.D.
Department of Biology, Winona State University, Winona, MN, USA

N.J. Temple, Ph.D. (✉)
Centre for Science, Athabasca University, Athabasca, AB, Canada, T9S 3A3
e-mail: normant@athabascau.ca

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Who Drinks Alcohol, How Much, and What Is Dose Equivalence?

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. 22.1) [1]. What can further confuse this message of a "standard" drink is the variability with regard to alcohol content. Beverage containers in the USA are required to state the alcohol content, but few consumers actually look at that information. For example, beer can have an alcohol content of 3.0–9.0%; a 12 oz (355 ml) delivering between 0.6 and 1.8 drink equivalents (8.4–25.2 g alcohol). When one considers the tremendous 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 which can lead to harmful health effects.

Alcohol is not technically a nutrient, but becomes a source of calories (7 cal/g) in the form 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 98 kcal.

Appreciating alcohol consumption patterns is important for making clinical recommendations. Consumption of alcoholic beverages increased between 1989 and 2012 when 80% of adult Americans reported consuming at least one drink in the last year [2]. Beer remained the largest single source of intake although wine consumption steadily increased to 29.6% of intake, especially in those aged over 60 years and women. In this regard, economic crises are known to be associated with an increase in alcohol consumption and alcohol-related health problems [3]. The economic crisis of 2008–2009 may therefore be related to changing patterns of alcohol intake. Sadly, access to healthcare and medical resources also declines during periods of stress and economic crisis, an association that is important for interpreting the health effects of alcohol consumption.

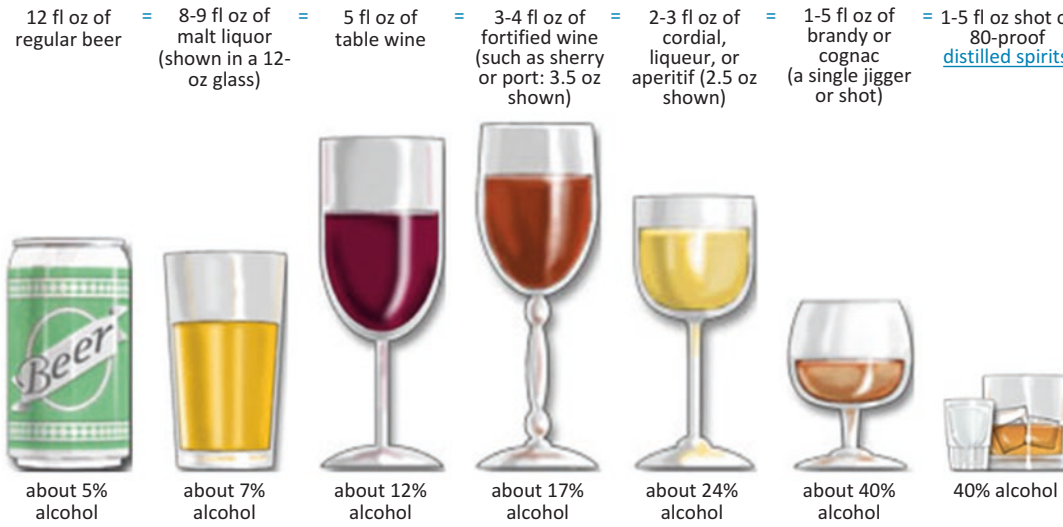

Fig. 22.1 Equivalent beverages volumes that provide the US definition of one "drink" containing 14 g of alcohol [1]

Health Benefits Associated with Alcohol Consumption

A substantial body of epidemiological evidence has accumulated over the past 20 years that demonstrates a strong negative association between moderate alcohol consumption and risk of CHD. Our best evidence is that moderate consumption reduces risk by at least 20%.

This epidemiological story has generated heated debate in the medical literature which reflects the pitfalls of 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. The debate on this question has been ongoing with little sign of settlement. However, the assumption is that a moderate intake of alcohol does indeed offer a significant degree of protection against CHD.

The so-called French Paradox was observed in France where a surprisingly low rate of CHD was observed, in comparison with some northern European countries, such as the United Kingdom [4]. 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 could be found in the popularity of red wine in that country. However, wine drinkers often have a healthier lifestyle and a higher socioeconomic status (a factor associated with a lower risk of CHD), as well as drinking pattern (a glass or two of wine with dinner several times a week is believed to be healthier than the same quantity of alcohol consumed in one or two "binges").

A major mechanism by which alcohol prevents CHD is believed to be by elevation of the blood level of HDL-cholesterol [5]. Furthermore, when consumed in moderation all types of alcoholic beverages—wine, beer, spirits—probably have a similar potency for CHD prevention although the phenolic compounds (i.e., catechin, resveratrol) may give red wine a more advantageous effect.

For several aspects of poor health status, there is a J-shaped relationship between alcohol consumption and risk [6, 7]. People who consume alcohol in moderation have a lower risk than that seen in either heavier drinkers or nondrinkers, while risk increases sharply in those with a high alcohol intake. Hypertension and the risk of stroke manifest this relationship. While a relatively high intake of alcohol (more than four drinks per day) is associated with an increased risk of both conditions, moderate consumers appear to be at relatively low risk. This association is seen most clearly in for ischemic stroke rather than hemorrhagic stroke.

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). 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 recent research has revealed that moderate drinkers actually have an enhanced cognitive ability or a slower rate of decline with aging [8, 9]. This effect is generally more pronounced in women. These benefits may even extend to the risk of dementia, mostly Alzheimer's disease. One of the most dramatic effects is seen with type 2 diabetes. Cohort studies report that moderate consumers of alcohol reduce their risk of the disease by between one-third and one half.

The effects of alcohol consumption on body weight are unclear. When men consumed 35 g/d of alcohol (a little less than three glasses of wine) for a period of 6 weeks, this did not affect body weight [10]. Similar results were seen this when overweight women consumed 25 g/day of alcohol, 5 days/week, for 10 week [11]. 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.

Several long-term cohort studies have been carried out. In 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 [12]. In 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 [13]. In sharp contrast, other cohort studies have reported a positive association between alcohol consumption and weight gain [14]. At present, therefore, it is far from clear whether alcohol intake is a risk factor for weight gain.

Harmful Effects of Alcohol

Alcohol consumption may also alter the efficacy, metabolism, and effect of medications, a topic reviewed in Chap. 34. 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 leads 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 correlated with alcoholism, cirrhosis, stroke, and accidental death than is the case with other alcoholic beverages.

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. FAS occurs at a level of alcohol intake which in a nonpregnant woman is well below the level that would be considered alcohol abuse. A subclinical form of FAS is known as fetal alcohol effects (FAE). Children with FAE may be short or have only minor facial abnormalities, or develop learning disabilities, behavioral problems, or motor impairments. Women who have an occasional drink during pregnancy should not fear doing irreparable harm to their fetus though it is now generally accepted that any woman who is or may become pregnant should abstain from alcohol.

Heavy consumption of alcohol is associated with an increased risk of numerous 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 alcohol/day [15]. 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: 1.16 for colorectal cancer, 1.8 for mouth and pharynx, 2.4 for esophagus, and 3.0 for liver [16]. Our best evidence is that lower intakes of alcohol produce proportionately smaller RRs. For all cancer combined, a significant risk is seen starting at an alcohol intake of two drinks per day, with an RR of 1.22 at 4 drinks per day [17].

Effect of Alcohol on Total Mortality

With the opposing health effects of alcohol, a critically important question is the effect of alcohol 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 associated with 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 causes a reduction in mortality [18]. At that age, the health benefits, especially the prevention of heart disease, dominate the picture. As a result, it is among this age group that a J-shaped relationship is seen 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].

Phytochemicals in Alcholic 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 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, a topic also discussed in Chap. 11. 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.

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, it is premature to make bold statements as to the disease-preventing action of specific substances.

What Advice Should a Physician Give?

Despite the potential health benefits of moderate drinking, medical experts should not recommend that non-drinkers commence light-to-moderate drinking. The reason for this is that around 5–10% of people in any society, where alcohol is available become abusers of the beverage. 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. 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 larger part a personal decision of the patient based upon clinical realities.

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Chapter 23
Dietary Fiber: All Fibers Are Not Alike

Johnson W. McRorie

Key Points

1. What is known about the health benefits of a high-fiber diet is derived primarily from epidemiologic studies, which can establish statistical associations, but lack the control necessary to establish causation.
2. The association between a high-fiber diet and a reduced risk of cardiovascular disease was used to establish adequate fiber intake guidelines. It is impossible, however, to separate the health effects of dietary fiber from other health-promoting dietary components of fruits, vegetables, and whole grains (e.g., phytochemicals).
3. In contrast, isolated fibers, such as fiber supplements, can be assessed for a direct effect on specific beneficial physiologic effects in well-controlled clinical studies.

   (a) 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)] have been shown to provide these effects, and these are highly correlated with the viscosity of the gelling fiber.
   (b) In the large bowel, not all fibers provide a laxative effect, and some can actually be constipating. Only fiber that resists fermentation and remains intact throughout the large bowel can be present in stool to provide a beneficial effect:

- Poorly fermented coarse insoluble fiber particles (e.g., wheat bran) mechanically irritate the gut mucosa, causing stimulation of water and mucous secretion, which bulks/softens stool. Finely ground insoluble fiber can be constipating. The mechanical irritation of insoluble fiber may not be optimal for patients with irritable bowel syndrome.
- Non-fermented soluble gel-forming fibers, such as psyllium, retain their high water-holding capacity to resist dehydration throughout the large bowel, providing a dichotomous stool normalizing effect: softens hard stool in constipation (superior to docusate), firms loose/liquid stool in diarrhea, and normalizes stool form in irritable bowel syndrome. Nonviscous fermentable fiber, such as wheat dextrin, can be constipating.

J.W. McRorie, Ph.D. (✉)
Global Clinical Sciences, Procter & Gamble,
8700 Mason-Montgomery Road, Mason, OH 45040, USA

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4. Conclusions: It is reasonable to recommend a diet rich in fruits, vegetables, and whole grains. The isolated fiber in supplements can be a convenient and concentrated source of fiber, but not all types of fiber provide beneficial physiologic effects.
   (a) It is important to recognize which physical characteristics of isolated fibers drive specific beneficial effects.
   (b) The most appropriate types of fiber supplements are those where there is evidence of clinically meaningful beneficial physiological effects.
   (c) For most fiber-related beneficial effects: "*Fiber needs to gel to keep you well*."

Keywords Dietary fiber • Insoluble fiber • Soluble fiber • Gel forming • Glycemic control • Colorectal cancer

Introduction

The Institute of Medicine (IOM) published a definition of total fiber that differentiated *dietary fiber* (non-digestible carbohydrates and lignin that are intrinsic and intact in plants) from *functional fiber* (isolated, non-digestible 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 (epidemiological) studies, which are useful for establishing "associations" between consumption of high-fiber diets and observed health effects (or low-fiber diets and increased risk of disease), but lack the control necessary to establish causation. This lack of control leaves unclear how much of an observed health benefit can actually be attributed to a direct effect of dietary fiber in the gut, versus how much might be attributed to other constituents; high-fiber foods tend to be rich in magnesium, potassium, and other micronutrients, as well as phytochemicals. Some of the benefit of high-fiber foods may be due to a reduction in fat/calorie intake.

The IOM Adequate Intake (AI) guidelines for adults, based on an association (epidemiologic data) between reduced risk of cardiovascular disease (CVD) and a high-fiber diet, recommends 14 g of dietary fiber per 1000 kcal consumed, which for 19–50-year-old adults is about 25 g/day for women and 38 g/day for men [1]. In contrast to this recommendation, the average American consumes only 15 g/day of dietary fiber [2]. It can be a challenge to consume a sufficient quantity of fruits, vegetables, and whole grains to meet recommendations for fiber consumption. While fiber supplements may appear to be a convenient and concentrated source of fiber to make up for this shortfall, many supplements do not provide the nutritional benefits associated with a high-fiber diet. In contrast to dietary fiber present in food, the isolated fibers typically found in fiber supplements have been assessed for their direct effect on specific health benefits in well-controlled clinical studies. The beneficial physiologic effects of fiber are primarily driven by the physical effects of fiber in the gut and can be divided into the classic "insoluble" (plastic) and "soluble" ("visco-elastic") effects in the small and large bowel [3]. This review will provide an appreciation for the underlying mechanisms that drive specific beneficial physiologic effects, and summarize which fiber supplements have clinical evidence of a beneficial effect.

Physical Effects of Fiber in the Small Intestine

Type 2 Diabetes/Glycemic Control

Epidemiological evidence consistently shows that high consumption of cereal fibers are associated with a reduced risk of developing type 2 diabetes (relative risk 0.77), but the evidence is less convincing for fruit fibers (relative risk 0.94) and vegetable fibers (relative risk 0.95) [4]. When isolated fibers are assessed in well-controlled intervention studies, only soluble gel-forming fibers significantly improve glycemic control, and the effect is proportional to the viscosity of the gelling fiber [5]. In the fed state, the motor activity of the small bowel comprises segmental (mixing) contractions. Chyme is normally low in viscosity and easily mixed with digestive enzymes for degradation. The large surface area of the mucosa (roughly equivalent to a tennis court) results in efficient absorption of nutrients, which typically occurs early in the proximal small bowel. Introduction of a gel-forming fiber [e.g., β-glucan (oatmeal), psyllium] significantly increases the viscosity of chyme, which slows the mixing of chyme with digestive enzymes, and slows nutrient absorption, which can decrease postprandial blood glucose concentrations [3, 5]. It is well established that this effect occurs only with consumption of a gel-forming fiber, and efficacy is highly correlated with the viscosity of the gel-forming fiber [6]. In a study published in 1978 [6], subjects underwent a glucose (50 g) tolerance test with and without several different fiber supplements. The study showed that high-viscosity gel-forming fibers had a significant effect on postprandial peak blood glucose concentration, but as viscosity declined, so did the effect ($r = 0.926$; $p < 0.01$) [6].

Gel-forming fibers also have a significant effect on long-term glycemic control. The delay of nutrient absorption can deliver nutrients to the distal ileum (where nutrients are not normally present), stimulating mucosal L-cells to release glucagon-like peptide-1 (GLP-1), a peptide that has significant metabolic effects: decreased appetite, increased pancreatic β-cell growth, improved insulin production and sensitivity, decreased glucagon-secretion, and stimulation of the "ileal brake" (slowing gastric emptying and small bowel transit) [3, 5]. Note that a viscous, gel-forming fiber can slow the absorption of nutrients, but it does not reduce total nutrient absorption [5]. The ileal brake phenomenon effectively slows gastric emptying and small bowel transit to impede the loss of nutrients to the large bowel [5]. Multi-month clinical studies have demonstrated that consumption of a viscous, gel-forming fiber (dosed with meals) can lower fasting blood glucose, insulin, and HbA_{1c} in patients with metabolic syndrome and patients being treated for type 2 diabetes mellitus (T2DM) [3]. The effectiveness of a gel-forming fiber is proportional to baseline glycemic control: no significant effect in euglycemia, a modest effect in pre-diabetes [e.g., −19.8 mg/dL (−1.1 mmol/L) for psyllium; −9 mg/dL (−0.5 mmol/L) for guar gum), and the greatest effect in patients being treated for type 2 diabetes [e.g., psyllium, −17.3 mg/dL (−1.0 mmol/L) to −89.7 mg/dL (−5.5 mmol/L)] [3]. A recent meta-analysis of 35 multi-month 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 [7]. The improvements in glycemic control observed with psyllium are additive to the effects of a restricted diet and stable doses of prescription drugs (sulfonylureas and/or metformin) [4]. Even though a gel-forming fiber will not directly cause hypoglycemia, 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 that can cause hypoglycemia.

Cardiovascular Disease/Cholesterol Lowering

Although the IOM AI guidelines were based on an association between high-fiber consumption and a reduced risk of CVD [1], a more recent (2016) comprehensive review found only a weak negative association between total fiber intake and risk of CVD (relative risk 0.92) [4]. Findings were similar for cereal fiber, fruit fiber, and vegetable fiber [4]. The reason for these weak associations may be due to the lack of differentiation between specific fiber characteristics within "dietary fiber" (e.g., insoluble versus soluble, nonviscous versus gel-forming). When specific isolated fibers were assessed for lowering elevated cholesterol, the results were similar to improvement in glycemic control: only gel-forming fibers lowered 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 [8]. The viscosity of a gel-forming fiber is actually a better predictor of cholesterol-lowering efficacy than the quantity of fiber consumed [9]. The primary mechanism by which soluble gel-forming fibers lower serum cholesterol is by trapping and eliminating bile acids [3, 5]. These are normally recovered in the distal ileum and recycled, potentially several times within a single meal. When bile acids are trapped in a gel-forming fiber and eliminated via stool, the reduction in the bile acid pool causes hepatocytes to compensate by increasing LDL-cholesterol clearance to synthesize more bile acids (cholesterol is a component of bile) to maintain sufficient bile acids for digestion. This clearance of LDL-cholesterol from the blood lowers serum LDL-cholesterol and total-cholesterol concentrations, without significantly affecting high-density lipoprotein (HDL) cholesterol concentration [3, 5]. Only viscous, gel-forming fibers (e.g., high molecular weight β-glucan, raw guar gum, psyllium), consumed with meals to coincide with bile release, effectively lower elevated serum cholesterol concentrations [3, 5, 7–11].

The importance of viscosity for a gel-forming fiber was demonstrated in a clinical study that compared the cholesterol-lowering effectiveness of several different viscosities of β-glucan (the fiber in oatmeal) [8]. The results showed that cholesterol lowering was highly correlated with the viscosity of the gel-forming fiber: the high-viscosity β-glucan (low heat and pressure processing) exhibited significant LDL-cholesterol lowering (–5.5%; $p < 0.05$ versus bran placebo), as did the medium-viscosity (–4.7%; $p < 0.05$), whereas the lower viscosity did not exhibit a significant cholesterol-lowering effect [8]. This means that it is not only important to recognize which raw fibers provide a specific physiologic effect, but to also consider how processing (e.g., heat/extrusion to create cereal shapes) may affect/eliminate viscosity and efficacy. Note that insoluble fiber (wheat bran) was used as a negative control in the study. Insoluble fibers (e.g., wheat bran, cellulose) and nonviscous soluble fibers (e.g., wheat dextrin, inulin) do not provide viscosity/gel-dependent physiologic effects and can be used as a negative control (placebo) in clinical studies [3]. It should also be noted that viscosity alone is not sufficient to provide gel-dependent cholesterol lowering. In a 2-month clinical study of 163 patients with hyperlipidemia, psyllium, a natural gel-forming fiber, significantly decreased both LDL and total cholesterol versus placebo (insoluble cellulose), while viscous methylcellulose (chemically treated wood pulp) and calcium polycarbophil (synthetic polymer) did not significantly affect cholesterol measures [10].

Psyllium has been well studied for its cholesterol-lowering effects (24 randomized, well-controlled clinical studies, totaling 1568 subjects) and showed reductions of 6–24% for LDL-cholesterol and 2–20% for total cholesterol, versus placebo [11]. Efficacy tends to be greater in studies assessing patients with higher baseline cholesterol concentrations, and studies where diet was not restricted (similar to many patients). Gel-forming fibers are also safe and effective in children. A 2014 study in 51 children and adolescents with hyperlipidemia assessed the effects of psyllium (7 g/day) versus placebo (cellulose) for cholesterol lowering while on a restricted diet [12]. After 2-months of treatment, both total cholesterol and LDL-cholesterol were significantly decreased (8% and 11%,

respectively) versus placebo. The authors noted that psyllium therapy was both safe and well tolerated [12]. There are two fibers approved by the Food and Drug Administration for claims of a reduced risk of CVD by lowering serum cholesterol: β-glucan (oats and barley) and psyllium, both viscous, gel-forming fibers [13].

A gel-forming fiber can be an effective lifestyle intervention/co-therapy for statins and bile acid sequestrants, with the potential to lower the required dose and/or side effects of the drugs [3]. In a 3-month study in 68 patients with hyperlipidemia, low-dose simvastatin (10 mg) combined with psyllium (15 g/day, divided doses before meals) was superior to low-dose simvastatin alone [LDL-cholesterol −63 mg/dL (−1.6 mmol/L) versus −55 mg/dL (−1.4 mmol/L), respectively; $p = 0.03$] [14]. The combination of psyllium and low-dose simvastatin was equivalent to high-dose (20 mg) simvastatin alone [both −63 mg/dL)(−1.6 mmol/L)] [14]. Similar results were observed for total cholesterol and apolipoprotein B, but there were no significant changes from baseline for triglyceride or HDL-cholesterol concentrations [14]. When combined with colestipol or cholestyramine, psyllium increased cholesterol-lowering efficacy and decreased symptoms associated with sequestrant therapy [3].

Weight Control

In addition to improved glycemic control and cholesterol lowering, both important factors in metabolic syndrome, a gel-forming fiber can also facilitate weight loss. A 6-month study assessed two soluble gel-forming fibers in 141 patients with the metabolic syndrome [15]. Patients were fed an American Heart Association step-2 diet alone (control group) or the same diet supplemented with psyllium or guar gum (3.5 g twice a day before breakfast and dinner). Both psyllium and guar gum showed significant improvement in fasting plasma glucose (−27.9%; −11.1%), insulin (−20.4%; −10.8%), and LDL-cholesterol (−7.9%; −8.5%), respectively [15]. Only psyllium exerted a significant improvement in plasma triglyceride concentration (−13.3%) and systolic (−3.9%) and diastolic blood pressure (−2.6%) [15]. Both the control diet and guar gum (readily fermented) showed an initial decrease in body weight, followed by weight regain (Fig. 23.1). In contrast to guar gum, psyllium (non-fermented) showed sustained weight loss across the entire 6-month test period. At the conclusion of the study, 12.5% of patients in the psyllium group no longer qualified for a diagnosis of the metabolic syndrome, versus 2.1% of patients in the guar gum group and none of the patients in the diet-control group [15]. It is important to recognize that the fermentation process results in calorie harvest (e.g., fatty acid production/absorption), so fermentable fibers are not calorie-free and may not be optimal for weight loss.

The figure shows mean subject weight over time for a 6-month study in patients with the metabolic syndrome. Only non-fermented psyllium plus diet showed continued weight loss over the 6-month treatment period.

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 [5]. It is a misconception that consuming the

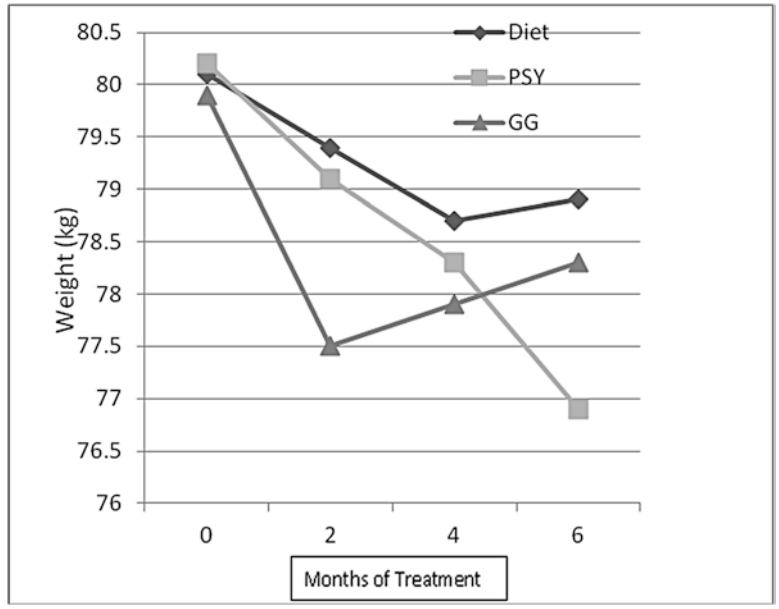

Fig. 23.1 Weight loss in a 6-month study comparing a restricted diet alone (Diet: AHA step 2 diet) to the same diet with added fiber supplements: psyllium (PSY) 3.5 g twice a day versus guar gum (GG) 3.5 g twice a day in patients with metabolic syndrome. Note that only psyllium showed weight loss across all 6-months of treatment

recommended levels of fiber will reduce the risk of constipation. As discussed previously, the adequate intake guidelines for dietary fiber were based on reducing the risk of CVD, not reducing the risk of constipation. The American Gastroenterological Association concluded that "Constipation was associated with low-dietary fiber intake in some, but not other studies. However, these associations do not necessarily indicate causation. Although it is reasonable to try and modify these risk factors, doing so may not improve bowel function" [16]. One reason for this inconsistency in population-based studies is that "dietary fiber" does not differentiate between specific fiber characteristics, and not all fiber types provide a laxative effect (some can actually be constipating). For fiber to soften stool and significantly increase stool volume, it must resist fermentation to remain intact and present throughout the large bowel (must be present in stool), and it must increase stool water content, which is the primary mechanism for both a stool-softening effect and increased stool bulk [17]. There are two mechanisms by which a fiber can significantly increase stool water content and stool bulk: (1) poorly fermented coarse insoluble fiber particles, such as wheat bran, mechanically irritate the gut mucosa, stimulating water/mucous secretion (fine/smooth particles only add to the dry weight of stool and can be constipating); and (2) non-fermented viscous/gel-forming fiber, such as psyllium, retains its water-holding capacity throughout the large bowel to resist dehydration [17]. Both mechanisms increase stool water content (softer stool) and stool bulk.

The texture of stool is correlated with percentage of water content, and small changes in stool water content can lead to large changes in stool texture: hard stool is $\leq$72%, normal/formed stool is $\approx$74–75%, soft/formed stool is $\approx$76%, and loose stool is $\approx$80% water [5, 17]. An effective fiber (e.g., coarse wheat bran, psyllium) will increase stool water content, resulting in a significant stool-softening effect and increased stool bulk, both of which make stools easier to pass without straining. In contrast, a fiber that adds only to the dry mass of stool, with no water-holding capacity [e.g., wheat dextrin [5]], will decrease the percentage of stool water content, resulting in harder stools (constipating effect).

The observation that coarse wheat bran has a greater laxative effect than fine wheat bran suggested that the insoluble particles themselves may have a direct effect in the large bowel and led to studies comparing insoluble wheat bran to inert plastic particles ("plastic effect") [18]. Coarse plastic particles and coarse wheat bran had a significant laxative effect, while fine/smooth plastic particles and finely ground wheat bran had no laxative effect [18]. Fine wheat bran, which does not mechanically stimulate the mucosa and has no water-holding capacity, added only to the dry weight of stool and caused a *decrease* in stool water content (stool-hardening/constipating effect) [18]. The laxative efficacy of insoluble fiber is highly dependent on particle size/coarseness, which is one reason why epidemiologic data assessing "dietary fiber" may be inconsistent.

In contrast to the mechanical irritating effects of coarse insoluble fiber, a non-fermented, soluble gel-forming fiber (e.g., psyllium) retains its high water-holding capacity throughout the large bowel, which significantly increases both stool bulk and stool water content (softens stool). In a clinical study of 170 patients with chronic idiopathic constipation, psyllium was shown to be superior to docusate for increasing stool water content (softer stools; $p = 0.007$) and the frequency of bowel movements ($p = 0.02$) [19]. If a soluble fiber is nonviscous, it has no water-holding capacity and can add to the dry mass of stool (similar to fine wheat bran), decreasing the percentage of stool water content (harder stools). Wheat dextrin, an artificially created "fiber" (heat/acid treated wheat starch), showed a *decrease* in stool water content (harder stools), consistent with reports of harder stools by healthy subjects consuming 15 g/day [20]. Even if a fiber is viscous/gel-forming but is readily fermented (e.g., guar gum, β-glucan), it loses its water-holding capacity and, like nonviscous fermentable fibers (e.g., wheat dextrin, inulin), has no laxative effect [17].

A gel-forming fiber that resists fermentation and retains its high water-holding capacity (e.g., psyllium) can actually exert a stool normalizing effect: softening hard stool in constipation and firming loose/liquid stool in diarrhea. Psyllium has been shown to be effective for softening hard stool in constipation [better than docusate [19]], firming loose/liquid stool in diarrhea [17], and reducing fecal incontinence episodes [21], making psyllium an effective fiber choice for irritable bowel syndrome [22].

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 (72–470 g/day) [23]. 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 ($r = -0.78$) [23]. 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 [24]. Recognize 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 processed meat [24]. 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 [24]. As of 2013, colorectal cancer is the fourth most common type of cancer in the United States, and constipation/laxative use have been hypothesized to increase the risk of colorectal cancer [25]. 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 [25]. The study

did not provide evidence of an association between constipation and colorectal cancer risk, but did show a significant increase in risk with *non-fiber*-laxative use. In contrast, the study also showed a decreased risk in developing colorectal cancer with *fiber*-laxative use [25]. 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., coarse wheat bran, 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, borborygmus (abdominal rumbling/gurgling), bloating, and discomfort in a dose-responsive manner, which can significantly limit the tolerable dose [17]. Even non-fermented fibers 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 [17]. If stool is of similar formed consistency in the distal large bowel, there is minimal deformation 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 [5]. Effective fiber therapy (e.g., coarse wheat bran, 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 distention of the bowel wall. This distention of the bowel wall is similar to that observed with colorectal balloon inflation in studies assessing the pain threshold in patients with IBS. Bowel wall distention stretches mechanoreceptors, causing sensations of discomfort to cramping pain proportional to the degree and rate of distention. This means that the term "cramping pain" is actually a misnomer in that it is caused by normal peristalsis resulting in acute distention of the bowel, not by spastic contraction [5]. Minimizing the risk of discomfort by gradually initiating an effective fiber therapy may improve long-term compliance. Constipated patients may benefit from elimination of hard stool (e.g., osmotic laxative) before initiating an effective fiber therapy.

Conclusions

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. The isolated fibers in supplements represent a convenient and concentrated source of fiber, but may not provide the beneficial physiologic effects associated with a high intake of dietary fiber. It is therefore important to recognize which physical characteristics of isolated fibers drive specific effects and to look for supplements with clinical evidence of meaningful physiologic effects (Table 23.1). Most beneficial physiologic effects are exerted by gel-forming fibers, and efficacy is proportional to the viscosity of the gel. In other words, "fiber needs to gel to keep you well."

Table 23.1 Clinically demonstrated beneficial physiologic effects of representative fiber supplements

	No water-holding capacity				Water-holding capacity		
	Insoluble	Soluble low/no viscosity			Viscous, gel-forming		Viscous, non-gelling
Fiber	Wheat bran	Wheat dextrin	Inulin	Partially hydrolyzed guar gum	B-glucan	Psyllium	Methylcellulose
Common brand name	"All-Bran®"	"Benefiber®"	"Fiber-Choice®"	"GNC Clear-mixing Super Fiber"	"Quaker Oats®"	"Metamucil®"	"Citrucel®"
Source	Wheat	Heat/acid-treated wheat starch	Chicory root	Guar beans	Oats, barley	Seed husk, *Plantago ovata*	Chemically treated wood pulp
Degree of fermentation	Poorly fermented	Readily fermented	Readily fermented	Readily fermented	Readily fermented	Non-fermented	Non-fermented
Cholesterol lowering				±[a]	+	+	
Improved glycemic control				±[a]	+	+	
Chronic constipation	+[b]					+	±[c]
Diarrhea						+	

[a]The efficacy of partially hydrolyzed guar gum depends on the viscosity of the final product
[b]If particle size is sufficiently large/coarse to stimulate the mucosa
[c]OTC indication for occasional constipation, but no placebo-controlled clinical studies identified in chronic constipation

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Suggested Further Reading

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Chapter 24
Dietary Fat: The Good, the Bad, and the Ugly

Marise M. Pinheiro and Ted Wilson

Key Points

- Depending on their chemical structure, fatty acids can be saturated, monounsaturated, or polyunsaturated.
- Some fats are called essential fatty acids and must be provided by the diet. Essential fats include $n-3$ fatty acids and $n-6$ fatty acids.
- Trans-fatty acids are formed during hydrogenation of oils but are also present naturally in some foods. They increase the risk of heart disease.
- Fish contains long-chain $n-3$ fatty acids. These fats help prevent heart disease and other chronic conditions.

Keywords Dietary fat • Saturated fatty acids • Polyunsaturated fatty acids • $n-3$ fatty acids • $n-6$ fatty acids • Hydrogenation • Trans-fatty acids • Heart disease

Introduction

Health professionals are often asked questions regarding fat intake:

- Are all fats bad for you?
- Are fats all the same?
- How much is too much fat?

The objective of this chapter is to shed light on dietary fat and the controversies that surround it. The human body needs a certain amount of fat in the diet in order to survive. Each gram of fat provides 9 kcal whereas protein and carbohydrate only provide 4 kcal/g. Fat provides energy and supplies raw materials for hormones, fat-soluble vitamins, and cell membranes. Dietary fat is important for the

M.M. Pinheiro, M.Sc.
Centre for Science, Athabasca University, #1 University Drive, Athabasca, AB T9S 3A3, Canada
e-mail: marisep@athabascau.ca

T. Wilson, Ph.D. (✉)
Department of Biology, Winona State University, 232 Pasteur Hall, Winona, MN 54603, USA
e-mail: twilson@winona.edu

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absorption of fat-soluble vitamins (vitamins A, D, E, and K, and carotenoids) from food. Fat also helps to insulate the body against high or low temperatures and provides padding for internal organs, which protects them from shock. Fats in food contribute to taste and texture, making foods more appealing. Essential fatty acids (EFA) cannot be synthesized in the human body (liver) and must therefore be provided by diet, much like vitamins. EFA play many important roles in the body and are examined later in this chapter.

Although fat is essential for survival, its consumption may be associated with obesity and coronary heart disease (CHD). These associations are discussed in more detail in Chaps. 8 and 11. The recommendation in this chapter provides a balanced, nutritious diet that includes adequate amounts of EFA as a way to help prevent obesity and chronic diseases.

Types of Fat

General Chemical Characteristics

Fatty acids are composed of a carboxyl group, a series of hydrocarbons that can be saturated ($-CH_2-CH_2-$) or unsaturated (−CH=CH–) with a methyl group (CH3) at the other end. They differ from each other according to their chemical structure including the number of carbon atoms, the degree of unsaturation, location of double bonds, and the configuration of their carbon structure. Biological systems contain only carbon–carbon bonds in the cis-configuration, although industrial food processing can produce carbon–carbon bonds in the trans-configuration. In the body fatty acids are transported as fatty acids that are carried by plasma protein albumen or transported as triglycerides (glycerol with ester linkages to three fatty acids) in either chylomicrons or very low density lipoproteins (VLDL).

Saturated Fatty Acids

Saturated fats contain no double bonds. Major food sources include red meat, poultry, fish, dairy foods (milk, eggs, cheese, and butter), and tropical oils (palm and coconut oil). Butter is an example of a food product rich in saturated fats and solid at room temperature and less solid when the summer kitchen temperature is 80 °F. In the human body, cell membranes also need some degree of rigidity and hence saturated fatty acids in the plasma membrane prevent cells from being too flexible (fragile). For this reason plants (e.g., the palm tree) and fish (e.g., snapper) that thrive in warmer growing environments typically contain more saturated fatty acids.

Unsaturated Fatty Acids

Unsaturated fatty acids contain one or more double bonds in the carbon chains. They are of two types: monounsaturated fatty acids (MUFA) that contain only one double bond and polyunsaturated fatty acids (PUFA) that contain two or more double bonds. Food sources of MUFA include olive and canola oils, nuts, and seeds. Major sources of PUFA include plant oils such as sunflower oils, soybean, safflower, and corn. Unsaturated fats have a lower melting point than saturated fats. For that reason many animal fats are solid at room temperature while unsaturated fats are typically liquid at room temperature. Too

much rigidity in a cell plasma membrane can also be detrimental and unsaturated fatty acids in the lipid bilayer prevent this. For this reason plants and fish that thrive in colder growing environments (e.g., walnut and cod) typically contain more unsaturated fatty acids.

Essential Fatty Acids

Essential fatty acids (EFA) are fatty acids that cannot be produced by the body or cannot be produced in sufficient amounts. They therefore need to be consumed in the diet. EFA are long-chain PUFA and fall into two groups, namely $n-3$ fatty acids (also known as omega-3 fatty acids) and $n-6$ fatty acids (also known as omega-6 fatty acids). The nomenclature stems from the position of the first double bond in relation to the methyl end (i.e., it is located in the third carbon in the case of $n-3$ or the sixth carbon with $n-6$).

The most important members of the $n-3$ family are alpha-linolenic acid, eicosapentaenoic (EPA), and docosahexaenoic acid (DHA). Alpha-linolenic acid is found in vegetable oils, including flaxseed oil (a rich source), soybean oil, and to a lesser extent, canola oil. Several species of cold-water fatty fish are rich sources of EPA and DHA, including herring, salmon, mackerel, sardines, and trout (Table 24.1). By contrast, white fish, such as cod, hake, and haddock, are poor sources. Some fish species have a possibly harmful level of mercury. The highest levels are found in king mackerel, shark, swordfish, and tilefish with lower levels in tuna. For that reason it is recommended that children and pregnant women refrain from eating these species.

Triglycerides

Triglycerides are fats formed by one molecule of glycerol as the backbone and three chains of fatty acids. Formation of triglycerides permits fatty acid transportation to the body in chylomicrons that originate in the intestine or as very low density lipoproteins for transportation out of the liver. Tissue-specific lipases in the blood cleave the fatty acids from triglycerides permitting fatty acid transport into fatty acid oxidizing cells such as cardiac myocytes. The same process transports fatty acids into adipocytes where the intracellular enzyme acyltransferase attaches free fatty acids to glycerol. By this means adipocytes can accumulate fat stores for caloric expenditure during times of low caloric intake.

Table 24.1 Content of $n-3$ fatty acids (EPA and DHA) in fish consumed in the USA

Fish	EPA + DHA (mg/100 g)
Anchovy	2060
Herring	2010
Salmon (farmed or wild)	1900
Mackerel	1200
Sardines	980
Trout	940
Tuna, white (albacore)	860
Shark	690
Pollock	540
Tuna, light (skipjack)	330
Halibut	235
Cod	160

Modified from [1]

Cholesterol and Sterols

Cholesterol is a complex lipid with a sterol-ring structure that can only be synthesized primarily by hepatocytes in the human at night. Sterols are the basic building blocks for vitamin D and steroid hormones. Cholesterol is absent from plant foods. It is found only in animal foods with eggs, shrimp, and crab representing the richest dietary sources, although paradoxically these foods are also rich in MUFA and PUFA.

Hydrogenated Fats and Trans-Fatty Acids

Hydrogenation is the chemical process by which hydrogen atoms are added to unsaturated fatty acids. By this means oils rich in unsaturated fats become more saturated and more solid. While much of the unsaturated fatty acids are converted to saturated fatty acids during hydrogenation, some are converted to an unnatural form of unsaturated fatty acids known as trans fatty acids which have the carbon-to-carbon double bonds in the trans-configuration. The process is valuable for the food industry as hydrogenated fats are more resistant to oxidation; the smell of rancid fish is the classic example of polyunsaturated fat oxidation. As a result, foods containing hydrogenated fats are more stable, less prone to rancidity, and have a longer shelf life. Trans fats have been used for many years in the production of baked goods and pastries such as doughnuts, cakes, and cookies, as well as the production of margarine. The serious negative health implications of trans-fatty acids are discussed below.

Dietary Fats and Health

Dietary fats have multiple health effects.

Dietary Fats, Body Weight, and Obesity

Fat-rich foods are energy dense and make it easy to overconsume food energy. The use of oils in cooking, processed foods, and the presence of oils in fast foods, fried foods, or the fettuccini heavy cream sauce on a plate of pasta facilitate caloric overconsumption of fat-rich foods. Caloric overconsumption is, of course, strongly predictive of excess weight gain.

The idea that a relatively high intake of dietary fat tends to cause excessive weight gain has been debated for several decades. Many prospective cohort studies have investigated whether the amount of fat in the diet is a predictor of weight change. These studies suggest only a weak association between dietary fat and excess weight gain [2, 3]. Many randomized trials have also been conducted. These have been analyzed in two systematic reviews and meta-analyses. One concluded that lowering the amount of fat in the diet leads to modest weight loss [2]. However, the other one, which was more recent and more extensive, concluded that lowering the amount of fat in the diet does not increase weight loss [4]. Taken as a whole, this evidence lends very little support to the view that diets with a high content of fat facilitate excess weight gain.

Dietary Fat and Heart Disease

For several decades, saturated fats were widely considered as being a major causal factor in coronary heart disease (CHD). The presumed mechanism of action was that saturated fat consumption raised LDL-cholesterol. Saturated fats worsen the blood lipid profile and increase the risk of CHD when they replace unsaturated fats. However, saturated fats have little or no harmful effect on risk when they replace refined carbohydrates in an isocaloric fashion; this is because any rise in LDL-cholesterol is cancelled out by the simultaneous rise in HDL-cholesterol. Thus, it is an oversimplification to say that "saturated fats raise the blood cholesterol." Another important finding to emerge from the prospective cohort studies was a failure to show any clear association between intake of saturated fats and risk of CHD [5]. Clinical studies that replace saturated fats with PUFA (mainly $n-6$ fatty acids) not only improve the lipid profile but also decrease CHD risk [6, 7]. Based on the balance of evidence, it is prudent to reduce the intake of saturated fat and replace them with foods containing PUFA, and perhaps also sources of MUFA such as olive oil and canola oil. However, this is just one component of a much broader dietary strategy against CHD.

The evidence is much more clear-cut for trans-fatty acids. Solid evidence has emerged demonstrating that these fats have a harmful effect on the blood lipid profile, both by raising the blood level of LDL-cholesterol and by lowering the blood level of HDL-cholesterol [8]. Cohort studies also clearly link trans-fatty acid intake with increased CHD risk [9]. It is therefore important to minimize their consumption (preferably well below 1% of energy intake). In response to this evidence, regulatory agencies in the USA and other countries have taken steps to reduce the amount of trans fats present in the diet. Hopefully, in coming years, their presence in food will be completely eliminated (with the exception of the small amounts found in some animal foods). As documented in Table 24.2, the cost-benefits of removal of these fats from the US food chain is strongly positive.

The beneficial effect of fish with a higher fat content in preventing heart disease has attracted much attention. A large body of evidence from cohort studies provides strong evidence that persons who regularly eat fish are at significantly reduced risk of cardiac death (~20–38% lower) than are people who seldom eat fish [11]. It is widely believed that long-chain $n-3$ fatty acids are mainly responsible for this benefit [1]. This has been tested numerous times in randomized clinical trials. However, the findings reveal that the reduction in risk of cardiac death is fairly small, roughly 9% [12]. However, CHD is associated with $320 billion in health costs and causes 376,000 annual deaths in the USA [13], and a 9% reduction in this statistic could potentially amount to $39 billion and 37,000 lives.

The major mechanisms responsible for the cardioprotective effect of $n-3$ fatty acids are believed to be related to antiarrhythmic effects, the stabilization of atherosclerotic plaques, and an improvement in endothelial relaxation and vascular compliance [14].

On balance, the evidence provides strong support for the view that people should be encouraged to eat fatty fish twice a week as a means to prevent heart disease. Fish is also a source of various other nutrients including vitamin D and selenium. However, eating fish can represent a challenge for individuals who are vegan or simply don't like fish. Fish can also be expensive and their availability on a

Table 24.2 Costs and benefits for the removal of partially hydrogenated fats

20-year net present value	Low estimate	Mean	High estimate
Costs	$2.8	$6.2	$11
Benefits	$11	$140	$440
Net benefits	$5	$130	$430

Costs are shown in billions of dollars. Modified from [10]

global scale is limited by ecological limits. For these individuals, supplementation with fish oil (one or two teaspoons daily) can be the next best option, although the efficacy of this is still to be confirmed. The extent to which *n*−3 fatty acids from plant sources are also preventive against heart disease is also unclear [6].

n−*3 Fatty Acids and Health Benefits*

A body of evidence suggests that the health benefits of *n*−3 fatty acids extend beyond heart disease. These dietary fats may also protect against the development of a number of other diseases such as some cancers, rheumatoid arthritis, and dementia. These benefits are generally more strongly associated with *n*−3 fatty acids from fish than from plant sources.

Conclusion

Fat has been the central point of many controversies in nutrition. Choosing healthy types of fat is important in health maintenance and the prevention of chronic diseases. Doubts have been raised regarding whether saturated fatty acids play a major role in the etiology of CHD. Looking at the evidence as a whole, it makes most sense to reduce the intake of saturated fatty acids and replace them with foods containing PUFA, and perhaps also MUFA. This dietary strategy improves the lipid profile and may decrease CHD risk. The major sources of these fats are oils of plant origin such as olive, canola, sunflower, soybean, and corn.

Trans-fatty acids increase the risk of CHD. Reducing their content in food has been proven to be a particularly important public health approach for the prevention of CHD. Evidence indicates that eating fatty fish regularly is another effective dietary strategy for the prevention of CHD. The active ingredient is believed to be long-chain *n*−3 fatty acids (EPA and DHA). These fats may also help prevent other chronic conditions. The extent to which alpha-linolenic acid, the major *n*−3 fatty acid from plant sources, achieves the same health benefits as *n*−3 fatty acids from fish is still uncertain.

With the realization that the type of dietary fat, rather than the amount, is the critically important factor, there has been less focus in recent years on reducing the total amount of fat in the diet. As a result, the trend for recommendations has shifted from “no more than 30%” to a more liberal 20–35% of calories.

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Chapter 25
Vitamins: The Essentials

Karen M. Davison

Key Points

- Vitamins are essential organic compounds which are not synthesized in sufficient amounts by the body and therefore must be obtained in small quantities from the diet.
- Vitamins may be classified according to their solubility in water or fat.
- Certain levels of vitamin intakes can lead to deficiency or toxicity; the latter is generally due to excess amounts derived from supplements.
- Vitamins function synergistically and are best derived from food. Supplementation may be warranted in certain subpopulations due to life-stage requirements, disease states, or having specific biomarkers or genomic markers.

Keywords Vitamins • Supplements

Introduction

The field of nutrition originated from the discovery of vitamins, a group of organic essential compounds. Vitamins are not synthesized by the body in amounts adequate to meet normal physiological functioning and therefore minute amounts obtained through diet are essential for maintenance, growth, development, and reproduction. Insufficient intake of micronutrients, both vitamins and minerals, leads to specific deficiency syndromes.

Traditionally, vitamins have been classified based on their solubilities. The fat-soluble vitamins (A, D, E, K) are absorbed passively, transported with dietary lipid, and tend to be stored in the liver and in body fat but 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. Table 25.1 provides an overview of the vitamins according to their functions, food sources, recommended levels of intake to support health, stability, as well as deficiency and toxicity symptoms.

K.M. Davison, Ph.D. (✉)
Department of Biology, Kwantlen Polytechnic University,
Fir Building, Room 339, 12666 72nd Avenue, Surrey, BC, Canada, V3W 2M8
e-mail: karen.davison@kpu.ca

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Table 25.1 Vitamins: reliable food sources, stability, associated body systems, functions, deficiency and toxicity symptoms

Vitamin and adult requirements[a]	Reliable food sources	Solubility and stability	Associated body systems, functions, deficiency/toxicity symptoms
Vitamin A	*Vitamin A (preformed retinol)*: fortified milk and margarine, milk fat, egg yolk, liver	Fat-soluble	*Systems:* Genito-urinary, immune, integumentary, nervous, respiratory
RDA: M: 900 μg RAE[b] F: 700 μg RAE[b]	*Carotenoid precursors*: yellow, orange, and dark green leafy vegetables; deep-orange fruits (cantaloupe, apricots, peaches)	Stable in presence of light, heat, usual cooking methods	*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
Provitamins: β-carotene (and related substances)		Destroyed by oxidation, drying, very high temperature, ultraviolet light	*Deficiency:* Night blindness, rough skin, susceptibility to infection, impaired growth, immunity, reproductive dysfunction
			Toxicity: Blurred vision, irritability, loss of appetite, ↑ activity of bone-dismantling cells causing ↓ bone density and bone/joint pain, skin disorders, liver disease, birth defects β-Carotene: harmless yellowing of skin
Thiamin (vitamin B_1)	Meat, pork, organ meat, fish, poultry, legumes, whole grain and enriched breads, cereals and grain products, nuts, potatoes	Water-soluble	*Systems:* Circulatory, digestive, genito-urinary, muscular, nervous
RDA: M: 1.2 mg F: 1.1 mg		Unstable in presence of heat, alkali, oxygen. Heat stable in acid solution	*Functions:* Helps enzymes release energy from carbohydrate; essential for growth, normal appetite, digestion, healthy nerves
			Deficiency: Beriberi: edema, heart irregularity, mental confusion, muscle weakness, apathy, impaired growth *Toxicity:* None reported
Riboflavin (vitamin B_2)	Milk and dairy foods, leafy green vegetables, organ meats, meat, whole grain or enriched breads, eggs	Water-soluble	*Systems:* Genito-urinary, integumentary, muscular, nervous
RDA: M: 1.3 mg F: 1.1 mg		Stable in presence of heat, oxygen, acid. Unstable in presence of light, alkali	*Functions:* Helps release energy from carbohydrate, fat, and protein; promotes healthy skin, normal vision
			Deficiency: Eye problems, cheilosis (fissuring of the lips), angular stomatitis (cracks in skin at corners of mouth), swollen magenta tongue, hypersensitivity to light, peripheral neuropathy

			Toxicity: None reported
Niacin (vitamin B_3)	Meat, eggs, poultry, fish, milk, grains (whole and enriched), nuts, legumes, peanuts	Water-soluble	*Systems:* Genito-urinary, integumentary, muscular, nervous
RDA: M: 16 mg NE[c] F: 14 mg NE[c] UL: 35 mg		Stable in presence of heat, light, oxidation, acid, alkali	*Functions*: Helps enzymes release energy from energy nutrients; promotes health of skin, nerves, digestive system *Deficiency:* Muscle weakness, anorexia, indigestion, skin eruptions. Pellagra characterized as dermatitis, dementia, diarrhea ("three Ds") *Toxicity*: Flushing, nausea, headaches, cramps, ulcer irritation, heartburn, abnormal liver function, rapid heartbeat with doses above 500 mg/day. Risks are greater with time-release forms of supplements. Intake of megadoses should be monitored
Pantothenic acid (vitamin B_5)	All plant and animal foods. Best sources: Eggs, kidney, liver, salmon, yeast. Possibly synthesized by intestinal bacteria	Water-soluble	*Systems*: Endocrine, genito-urinary, muscular, nervous
AI: 5 mg		Unstable in presence of acid, alkali, health, certain salts	*Functions*: Essential for energy production from major nutrients and synthesis reactions *Deficiency:* Impaired lipid synthesis and energy production; paresthesia in feet; depression, insomnia, weakness *Toxicity:* None reported
Vitamin B_6 (pyridoxine, pyridoxal, pyridoxamine)	Meat, poultry, fish, shellfish, legumes, fruits, soy products, cereal bran and germ, milk, egg yolk, oatmeal, legumes	Water-soluble	*Systems:* Genito-urinary, muscular, nervous
RDA: M: 1.3–1.7 mg F: 1.3–1.5 mg UL: 100 mg/day		Stable in presence of health, light, and oxidation	*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, possible impaired immunity *Toxicity*: Sensory and motor neuropathy; depression, fatigue, irritability, headaches, numbness, damage to nerves, difficulty walking

(continued)

Table 25.1 (continued)

Vitamin and adult requirements[a]	Reliable food sources	Solubility and stability	Associated body systems, functions, deficiency/toxicity symptoms
Folate (folic acid) (vitamin B_9)	Green leafy vegetables, liver, legumes, seeds, citrus fruits, melons, enriched breads and grain products, yeast	Water-soluble	*Systems*: Circulatory, genito-urinary, muscular, nervous
RDA: 400 μg		Stable in sunlight when in solution. Unstable in presence of heat in acid	*Functions*: Essential for synthesis of DNA, RNA, and maturation of red blood cells; protein metabolism; new cell division
UL: 1000 μg			*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, certain cancers
			Toxicity: Diarrhea, insomnia, irritability; may mask vitamin B_{12} deficiency
Vitamin B_{12}	Animal products: meat, fish, poultry, shellfish, milk, cheese, eggs; fortified cereals. Vegans require supplement	Water-soluble	*Systems*: Circulatory, genito-urinary, muscular, nervous
RDA: 2.4 μg		Slowly destroyed by acid, alkali, light, oxidation	*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: anemia, smooth red tongue, fatigue: nerve degeneration progressing to paralysis. May occur due to inadequate production and secretion of intrinsic factor
			Toxicity: None reported
Vitamin C	Citrus fruits, brassica vegetables (Brussels sprouts, cauliflower, broccoli), tomatoes, potatoes, bell peppers, strawberries, guava, pineapple, kiwi (fruits and vegetables in fresh form are best sources)	Water-soluble	*Systems*: Circulatory, genito-urinary, integumentary, immune, muscular, nervous, respiratory, skeletal
RDA: M: 90 mg F: 75 mg		Unstable in presence of heat, alkali, and oxidation, except in acids. Destroyed by storage	*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
UL: 2000 mg			*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	Self-synthesis with sunlight; fortified milk, fortified margarine, egg yolk, liver, fish	Fat-soluble	*Systems*: Circulatory, endocrine, genito-urinary, integumentary, immune, nervous, skeletal
RDA: 5 µg 51–70 year: 10 µg >70 year: 15 µg UL: 50 µg		Stable in presence of heat, oxidation	*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 impairment, abnormal bone growth
Vitamin E	Wheat germ, vegetable oils, green leafy vegetables, whole grain products, liver, egg yolks, nuts, seeds	Fat-soluble	*Systems*: Circulatory, genito-urinary, immune, nervous, respiratory
RDA: 15 mg		Stable in presence of heat and acids. Destroyed by rancid fats, alkali, oxygen, lead, iron salts, and UV irradiation	*Functions*: Strong antioxidant (protects fat-soluble vitamins and polyunsaturated fats); stabilizes cell membranes; protects red blood cells from hemolysis; epithelial tissue maintenance; prostaglandin synthesis
UL: 1000 mg			*Deficiency*: Weakness, breakage of red blood cells, anemia, hemorrhaging *Toxicity*: May increase blood clotting time
Vitamin K	Liver, soybean and other vegetable oils, green leafy and cabbage-type vegetables, wheat bran. Synthesized by intestinal tract bacteria	Fat-soluble	*Systems*: Circulatory, endocrine, genito-urinary, immune, nervous, skeletal
RDA: M: 120 µg F: 90 µg		Resistant to heat, oxygen, and moisture. Destroyed by alkali and UV light	*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's Dietary Reference Intakes (adults 19 years+): Recommended Dietary Allowance (RDA), Adequate Intakes (AI), and Tolerable Upper Intake Level (UL)

[b]*RAE* retinal 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 the Precursor β-Carotene

Vitamin A (retinoids) refers to three preformed compounds (retinol, retinal or retinaldehyde, and retinoic acid) that are only found in animal products and exhibit metabolic activity. β-Carotene is a member of the carotenoid family and is regarded as an antioxidant in addition to other functions [1]. It can yield retinoids when metabolized.Plants also contain other carotenoids, such lutein and lycopene. Some of these carotenoids have vitamin A activity.

Vitamin A has separate roles in vision and various system functions, including cell differentiation, surface function (e.g., cell recognition), growth and development, bone function, immune function, reproduction (e.g., sperm production, fetal development), the reception of light by the eyes, and gene expression. Deficiency symptoms of vitamin A include impaired embryo development, sperm production, and immunity, and alterations in the bone. Other deficiency symptoms include keratinization of the mucous membranes that line the respiratory tract, alimentary canal, urinary tract, skin, and epithelium of the eye which can impair light reception and cause night blindness. Persistent large doses of vitamin A (>100 times the required amount) can overextend the liver's storage capacity and lead to joint pain, dryness and peeling 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 is important for immune system function where it maintains mucosal surfaces of the respiratory, gastrointestinal, and genito-urinary tracts and plays a key role in differentiation of immune system cells. 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].

The B Vitamins

The B vitamins have important roles in energy metabolism.

Thiamin

Thiamin has essential roles as a coenzyme in carbohydrate metabolism. It may also have other roles related to neural function [4]. Thiamin is vital to the functioning of the entire body; a deficiency affects the muscles, nerves, heart, and other organs. A severe deficiency, called beriberi, causes extreme mental confusion, muscle 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 abuse alcohol or have used diuretics long term. Affected individuals can develop Wernicke–Korsakoff syndrome, where the signs vary from mild confusion to coma. Thiamin appears to have minimal toxic effects.

Riboflavin

Riboflavin acts as a coenzyme in energy-releasing reactions. Because riboflavin has a fundamental role in metabolism, a deficiency tends to be first evident in tissues that have rapid cellular turnover such as the skin and epithelia. Riboflavin deficiency tends to occur in combination with deficiencies of other water-soluble vitamins. No adverse effects of high riboflavin intake in humans are known.

Niacin

Niacin is the term for nicotinamide and nicotinic acid. Coenzymes that contain niacin are central in the metabolism of carbohydrates, fatty acids, and amino acids and may also be involved in DNA repair and genome stability [5]. 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. In some clinical cardiovascular guidelines, pharmacologic doses of niacin (10–15 times the RDA) have been recommended to improve abnormal lipid profiles [6]. 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. 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 the biologic activity of pyridoxine. The metabolically active form of vitamin B_6 is pydridoxal phosphate (PLP) which is a coenzyme for numerous enzymes involved in the metabolism of amino acids, neurotransmitters, glycogen, sphingolipids of nerve cells, heme, and steroid hormones. Vitamin B_6, like folate and vitamin B_{12}, is involved in lowering blood levels of homocysteine. It is also required for the conversion of tryptophan to niacin.

A person's requirement for the vitamin 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, oral contraceptives), pregnancy, alcohol abuse, and some diseases. The vitamin has a low toxicity although high doses (several grams daily) have produced sensory and motor neuropathy [7].

Folate

Folate is a general 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 build-up 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. As intake is often low, the folic acid is added to cereal foods sold in the USA and Canada. This has been credited with greatly reducing the incidence of infants with neural tube defects. Women who are pregnant or who may become pregnant are often advised to boost their folate status with a dietary supplement.

Folate deficiency can also cause macrocytic anemia and symptoms such as fatigue, diarrhea, irritability, forgetfulness, lack of appetite, and headache. Folate deficiency can result from dietary insufficiency, heavy alcohol consumption, conditions such as cancer that increase rates of cell division, malabsorption (e.g., inflammatory bowel diseases and celiac disease) [8], the use of several medications, and genetic diseases affecting its absorption or metabolism. Because high levels of blood folate can mask a true vitamin B_{12} deficiency, total folate intake should not exceed 1 mg daily [9]. 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 and is essential for the normal metabolism of all cells, especially those of the GI 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. Cobalamin 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 GI function.

Food sources of vitamin B_{12} are found exclusively in animal foods. Strict vegetarians need to find alternative sources such as vitamin B_{12}-fortified soy beverages, fortified cereals, or B_{12} supplements. 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) functions as an antioxidant, much like β-carotene. It is also involved in the synthesis of collagen in the skin and other connective tissues. It promotes resistance to infection through its involvement with the immune activity of leukocytes, inflammatory reaction processes, and mucous membrane integrity. Megadoses of vitamin C are often promoted as a means to prevent and treat the common cold; however, the evidence provides only weak support for this claim [10]. Vitamin C deficiency results in scurvy.

Vitamin D

Vitamin D is essential in bone health by regulating calcium and phosphorus. Because the body can make vitamin D with the help of sunlight, people can meet their requirement via sun exposure, as well as from the diet. Direct sun exposure to the skin for 30–60 min weekly is sufficient to maintain

vitamin D status for most white people. However, people with dark-colored skin and older adults synthesize less vitamin D from sun exposure. Individuals who apply sunscreen with an SPF factor of 10 can reduce vitamin D production by 90%. Those who reside at latitudes around 40° north or south have insufficient UVB radiation available for at least 5 months of the year. For these people, a diet containing ample amounts of vitamin D-rich foods or supplements is particularly important. Vitamin D also exhibits many non-skeletal effects, particularly on the immune, endocrine, and cardiovascular systems [11, 12].

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. This function of vitamin E is particularly critical in protecting the lungs as they are constantly exposed to free radicals. Vitamin E also 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 related to oxidative stress but evidence from clinical trials of supplements has been mostly negative. Vitamin E may also regulate cell signaling and gene expression [13]. Deficiencies and toxicities 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 [14]. Vitamin K_1 (phylloquinone) is the primary dietary source of vitamin K. Some vitamin K is synthesized by human intestinal microbiota.

Vitamin K deficiency has been associated with lipid malabsorption, destruction of intestinal flora from chronic antibiotic therapy, liver disease, and increased risk of hemorrhage. 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 [15].

Vitamins: How Much Do We Really Need?

As the science of nutrition progresses and we consider factors such as the *Dietary Reference Intakes*, the role of vitamins in prevention of disease, and movements toward personalized medicine, the answer to the question of how much of each vitamin we need is not straightforward.

The Dietary Reference Intakes

The *Dietary Reference Intakes* (*DRI*s) are discussed in detail in Chap. 29. Briefly, they 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) represents 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 poses 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 of Chronic Disease

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 that particular nutrient. Supplementation with the vitamin 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 RDA and exceeds the UL, toxicity symptoms may appear.

Studies have demonstrated that a number of vitamins may have roles beyond those functions normally given to them in the prevention of symptoms of deficiency diseases, and 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. There is also evidence that vitamin D deficits can predispose individuals to cardiovascular disease and cancer (especially colon cancer) [11, 16, 17].

Given that dietary intake measurement at a population level indicates that there are widespread intake deficits for many nutrients and that vitamins have roles beyond preventing deficiency diseases, we must now pose the following question: Should vitamin supplements be recommended? Most nutrition experts would generally answer this question with a "no" and place emphasis on consuming a high-quality 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 looked at more closely in Chap. 32.

Personalized Medicine

> "***I think the future of avoiding the degenerative diseases of aging is not drugs but getting your metabolism and nutrition tuned up. In the future, you will put your finger in a machine and have all the marker proteins in blood analyzed from a finger prick. The machine will say, 'You're low on magnesium' and send a message to your iPhone that you should eat a big plate of spinach or kale every once in a while. Everybody knows their cholesterol number, but in the future they'll know their magnesium number, vitamin D number, and more***."
>
> Bruce Ames, PhD
> Mutagens and Multivitamins
> by Megan Scudellari, The Scientist, June 1, 2014

This quote from Bruce Ames that predicts a future of personalized nutrition approaches based on instantaneous readouts from one's biomarkers is not all that far-fetched. Nutrigenomics, the study of the relationship between genes, diet, and eating behaviors [18], and personalized nutrition, the tailoring of diet to individual needs which can be gene based, has emerged as its own entity in nutritional care. 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 will improve our ability to provide definitive individualized recommendations for vitamin intakes.

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Suggested Further Reading

Institute of Medicine. Dietary Reference Intakes: the essential guide to nutrient requirements. Washington, DC: National Academies Press; 2006.

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

U.S. 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

Chapter 26
Mineral Nutrients: From Macro-Level to Ultra Trace

Karen M. Davison

Key Points

- Minerals are essential inorganic compounds that are required by the body to regulate chemical reactions and provide structure; many serve more than one function.
- 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.
- Mineral bioavailability is affected by body needs, interactions with other nutrients, inhibitors such as phytates and oxalates, and enhancers such as ascorbic acid.
- Deficiencies of certain minerals are global health problems; ingestion of large doses leads to accumulation in the body and can be fatal.
- Select groups may need mineral supplementation, typically as part of a multi-nutrient formula; this is usually due to certain physiologic states (e.g., pregnancy, anemia, disease) and lifestyle choices (e.g., athletes).

Keywords Minerals • Electrolytes • Dietary supplements • Bioavailability

Introduction

Minerals are nutrients are essential for human function, much like vitamins. The minerals represent about 5% of body weight, most of which comes from calcium and phosphorus. The minerals are subdivided into: (1) macrominerals that are present in the body in an amount >0.01% of weight and where >100 mg/day is needed from the diet and (2) microminerals or trace elements which are present in the body in an amount of ≤0.01% of weight and required dietary intake is <15 mg/day. Studies of total parenteral nutrition (TPN) have determined the essentiality of ultra-trace minerals, where daily dietary requirements are in micrograms. Exact requirements have not been established for all of the minerals.

K.M. Davison, Ph.D. (✉)
Department of Biology, Kwantlen Polytechnic University,
Fir Building, Room 339, 12666 72nd Avenue, Surrey, BC, Canada, V3W 2M8
e-mail: karen.davison@kpu.ca

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All minerals, except heme iron, are absorbed in the ionic state. Therefore, minerals that remain bound to organic molecules (chelated) or remain as inorganic complexes after digestion usually are not biologically available. Some minerals may be absorbed better in a chelated form when they are bound to an amino acid (e.g., selenomethionine). Most minerals, especially cations, rely on active transport mechanisms to be absorbed. Unabsorbed minerals remain in the intestinal cells; when the intestinal cells die and slough off, the minerals they contained are excreted. This may be a protective mechanism to prevent toxicity from excessive absorption.

Bioavailability refers to the proportion of a mineral that can be absorbed after its digestion and before its use in tissues and cells. Factors that can reduce bioavailability include the formation of soaps (e.g., calcium and magnesium binding to free fatty acids in the intestinal lumen due to fat malabsorption) and from precipitation when one of a pair of ions (e.g., calcium, which combines with phosphates) is present in the lumen in high concentrations. Mineral–mineral interactions, such as excess zinc intake that reduces copper absorption, can also reduce bioavailability.

Many organic molecules in foods can either inhibit or enhance absorption. Examples of inhibitors include the binding of calcium and other divalent cations by phytates and oxalates. Enhancers include ascorbate for nonheme iron or the hemoglobin protein for iron. Vegetarians tend to consume foods with higher quantities of inhibiting factors, but they also typically ingest more ascorbic acid, which is an enhancer. Other factors that affect mineral bioavailability include gastric acidity, homeostatic adaptations, and stress, which can alter gastrointestinal function. Certain minerals have low bioavailability from foods (e.g., iron, chromium), whereas others have high bioavailability (e.g., sodium, potassium, chloride, iodide, fluoride). Table 26.1 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

Calcium is mainly found in the bones and teeth; about 1% is in the blood, extracellular fluids, and within all tissue cells, where it regulates metabolic functions. Bone is a dynamic tissue that returns calcium to the extracellular fluids and blood when required and takes up calcium from the blood during the postprandial period. In late life, bone retention of calcium derived from food and supplements is limited unless the calcium is consumed along with sufficient vitamin D or provided as an adjunct to antiresorptive medications (e.g., biphosphanates) that slow or stop the breakdown of bone tissue. Adequate dietary calcium is needed to permit optimal gains in bone mass and density in the prepubertal and adolescent years, which provides protection against osteoporosis after menopause. Additional amounts of calcium are recommended to meet the needs of pregnancy, infancy, childhood, adolescence, and lactation. Calcium has many functions apart from its role in bone; these include blood clot formation, nerve transmission, intracellular signaling, and smooth muscle contractility.

Table 26.1 Minerals: reliable food sources, stability, associated body systems, functions, deficiency, and toxicity symptoms

Minerals and adult requirements[a]	Reliable food sources	Associated body systems, functions, deficiency/toxicity symptoms	Probability of deficiency
Macrominerals			
Calcium	Milk and milk products, small fish (with bones), tofu, certain green vegetables, legumes, fortified foods	*Systems:* Circulatory, endocrine, immune, muscular, nervous, skeletal	Bones serve as homeostatic mechanism; long-term deficiency leads to osteoporosis later in life
AI: 1000 mg; >50 year: 1200 mg		*Functions*: Bone and tooth structure, nerve transmission, muscle contraction, blood clotting, blood pressure regulation, hormone secretion	*At risk*: Postmenopausal women; elderly people; individuals who consume a vegan diet, are lactose intolerant, or have kidney disease
UL: 2500 mg		*Deficiency*: Stunted growth in children; bone loss (osteoporosis) in adults *Toxicity*: Elevated blood calcium, kidney stones	
Magnesium	Dark greens, whole grains, nuts, seeds, legumes, seafoods, cocoa	*Systems:* Circulatory, endocrine, immune, muscular, nervous, skeletal	Conditional deficiencies are common with surgery, alcoholism, malabsorption, loss of body fluids, and certain hormonal and renal diseases
RDA: M (19–30 year): 400 mg; (>31 year): 420 mg F (19–30 year): 310 mg; (>31 year): 320 mg		*Functions*: Bone structure, ATP stabilization, enzyme activity, nerve and muscle function	*At risk*: Individuals with alcoholism, kidney or gastrointestinal disease
UL: 350 mg from nonfood sources		*Deficiency*: Nausea, vomiting, weakness, muscle pain, confusion, depressed pancreatic hormone secretion, growth failure *Toxicity*: Excess intakes (from overuse of laxatives) has caused low blood pressure, lack of coordination, coma, death	
Phosphorus	Meat, poultry, fish, dairy products, soft drinks, processed foods	*Systems*: Circulatory, endocrine, immune, nervous, skeletal	Inadequacy is unlikely if protein and calcium intake are adequate
RDA: 700 mg		*Functions*: Structure of bones, teeth, membranes, ATP, DNA; acid–base balance	*At risk*: Premature infants; individuals who abuse alcoho; elderly
UL: 4000 mg		*Deficiency*: Bone loss, weakness *Toxicity*: May cause calcium excretion; calcium deposits in soft tissues (e.g., kidneys)	

(continued)

Table 26.1 (continued)

Minerals and adult requirements[a]	Reliable food sources	Associated body systems, functions, deficiency/toxicity symptoms	Probability of deficiency
Potassium	All whole foods: meats, milk, fruits, vegetables, grains, legumes	*Systems*: Circulatory, endocrine, muscular, nervous, skeletal	Rare in healthy individuals
AI: 4700 mg		*Functions*: Protein synthesis, fluid balance, nerve transmission, and muscle contraction. Potassium helps lower blood pressure	*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
		Deficiency: Muscle weakness, paralysis, confusion; can cause death; accompanies dehydration. Mildly low intake is associated with raised blood pressure	Mildly low intake is very common
		Toxicity: Causes muscular weakness; triggers vomiting; high doses of supplements or IV administration causes irregular heartbeat	
Sodium	Salt, soy sauce; processed foods such as cured, canned, pickled; many packaged foods	*Systems*: Circulatory, endocrine, immune, nervous, skeletal	Extremely rare
AI (19–50 year): 1500 mg		*Functions*: Fluid and acid–base balance; nerve impulse transmission. Salt in the diet also provides chloride which is part of hydrochloric acid found in the stomach, necessary for proper digestion, fluid balance	*At risk*: Active people who drink large volumes of water and fail to replace sodium; people consuming a severely sodium restricted diet
UL: 2300 mg		*Deficiency*: Muscle cramps, mental apathy, loss of appetite	
		Toxicity/high intake: High blood pressure	
Microminerals			
Fluoride	Fluoridated water (1 ppm), tea, coffee, rice, soybeans, seafood	*Systems*: Skeletal	Occurs in areas where fluoride content in water is low (<1 ppm)
AI: M: 4 mg F: 3 mg		*Functions*: Formation of bones and teeth; resistance to tooth decay	*At risk*: Populations in areas with unfluoridated water; those who drink mainly bottled water (deionized, purified, demineralized, or distilled water may contain no or only trace amounts of fluoride)
UL: 10 mg		*Deficiency*: Susceptibility to tooth decay	
		Toxicity: Fluorosis (discoloration of teeth), kidney damage, bone abnormalities	

(continued)

Table 26.1 (continued)

Minerals and adult requirements[a]	Reliable food sources	Associated body systems, functions, deficiency/toxicity symptoms	Probability of deficiency
Iron	Red meats, fish, poultry, shellfish, eggs, legumes, dried fruits, molasses, whole, enriched, or fortified grains	*Systems*: Circulatory, endocrine, immune, muscular, nervous	Common in at-risk groups. Deficiency may be associated with unusual blood loss, parasites, malabsorption
RDA: M: 8 mg F (19–50 year): 18 mg; (>50 year): 8 mg		*Functions*: Part of hemoglobin and myoglobin; electron carriers in electron transport chain; immune function	*At risk*: Infants and preschool children; adolescents; women of childbearing age; pregnant women; athletes; vegetarians
UL: 45 mg		*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	
Zinc	Meats, seafood, poultry, whole grains, legumes, wheat brain, eggs	*Systems*: Immune, integumentary, muscular, nervous, reproductive	Extent of inadequacy unknown. Conditional deficiency can occur with systemic childhood illness and individuals who are nutritionally depleted or have experienced severe stress such as surgery
RDA: M: 11 mg F: 8 mg		*Functions*: Regulates protein synthesis; functions in growth, development, wound healing, immunity, antioxidant protection, vitamin A transport, making sperm, fetal development	*At risk*: Vegetarians; low-income children; elderly
UL: 40 mg		*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	
Ultra-trace minerals			
Copper	Organ meats, seafood, nuts, seeds, whole grains, cocoa	*Systems*: Immune, muscular, nervous	No evidence
RDA: 900 μg		*Functions*: Part of proteins needed for iron absorption, lipid metabolism, collagen synthesis, nerve and immune function, antioxidant protection	*At risk*: Those who over-supplement with zinc; Menkes disease is a genetic disorder resulting in copper deficiency
UL: 10 mg		*Deficiency*: Anemia, poor growth, bone abnormalities *Toxicity*: Vomiting, diarrhea	

(continued)

Table 26.1 (continued)

Minerals and adult requirements[a]	Reliable food sources	Associated body systems, functions, deficiency/toxicity symptoms	Probability of deficiency
Chromium	Brewer's yeast, meats, nuts, whole grains, mushrooms	*Systems*: Endocrine	Found in those with severe malnutrition and may be a factor in diabetes development in older adults
AI: M (19–50 year): 35 μg F (19–50 year): 25 μg		*Functions*: Associated with glucose metabolism; enhances insulin action	*At risk:* Malnourished children
		Deficiency: Abnormal glucose metabolism; high blood glucose	
		Toxicity: Can occur with occupational exposure; causes damage to skin and kidneys	
Iodine	Iodized salt, seafood, bread	*Systems*: Endocrine	Iodization of table salt recommended, especially in areas where food is low in iodine
RDA: 150 μg		*Functions*: Needed for synthesis of thyroid hormones; constituent of T_4 and related compounds synthesized by the thyroid gland; T_4 functions in reactions involving cellular energy	*At risk*: Populations in areas with low-iodine soil and iodized salt is not used
UL: 1100 μg		*Deficiency*: Goiter, cretenism, intellectual disability, growth and developmental abnormalities	
		Toxicity: Enlarged thyroid; depressed thyroid activity	
Selenium	Grains, organ meats, milk, seafood, eggs; varied amounts in vegetables depending on selenium content of soil	*Systems*: Endocrine, integumentary	Has occurred in patients receiving long-term TPN without selenium supplementation
RDA: 55 μg		*Functions*: Involved in fat metabolism, spares vitamin E; acts as an antioxidant as part of glutathione peroxidase; synthesis of thyroid hormones	*At risk*: Populations in areas with low selenium in soil
UL: 400 μg		*Deficiency*: Muscle pain, weakness, Keshan disease	
		Toxicity: Vomiting, diarrhea, hair and nail changes	

[a]Requirements are based on the Institute of Medicine's Dietary Reference Intakes (adults 19 years+): Recommended Dietary Allowance (RDA), Adequate Intakes (AI), and Tolerable Upper Intake Level (UL)

Milk and milk products are the richest food sources of calcium. The calcium in these foods is highly bioavailable. Other prominent sources are green vegetables, such as broccoli, kale, and bok choy, and a few types of fish and shellfish. Inadequate calcium intake may pose a risk of osteomalacia and osteoporosis. Excess intakes (>2000 mg/day) can cause hypercalcemia and calcification in soft tissues, especially the kidneys, and can interfere with the absorption of other divalent cations such as iron and zinc.

Phosphorus

Most phosphorus is present in the skeleton and teeth as calcium phosphate crystals. The remaining phosphorus exists in a metabolically active pool in body cells and in the extracellular fluid compartment. The mineral is present as part of phospholipids in cell membranes.

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 intakes.

Magnesium

Most magnesium is found in bone followed by muscle, and the remainder is in soft tissues and body fluids. Magnesium is a cofactor for more than 300 enzymes involved in many aspects of cellular metabolism including fatty acid and protein synthesis and phosphorylation of glucose.

Moderate depletion is prevalent in older populations in Western nations [1]. A high-quality diet will supply adequate magnesium, but as most people do not eat such a diet, the intake tends to be below the RDA for much of the population. Deficiency may be secondary to poor dietary intakes or conditions such as an increased loss of electrolytes or a shift in electrolyte balance, especially decreases in potassium. Magnesium intakes well below the RDA may be related to insulin resistance, metabolic syndrome, high blood pressure, and heart failure [2, 3]. Leukocyte magnesium is the most reliable indicator of the status of the mineral. The tolerable upper intake level (UL) is based only on supplemental and pharmacologic sources. Those with renal insufficiency should avoid large doses of supplemental magnesium as it can have adverse effects on the central nervous system.

Sodium

Sodium regulates both extracellular and plasma volume and is also important in neuromuscular function and acid–base balance. The major source of sodium is sodium chloride (table salt). Nearly, all dietary chloride comes from sodium chloride (Table 26.1). Actual minimum requirements of sodium are estimated to be as low as 200 mg/day; however, the mean daily salt intake in Western societies is about 7–8 g, largely from sources such as food eaten at restaurants and fast-food establishments, and processed foods. Healthy kidneys are usually able to excrete excess sodium intake; however, persistent excess sodium intake can lead to hypertension [4, 5]. An upper limit of intake has been set at 2300 mg/day of sodium, equivalent to about one teaspoon of salt.

Potassium

Potassium is the major cation of intracellular fluid and is present in small amounts in extracellular fluid. With sodium, potassium is involved in maintaining fluid balance, osmotic equilibrium, and acid–base balance. In addition to calcium, it is important in the regulation of neuromuscular activity. Increasing the potassium in the diet can promote sodium excretion under most circumstances and thereby helps to lower the blood pressure [6]. Whole foods of all kinds, including fruits, vegetables, grains, meats, fish, and poultry, are rich sources of potassium. As is the case with magnesium, adequate potassium can be obtained from a healthy diet that minimizes processed foods, but because most of the population consumes a low-quality diet, intake below the RDA is common.

Microminerals

Fluoride

Fluoride is found in nearly all drinking water and soil; however, content varies greatly throughout the world. Although there is no known requirement for fluoride in human metabolic pathways, this anion is known to be important for the health of bones and teeth. The drinking water in many communities is fluoridated as a public health measure. Mild fluorosis can develop from daily doses of 0.1 mg/kg/day or amounts more than 2–3 ppm of fluoride in drinking water. Intakes of fluoride may vary greatly depending on consumption of fluoridated water, the use of dentifrices, and other sources. As a result, some children may ingest total amounts of fluoride that exceed the optimum intake level of 0.05–0.07 mg/kg/day.

Iron

The adult body contains iron in two major pools: functional iron in hemoglobin, myoglobin, and enzymes, and storage iron in ferritin, hemosiderin, and transferrin (transport protein in blood). Adult women have much lower amounts of iron in storage than do men. Iron is well conserved by the body; about 90% of it is recovered and reused every day. The rest is excreted, primarily in bile. For that reason, dietary iron must be available to maintain iron balance.

The functions of iron relate to its ability to participate in reduction and oxidation (redox) reactions [7]. Iron is a highly reactive element that can interact with oxygen to form intermediates with the potential of damaging cell membranes or degrading DNA. Iron must be tightly bound to proteins to prevent these destructive effects. Iron metabolism is involved in red blood cell function, myoglobin activity, and the roles of numerous heme and nonheme enzymes. Because of its redox properties, iron has a role in blood and respiratory transport of oxygen and carbon dioxide, the functions of cytochromes (enzymes) involved in cellular respiration, and ATP generation. Iron is also important for immune function and cognition.

Dietary iron exists in two chemical forms: (1) heme iron, which is found in hemoglobin, myoglobin, and some enzymes; and (2) nonheme iron, which is mainly found in plant foods, nonheme enzymes, and ferritin. Several factors affect the intestinal absorption of iron, especially nonheme iron. Ascorbic acid is a potent enhancer of iron absorption which reduces ferric to ferrous iron and forms a chelate with iron that remains soluble in the alkaline pH of the lower small intestine. However, the effect of prolonged daily dietary increases in ascorbic acid on iron absorption appears to be insufficient for improving iron status over time without additional iron supplementation [8]. Other enhancers include sodium ethylenediaminetetraacetic acid (EDTA), sugars, and sulfur-containing amino acids that help iron entry by forming chelates with ionic iron, and animal proteins from beef, pork, lamb, fish, and chicken which provide the “meat factor” (a substance that is not fully understood). Foods with high phytate content (e.g., whole grains, nuts, and legumes) have low iron bioavailability, but whether phytate is the cause is unclear. Oxalates, found in foods such as dark green vegetables, berries, black tea, nuts, soy/soy products, and wheat bran, can inhibit iron absorption. Tannins, which are polyphenols, in tea also reduce nonheme iron absorption. Conversely, the presence of an adequate amount of calcium helps to remove phosphate, oxalate, and phytate that would otherwise combine with iron and inhibit its absorption. Some antacids can bind with iron and prevent the mineral’s absorption. The availability of iron from different compounds used for food enrichment or as supplements varies widely according to their chemical composition. Although ferrous forms of iron are readily absorbed, compounds such as ferrous pyrophosphate, citrate, or tartrate are poorly absorbed. Iron is usually added to baby foods in an elemental form; the amount that is absorbed depends on the iron particle size.

Two concerns about iron status predominate: the incidence of iron deficiency anemia and the hazards of excess iron intake. Iron deficiency anemia, and its precursor, deficiency of dietary iron, are quite common. Those at highest risk include infants less than 2 years of age, adolescent girls, pregnant women, older adults, and females involved in endurance sports. The final stages of iron deficiency include hypochromic, microcytic anemia and can be corrected by providing supplements of ferrous sulfate or ferrous gluconate until blood parameters return to normal. Subsequent anemia can be prevented by an iron-rich diet derived from food sources, such as red meat, poultry, fish and oysters, whole grains, enriched and fortified breads and cereals, and dried beans. In addition to an insufficient intake of iron, causes of iron deficiency include injury, hemorrhage, or illness (e.g., gastrointestinal diseases that interfere with absorption), and an unbalanced diet that is inadequate in protein, folate, and vitamin C.

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. Hemosiderosis is an iron-storage condition that develops in individuals who consume abnormally large amounts of iron or who have a genetic defect. Iron supplements may not be beneficial for postmenopausal women or older men because of the associated increased risk for heart disease and cancer. Intake that exceeds the RDA, which can occur if many fortified foods and supplements are consumed, may contribute to an enriched oxidative environment. This may lead to arterial vessel damage and excessive amounts of free radicals that attack cellular molecules and may generate potentially carcinogenic molecules within cells [9].

Zinc

Zinc functions in association with more than 300 different enzymes involved in either synthesis or catabolism of carbohydrates, lipids, proteins, and nucleic acids. This trace mineral has a structural role in several proteins. Zinc is also involved in transport processes, immune function, insulin function, and gene expression. Although widely promoted to cure or prevent the common cold, zinc-containing products such as lozenges do not appear to be effective [10].

The most widely available form of zinc occurs in red meat and poultry. Meat intake is frequently low in preschoolers, which has led to fortification of infant and children's foods, especially cereals, with zinc. Although milk is a good source of zinc, a high intake interferes with the absorption of iron and zinc. The phytates from whole grains in unleavened breads may limit zinc absorption. Zinc deficiency is common in developing countries. In Western nations, those most at risk include individuals with alcoholism, pregnant women, older adults, and athletes. Zinc deficiency results in various immunologic defects such as deficient thymic hormone activity. Excess zinc supplementation can interfere with copper absorption and result in an iron imbalance. Zinc sulfate in excess of 2 g/day may cause gastrointestinal irritation and vomiting.

Ultra-Trace Minerals

Copper

Copper is a component of many enzymes involved in functions such as energy production and antioxidation. Deficiency is rare in adults probably because copper accumulates in the liver throughout life in most people. Similar to zinc, low copper intakes may contribute to reduced immune responses in healthy individuals.

Iodine

The body contains 20–30 mg of iodine, most of which is stored in the thyroid gland. Iodine is needed for the synthesis of thyroid hormones which regulate body temperature, metabolic rate, reproduction, and growth. Uptake of iodide ions by the thyroid cells may be inhibited by goitrogens, substances that exist naturally in such foods as cabbage, turnips, peanuts, cassava, sweet potatoes, kelp, and soybeans. Goitrogens are inactivated by heat.

Iodine deficiency causes goiter, a condition estimated to affect 200 million people worldwide. About two billion people living in less developed nations remain at risk for moderate iodine deficiency which may not show an obvious goiter. Iodine deficiency during gestation and early postnatal growth results in cretinism in infants, a syndrome characterized by mental impairment, shortened stature, and hypothyroidism. Less severe variations manifest as moderate impairment in intellectual or neuromotor maturation.

The amount of iodine in foods reflects the amount present in the soil in which plants are grown or on which animals graze. Soil iodine is highest along the coastal regions. It is advised that most people use iodized salt to maintain an adequate iodine intake. Seafood is a good dietary source of iodine. The level of iodine in most Western diets is appropriate for good health, but for some with underlying thyroid pathologic conditions, excess iodine in the diet may result in hypothyroidism, goiter formation, or hyperthyroidism [11].

Selenium

Tissue levels of selenium are influenced by dietary intake and the geochemical environment. Selenium, as selenomethionine or selenocysteine, is widely distributed in the body. The antioxidative effects of selenium and vitamin E may reinforce each other by the overlap of their protective actions against oxidative damage.

Selenium deficiency takes years to develop when food intake is inadequate. Cases of severe deficiency have only been reported for regions in China, where the soil has an exceptionally low content of the mineral. Likewise, Keshan–Beck disease has been found in Mongolia in preadolescent and adolescent children also due to low amount of selenium in the soil. A relatively low intake of selenium may increase the risk of cancer [12]. Evidence of selenium toxicity has been reported in China and Australia.

Chromium

Chromium was deemed essential when patients receiving TPN exhibited abnormalities of glucose metabolism that were reversed with chromium supplementation. Chromium potentiates insulin action and, as a result, influences carbohydrate, lipid, and protein metabolism. The proposed role of chromium with the so-called glucose tolerance factor (GTF) is controversial. Chromium, similar to zinc, may regulate gene expression. Chromium deficiency can result in insulin resistance and some lipid abnormalities. Cases of toxicity have been reported in athletes and power lifters taking chromium picolinate supplements in high doses.

Other Trace Elements

There is evidence that manganese, molybdenum, vanadium, boron, arsenic, nickel, and silicon may be essential in humans. These elements may be necessary in extremely small amounts but can be toxic in excess.

How Much Minerals Do We Really Need?

Select groups within the population may have an increased likelihood for requiring supplementation. For example, dietary intake inadequacies have 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 26.1.

Generally speaking, 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 don't. 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 an 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 [13].

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. Men's multivitamin and mineral formulations 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 single mineral supplements. The pros and cons of taking dietary supplements are examined in more depth in Chap. 32.

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Chapter 27
Issues of Food Safety and Quality: Are "Organic" Foods Better?

Gianna Ferretti, Davide Neri, and Bruno Borsari

Key Points

- Organically grown foods have become increasingly popular with the consumer because of a desire to improve nutrition and prevent environmental contamination.
- Fruits and vegetables are cultivated according to different approaches: conventional (chemical-based agriculture), integrated farm management, organic agriculture.
- Experimental evidence suggests that higher levels of micronutrients and phytonutrients are associated with organically grown fruit and vegetables.
- Cultivation systems affect the amount of chemical residues in products and the risk of its possible biological contamination, whereas synthetic pesticide and additive residues can be avoided in properly managed organic systems.
- Overall, however, the differences between foods grown under different agricultural methods may not be sufficient to declare organic produce as superior quality food when compared to their conventional or integrated counterparts.
- Concerns about the consumption of transgenic foods (GE) are rising among consumers and this situation is aggravated in the USA by the reluctance of governmental authorities to enforce labelling of genetically engineered (GE) foods.

Keywords Organic food • Pesticides • Food safety

G. Ferretti, Ph.D.
Dipartimento di Scienze Cliniche Specialistiche e Odontostomatologiche, Università Politecnica delle Marche, Via Brecce Bianche, Ancona 60131, Italy
e-mail: g.ferretti@univpm.it

D. Neri, Ph.D.
Dipartimento di Scienze Agrarie, Alimentari e Ambientali, Università Politecnica delle Marche, Via Brecce Bianche, Ancona 60131, Italy
e-mail: d.neri@univpm.it

B. Borsari, Ph.D. (✉)
Department of Biology, Winona State University, 175 West Mark St., Winona, MN 55987, USA
e-mail: bborsari@winona.edu

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Introduction

The promotion of diets capable of insuring a balanced nutrient intake to enhance harmonious growth and health has become a priority in developed and in developing countries [1]. However, this may occur at the cost of increased levels of contaminants and agriculture no longer being sustainable. Since the 1970s U.S. agricultural systems have been geared towards a maximal "production" focus, yet, in more recent times, food "quality" has also become an important issue. Quality has translated into an increased public awareness of and demand for foods grown under organic conditions. Plants absorb minerals and trace elements from their environment, along with potentially harmful xenobiotics, and synthesize vitamins and other nutrients (fat, protein, fatty acids, amino acids, sugars, and fiber). Animals eat plants thus absorbing nutrients into their own tissues, as well as accumulating xenobiotics from pesticides and other toxins, when these are present in the environment.

Growing Demand for Organic Food

Consumers' demand for organic foods has increased at an astonishing rate of about 20% per year and was estimated to be worth over $20 billion in 2003 [2]. In the meantime, organic agriculture has become one of the fastest growing markets in the U.S. agricultural sector (Fig. 27.1), and also in many other countries.

The latest global data on organic farming presented by the Research Institute of Organic Agriculture (FiBL) and IFOAM—Organics International at the BioFach fair 2016 in Nuremberg, Germany, show that there are 43.7 million hectares of agricultural land worldwide that are farmed organically (Fig. 27.2).

Pricing for organic produce in 2004 was approximately 33% higher than conventionally grown produce [4]. Consumer reports (http://www.consumerreports.org) reported that in 2015 the price of organically produced fresh fruits and vegetables was between 10 and 70% higher than for conventionally grown foods [5]. For different types of meat, the price may be as much as 200% higher. Organic food in Canada costs about 50–70% more than conventionally grown food. This variance in price includes seasonality and consequently, all the associated and added costs for conservation and

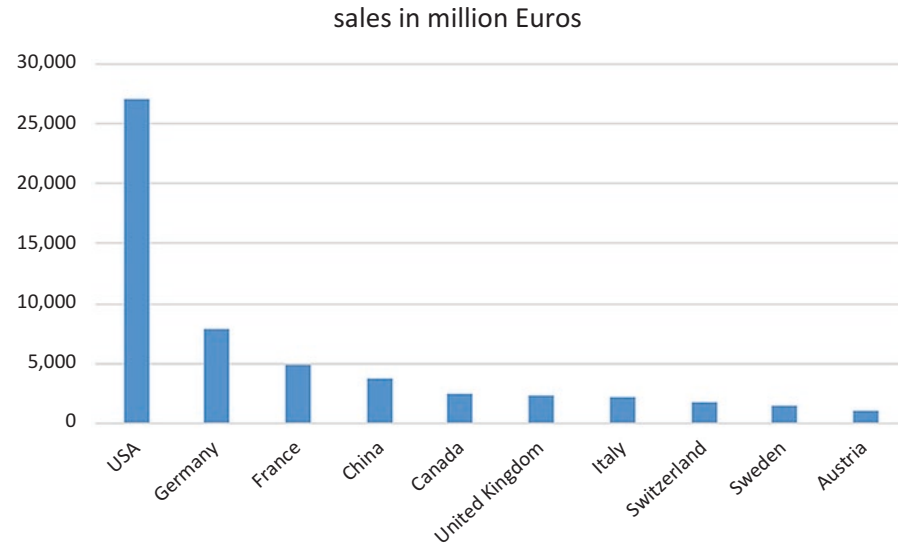

Fig. 27.1 Market growth for organic foods. Modified after: Research Institute for Organic Agriculture (FiBL) [3]. 1 euro = 1.13 US dollars

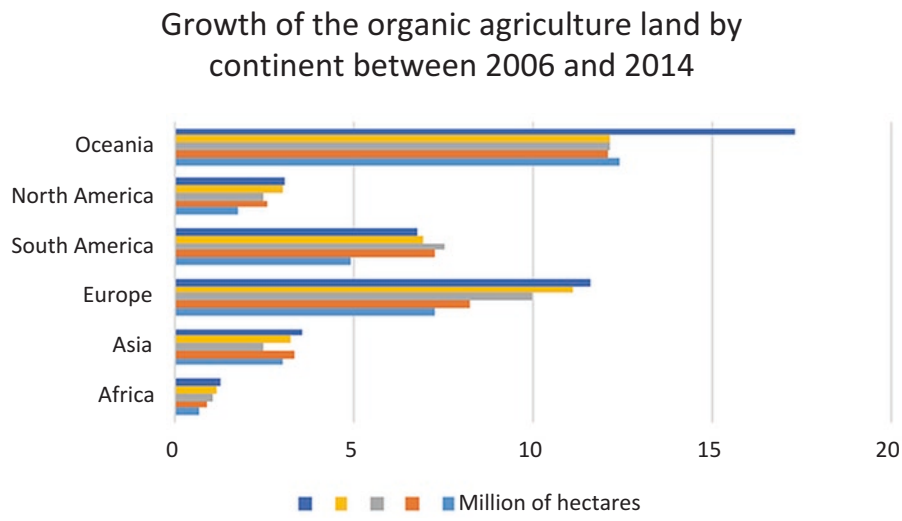

Fig. 27.2 Increased hectarage that was converted to organic food production, worldwide, in recent years. Modified after: Research Institute for Organic Agriculture (FiBL) [3]. 1 hectare = 2.47 acres

transportation to market. However, an accurate determination of whether organically grown foods are of greater nutritional "quality" than conventional foods remains difficult to verify. Even if organically produced foods are nutritionally superior, it is challenging to determine whether the benefits they possess are deserving of their added cost to consumers. In addition to this, evaluating the safety of engineered foods (GE) for human consumption remains a gap of transparency between the agroindustry and consumers, despite continued support by many governments for an increasing employment of GEs in agriculture, even in developing countries [6].

Despite these concerns, we argue in support of the idea that there are many reasons to believe that organically produced foods are worth the added production costs and wish to defend our position in this chapter.

Conventional and Organic Food Production Systems

Food production systems are designed according to an integration of resource use (environmental, genetic, technological, and human), services, and economic means. Conventional, large-scale food production relies heavily on pesticides, fertilizers, and fossil fuels, which pose substantial risks of contamination to plant and animal products. These constitute legitimate concerns to food systems safety and to the environment, with a reduction of biodiversity and an enhancement of soil degradation and erosion [6, 7]. Two main alternative production systems are available at present [8]: integrated farm management (IFM) and organic agriculture (OA). IFM consists in employing multiple tactics (such as integrated pest management, IPM) in a compatible manner to maintain pest populations at levels below those causing economic injury, while providing better protection to humans, domestic animals, plants, and the environment from the residues of agrichemical products. "Integrated" means that a broader, interdisciplinary approach is adopted in agriculture. This integration of techniques, however, should be compatible with the crop being produced and marketing systems in which farming takes place. OA instead has a more holistic approach. In practical terms, it is distinguishable from other farming methods by three main principles: synthetic soluble mineral inputs (fertilizers) are prohibited (as well as growing GE crops), and, finally, synthetic herbicides and pesticides are rejected in favor of natural pesticides and organic soil management practices. Food production systems based

on these principles result in more costly products and less yield per acreage [8, 9]. However, this approach to food production may yield foods that contain fewer added chemicals, even though some are permitted in production protocols of processed foods, as outlined in Table 27.1, and this can be a surprising revelation to some consumers.

What Makes a Food Safe?

Food safety hazards include contamination by biological, physical, or chemical substances (see Table 27.2). These may pose significant health risks to consumers. The contamination of food may occur through environmental toxins (such as heavy metals, PCBs, and dioxins), or through the intentional use of various chemicals (such as pesticides, animal drugs, and other agrichemicals). Food additives and contaminants resulting from food manufacturing and processing can adversely affect human health [10]. It remains challenging to identify possible sources of biological contamination of foods that inevitably cause periodic accidents in any type of production system. Regretfully, this remains an endemic problem that since the dawn of human civilization has affected public and community health. A recent review article by Everstine and her collaborators pointed out that intentional food adulterations have been occurring in several instances (137 cases) and for a broad variety of food products, since 1980, in the USA. Among these, the most notable was the fraudulent addition of melamine to milk, baby formulas, and other dairy products to increase nitrogen levels, which indicate a high nutritional value for proteins in these foods. However, such adulteration affected infants' health, many of whom developed kidney stones by consuming these food products [11]. Despite continuous efforts for

Table 27.1 Additives legally permitted for use in the preparation of organic foods produce in Europe

Colorants	Foods
E153—Vegetable carbon[a]	Concentrated fruit juices, jams, jellies, and liquorice
E160b—Annatto, Bixin, Norbixin	Concentrated fruit juices, jams, jellies
Alkali, anticaking agent, dough conditioner, drying agent, firming agent	
E170—Calcium carbonates	Some bakery products, frozen desserts, and flour
Preservatives	
E220—Sulfur dioxide or E223 (sodium metabisulfite) or E224 (potassium metabisulfite)	Wine, dried fruit
Acidity regulators, anticaking agents, anti-foaming agents, bulking agents, carriers and carrier solvents, emulsifying salts, firming agents, flavor enhancers, flour treatment agents, foaming agents, humectants	
E270—Lactic acid, E290—Carbon dioxide	Bread, cakes, snacks
E500—Sodium carbonates, E509—Calcium chloride	
Antioxidant	
E306—Tocopherol-rich extract	Fruit juice, cakes, snacks
Emulsifiers, stabilizers, thickeners, and gelling agents	
E322—Lecithin	Bakery products, cheese, frozen desserts, fruit butters, jellies, and preserves
E400—Alginic acid, E406—Agar	
E407—Carrageenan, E410—Locust bean gum	
E410—Sodium alginate and E402 (potassium alginate), E412—Guar gum	
E414—Arabic gum	Cheese, including processed cheese, ice cream, jelly and preserves, and dressings
E415—Xanthan gum	Canned fruit, fruit butters, jellies
E440(i)—Pectin	
E464—Hydroxypropylmethylcellulose	
Packaging gases	
E938—Argon; E939—Helium	
E941—Nitrogen, E948—Oxygen	

[a]Banned as a food additive in the United States

Table 27.2 Food safety: factors involved in food production and storage

Physical hazards: foreign objects (e.g., wood, plastic, glass) from the environment or equipment
Biological hazards: microorganisms, such as bacteria, viruses, parasites, and molds (source of aflatoxins)
Chemical risks in food: acrylamide, PCBs, and dioxins; persistent organic pollutants (POPs); organic compounds that are resistant to environmental degradation through chemical, biological, and photolytic processes
Allergens: milk, eggs, fish, crustacean shellfish, tree nuts, peanuts, soybeans
Antimicrobials: cephalosporin antibiotic resistance
Food additives and contaminants: melamine

reducing these and similar risks in any type of food production system, it ought to be clear that in this present global market economy, not even organically certified foods may be exempt from fraudulent, intentional adulterations. Therefore, we remain convinced that the risk of food contamination increases where food is grown on the largest scale and for the most distant markets, whereas, conversely, potential risks for contamination by xenobiotics are minimized when food is grown under organic conditions and for a local market.

Nutritional Value of Organic Versus Conventional Fruit and Vegetables

Levels of macronutrients, micronutrients, and phytonutrients (e.g., flavonols and anthocyanidins, carotenoids) vary, within a relatively wide range, according to the plant species and plant organ (stem, leaf, fruit). Phytonutrients have been suggested to have potential for health promotion and disease prevention [12, 13]. External (genotype-independent) and internal (genotype-dependent) factors affect the levels of nutrients important for human health. Synthesis of plant nutrients is also affected by the conditions of stress of the plant [13].

Comparison of Organically Grown and Conventionally Grown Products

Organically grown products tend to have a higher content of dry matter and secondary plant metabolites than conventionally grown products [14]. Some recent works have compared the nutritional quality of organic and conventional foods [15–20]. The topic has been recently reviewed by Hunter et al. [15] and Crinnion [16]. The content of micronutrients was more frequently reported to be higher for organic vegetables and legumes compared to their conventional counterparts. Some findings about the content of phytonutrients in organic and conventional products are summarized here for common fruits and vegetables.

Grapes and Wine

The content of resveratrol, a phenolic grape (*Vitis vinifera*) phytoalexin, in organic wine was 26% higher in organic than in conventional wines in paired comparisons of the same grape variety [17].

Red Oranges

Higher levels of total phenolics, total anthocyanins, and ascorbic acid are typically observed in organic oranges and juices relative to their nonorganic counterparts. Organic orange extracts help protect against free radical and oxidative damage to cells from rats when compared with conventional extracts from conventionally grown sources [18].

Apples

Apples are one of the main sources of flavonoids in the Western diets, providing approximately 22% of the total phenols consumed per capita in the United States [20]. The nutrient content of organic and conventional apples has been widely investigated. Genotype-related differences may contribute to the higher content of antioxidants, such as polyphenols and flavonols in organic apples. Higher levels of antioxidants in local varieties of apples (Mela Rosa) compared with Golden Delicious apples were verified, with higher levels observed even after storage both in organic and conventional agriculture [21]. In other experimental trials, the quality attributes of apples coming from different regions, and different production systems, did not differ significantly at harvest or after storage [19].

Peaches, Plums, and Pears

The concentration of polyphenols together with the content in ascorbic acid, citric acid, and alpha- and gamma-tocopherol is higher in organic, old local peaches (*Prunus persica* L., cv. Regina bianca) and pears (*Pyrus communis* L., cv. Williams) [22]. These results are less evident in modern varieties under intensive cultivation. Higher levels of polyphenols have been observed in organic plums [22].

Tomatoes

A study found that organically grown tomatoes contained an equal or higher concentration of vitamin C, carotenoids, and polyphenols than did conventional tomatoes. The concentration of vitamin C and polyphenols remained higher in purees after processing from organic tomatoes. The levels of phytonutrients are reflected in a higher antioxidant potential [14, 23].

Eggplants

The influence of organic and conventional farming practices on the phenolic content of plant also has been studied in eggplant samples of two varieties. A higher phenolic content was observed in one of the organic varieties compared to conventionally grown samples [24].

Although organic fruits and vegetables generally have a higher content of antioxidants and micronutrients when compared to equivalent conventional produce, it remains difficult to insure their superior nutritional quality and healthy attributes [25].

Other Causes of Differences in Organic and Conventional Foods

Differences among food production systems also emerge from the farming protocols and delivery systems. These may be more or less sensitive to a sustainable approach to food production and environmental stewardship. It is also worth noting that “stewardship” and “value system” concerns may impact human nutrition and health by affecting consumers’ selection and consumption of foods. Anemia resulting from iron deficiency among “true” vegan vegetarians is one such example where philosophical decisions about “what to eat or not to eat” may affect people’s health. Concerns in this regard are important to nutritionists and have led to recent discussions about the need for improvements in the USDA inspection process of evaluating meats, produce and their quality.

Pesticides

There is growing concern about the "cocktail effect" that multiple pesticide residues that are present in conventional foods may have on human health. Despite the fact that residues of individual pesticides that were applied during the production cycle may be present at a concentration below the threshold level, thus guaranteeing food safety, nevertheless their presence (even in traces) is a cause for concern to an increasing number of consumers [6, 25].

Synthetic pesticides or herbicides are prohibited in organic farming. However, these crops may not be totally free of insecticide residues, although at a significantly lower level than in foods grown by nonorganic methods. Biological measures to control pests are permitted in organic agriculture, for example, by applying *Bt*-bacteria to plant leaves in order to control insect–crop infestations. A recent meta-analysis showed that consumption of organic foods may reduce exposure to pesticide residues [26].

Food Poisoning

The risk of biological contamination, both in the field and postharvest, may affect food quality and safety. However, there is no evidence linking organically produced foods to an increased risk of food poisoning. A recent survey gave organic food a clean bill of health and confirmed expectations that organic methods, such as careful composting of manure, minimize risks of food contamination [26]. Spadaro and his coworkers [27] found no significant difference between conventional and organic apple juices for patulin and other fungal contaminants. Nonetheless, as we have already pointed out, mycotoxins and bacteria in food and feed pose a constant threat to the health of consumers; these problems are most likely to arise during the transport and/or storage of the foods [28].

Are Genetically Engineered Foods Safe to Eat?

There is currently a harsh debate about the safety of genetically engineered (GE) foods for human consumption [2, 26]. In a recent review, Borsari and his collaborators highlighted major concerns regarding the use of GE crops [6]. Landigran and Benbrook made a robust case against GE foods because of the increasing use of herbicides and their possible carcinogenicity [29]. Nevertheless, the reluctance of the USDA to label GE foods is not helping a growing segment of society to accept these foods willingly, and this skepticism has sparked even more interest in organically produced foods. It is speculated that food companies do not want consumers to learn how much genetic manipulation has been occurring already to foods available at supermarkets; indeed, ingredients from GE crops can be found in a broad variety of foods derived from plants and animals. For example, many processed foods containing corn starch, corn meal, corn syrup, glucose, dextrose, canola oil, cotton seed, or soy oil, soy flour, or soy lecithin are probably derived from GE crops. This includes foods containing sugar from sugar beets since 95% of sugar beet grown in the USA is now Roundup Ready, genetically modified [30]. As the majority of livestock are fed with similar products, it is legitimate to infer that more foods, such as meat, dairy products, and eggs, could be affected by GE technologies. Hopefully, the techniques to introduce genes from compatible species, or to modify target gene expression and the type of modification, will improve so as to better mimic natural variability and selection, thus opening different perspectives and possibly safer solutions for food production. Such developments might even be acceptable for organic farming. But for now GE products and their derivatives are prohibited from organic foods.

Antibiotics

The routine, growth-promoting or prophylactic use of antibiotics is prohibited in organic standards for animal husbandry [25]. There is growing concern over the risk to human health and concerns that microorganisms may develop antibiotic resistance because of the misuse and overuse of antibiotics in livestock rearing [10]. A recent report suggested that bacterial isolates from foods produced from organically raised animals are less resistant to antimicrobial treatment when compared to conventionally raised animal foods [14]. Concerns of microbial pathogenesis have not been fully addressed by the USDA, although these issues are an additional source of consumers' growing interest in organically produced foods.

Food Additives

More than 500 additives are permitted for use in non-organically processed foods, compared with about 30 permitted in organic food processing (Table 27.1). Even though organic standards limit the use of additives linked to allergic reactions, headaches, asthma, growth retardation, hyperactivity in children, heart disease, and osteoporosis [18], some of them could trigger allergic reactions in consumers who are already predisposed to these or similar conditions.

Food Palatability

Given that the incidence of cardiovascular disease and cancer is negatively correlated with increasing daily fruit and vegetable intakes, by simply increasing food palatability one may increase fruit and vegetable intake and reduce the incidence of these chronic diseases. Also, recent studies have dealt with the topics of taste and "quality" of organic food versus conventional, yielding contrasting results. Although higher prices could limit a further expansion of the actual organic food market niche, we envision that in the not too distant future, high-quality, environmentally sound food will become a standard for consumers. In the meantime, we support large-scale consumption of food produced by integrated farm management (IFM) as a temporary solution to the achievement of quality foods for all. Consequently, we envision a higher emphasis on organic farming being spurred by a more equitable allocation of resources in its favor. This will reduce production costs while making organic foods more affordable to larger segments of consumers.

Conclusion

Recent accidents in the US food system have resulted in the withdrawal from the market of contaminated tomato, spinach, corn, and other commodities. These incidents indicate that large-scale, highly centralized food systems remain fragile and that their ability to ensure food safety remains often questionable.

A recent meta-analysis supported the environmental benefits of organic production [30]. Organic farms tend to store more soil carbon, have better soil quality, and reduce soil erosion. Organic agriculture also decreases soil and water pollution, it does not rely on synthetic fertilizers or pesticides, and it also enhances biodiversity of plants, animals, insects, and microbes as well as genetic diversity [31]. Consumers wishing to improve their intake of minerals, vitamins, and phytonutrients, while reducing their exposure to potentially harmful pesticide residues, nitrates, additives that are used in food processing, and GE foods should, wherever possible, choose organically produced fruits and vegetables.

The compositional data of organic and conventional vegetables could be used in public health campaigns to increase the consumption of products able to provide improved health protection and the prevention of chronic diseases. However, the crucial question of whether organic is “worth the extra cost” will probably remain one that needs to be determined by consumers only.

Further research is urgently needed to clarify the exact relationship between agricultural management and the nutritional quality of crops. However, decisions on appropriate sites, cultivars, and harvest criteria can differ between the organic and nonorganic sectors of agriculture. A better understanding of the cultivation systems available to consumers has become crucial to an improved understanding of public health enhancement in modern nutrition.

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Part IV
Diet and Health: A Summary

Chapter 28
What Is a Healthy Diet? From Nutritional Science to Food Guides

Norman J. Temple

Key Points

- This chapter summarizes the key features of a healthy diet.
- Various food guides are described and critically evaluated. These include MyPlate; the Healthy Eating Pyramid and the Healthy Eating Plate (produced by Harvard School of Public Health); the DASH Eating Plan; and Canada's Food Guide.

Keywords Dietary fat • Food-based dietary guidelines • Food guides

Defining a Healthy Diet

Since the 1970s our knowledge of the relationship between diet, health, and the risk of chronic diseases of lifestyle has increased tremendously. Based on this information, we can now characterize the essential features of a healthy diet, meaning one that assists in achieving optimal health and minimizes risk of chronic disease. This chapter summarizes the relationship between diet, health, and risk of disease. Detailed information is presented in other chapters.

But before turning attention to a healthy diet we can briefly summarize the typical American diet. Consumption of fruits and vegetables by Americans is currently around two to three servings per day, about half the recommended intake [1]. Foods prepared with whole grains are nutritionally much superior to those made from refined grains [2]. Alas, the great majority (about 86%) of grains present in the diet are refined. Intake of whole grains is only about 28 g/day, equivalent to less than one serving which is roughly one-third of the recommended intake. The above numbers indicate no improvement compared to 1970 [1]. Americans consume, on average about 77 g/day of added sugar (i.e., sugar that is added to food; this excludes that naturally present in fruit); this represents almost 15% of energy intake [3]. The net effect of this dietary pattern is that well over half of all food calories in the American diet come from highly processed, nutrient-depleted foods. By one estimate, 58% of the

N.J. Temple, Ph.D. (✉)
Centre for Science, Athabasca University, Athabasca, AB, Canada, T9S 3A3
e-mail: normant@athabascau.ca

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calories in the American diet come from what the researchers termed "ultra-processed foods" which include most bread, cakes, soft drinks, French fries, pizza, and desserts [4]. As these foods have a poor content of nutrients, the diet as a whole, not surprisingly, is also low in many nutrients. Surveys of the American diet reveal a widespread problem of low intakes of magnesium, potassium, folate, vitamins B_6, C, and E, as well as of dietary fiber [5–7]. In summary, the American diet is a recipe for ill health.

Exercise and the Control of Body Weight

There is perhaps no better starting point than weight control. The ideal BMI is generally agreed to be in the range 18.5–25. Alas, an epidemic of obesity that started around 1980 has now swept the Western world. It has led to a secondary epidemic of diabetes and other conditions. All physicians therefore need to make weight control a priority issue. The core advice was neatly encapsulated by Orson Welles: "My doctor told me to stop having intimate dinners for four. Unless there are three other people."

Integral to this is the encouragement for all patients to engage in regular physical activity. For health, an appropriate goal is 30 min of exercise, of at least moderate intensity, such as brisk walking, on most days of the week. Increasing the intensity to vigorous (such as jogging or fast walking) or duration (to 1 h) is better. People should be encouraged to engage in whatever form of exercise they enjoy and are therefore most likely to do on a regular basis (hiking, cycling, swimming, soccer, etc.). Where weight loss is a goal of exercise, then the laws of physics are crystal clear: more exercise burns more calories.

The optimal amount of exercise has been much debated. Our best evidence comes from a pooled analysis of cohort studies [8]. The researchers used the 2008 Physical Activity Guidelines for Americans as their reference point. This calls for 75 min/week of vigorous exercise or 150 min/week of moderate intensity exercise. Compared to people who have no exercise the mortality risk was reduced by 20% for those who exercise but at a level below the reference level, and by 31%, 37%, and 39% at 1–2, 2–3, and 3–5 times the reference level, respectively. Based on this evidence, everyone should be strongly encouraged to exercise at least to the reference level but preferably at double that level.

Fat in the Diet: How Much? What Type?

Recommendations for fat intake have been in flux in recent years; the goal has gone from "less than 30%" of energy intake to a more liberal 20–35%. A major reason for this is that many studies have failed to furnish clear evidence that diets with a high fat content are linked to risk of such diseases as cancer, heart disease, or type 2 diabetes [9]. What the research does clearly show is that it is *foods* that are linked with risk of disease [9].

One reason for this increase in the upper limit of fat is because the emphasis on a low-fat diet had a major negative consequence: as people lowered the fat content of their diets, they replaced the calories, at least in part, with refined carbohydrates, such as white bread and sugar. Indeed, many low-fat foods, such as yoghurt and cookies, have had their fat replaced with highly refined carbohydrates, either sugar or starch. Our best evidence reveals that refined carbohydrates are considerably unhealthier than is dietary fat. These dietary changes have negated the intended nutritional benefit of reducing the fat content of the diet.

But what about the type of fat? The cause-and-effect relationship between saturated fat, blood cholesterol, and heart disease has been widely accepted for decades. However, evidence that has

emerged in recent years suggests that the causal role of saturated fat in heart disease may, in actuality, be quite weak or even nonexistent [9]. These words would have been dismissed as nutritional heresy just a few years ago! Nevertheless, prudence suggests that these fats should still be restricted. The diet should therefore be limited in its content of meat (especially meat with a high fat content), milk with 2% or more fat, and hard margarine. Tropical oils (palm and coconut) are also rich in saturated fats whose intake should be limited if possible.

Closely related to saturated fats are the trans fats, which have also been linked to the risk of heart disease. Here, the evidence is convincing. These fats are formed in oils during the hydrogenation process. Trans fats are commonly found in hard margarine and in many baked goods such as donuts, croissants, chips, and cookies. As far as possible these fats, including margarine containing hydrogenated fats, should be avoided. In response to the large amount of media attention that has focused on trans fats, the food industry has greatly reduced the quantity added to processed foods. The Food and Drug Administration in the United States has recently ruled that the use of partially hydrogenated vegetable oils is no longer "generally regarded as safe." This should effectively eliminate the majority of industrial trans fats from the US food supply. Several countries have more or less eliminated the presence of partially hydrogenated vegetable oils in the food supply by means of legislation.

The body requires essential polyunsaturated fats for normal functioning. Vegetable oils, such as corn oil, sunflower oil, and most brands of soft margarine and mayonnaise, are rich sources. These fats mostly provide n-6 fats, such as linoleic acid. Strong evidence shows that these fats are protective against disease, especially heart disease, and are greatly preferable to either saturated fats or refined carbohydrates [9].

What is often lacking are n-3 fats. Sources include flaxseed oil (a rich source), followed by soybean oil and then canola oil. Fatty fish, such as sardines, mackerel, salmon, trout, and herring, are also a rich source of n-3 fats. However, whereas the n-3 fats in plant oils are mainly linolenic acid, fish oils are particularly rich in the long-chain n-3 fatty acids (DHA and EPA) that appear to be most protective against heart disease. This is based on a strong body of evidence that consistently demonstrates that fatty fish (cold water fish) has a strong protective association with risk of heart disease, especially fatal heart disease [9].

Meat, Fish, Legumes, and Nuts

A diet needs some protein-rich foods. But which type? For reasons stated above fatty fish (cold water fish) is most preferred, followed by low-fat fish. One issue with fish is mercury contamination. The fish species with the highest levels are king mackerel, shark, swordfish, and tilefish. Considering that mercury can impair brain development, it is recommended that children and pregnant women refrain from eating these predatory species.

Next in preference is poultry which comes higher up the pecking order than does meat. Much evidence has accumulated documenting the close link between regular consumption of red and processed meat and risk of disease, including cardiovascular disease, diabetes, and some types of cancer. The evidence of harm is consistently stronger for processed meat, such as ham, bacon, and salami, than for red meat, such as beef and pork [10]. Legumes (beans and lentils) and nuts make an excellent alternative to meat and can be well recommended.

Carbohydrates: Good and Bad

There is an abundance of evidence showing the health benefits coming from eating a generous amount of whole grain cereals. In particular, these foods are strongly linked to protection against heart disease

and type 2 diabetes (and probably colon cancer). Dietary fiber is no doubt responsible for much of this benefit though micronutrients and phytochemicals also deserve some of the credit. (Phytochemicals are the non-vitamin organic substances present on plant foods.) And how does the average shopper figure out which cereal products are whole grain and which are refined grains? This can be confusing as the list of ingredients is often confusing. A good rule of thumb is that the Nutrition Facts panel should indicate that the product has a ratio of at least 1 g of dietary fiber per 10 g of total carbohydrate.

Most people need to reduce their intake of refined sugars: less is definitely better. In this context, "sugar" means both sucrose and high-fructose corn syrup that is ubiquitous in soft drinks. The disorders where the evidence against sugar is strongest are obesity and dental caries. A reasonable upper limit for intake of sugar is 10% of energy. However, an intake of below 6% of energy is preferable, especially among those at risk of the harmful effects of sugar, namely those who are overweight, have prediabetes, or who habitually drink non-fluoridated water (and are therefore at risk of tooth decay).

When whole grains are refined so as to produce such products such as white bread and white rice, the resulting foods are depleted in fiber and several micronutrients such as magnesium, potassium, and vitamin B_6. Nutritionally speaking, refined cereals lie midway between whole grains and sugar.

Fruits and Vegetables

A generous intake of fruits and vegetables is strongly recommended. There are several good reasons for this. In particular, these foods provide significant protection against cancer and several other diseases. The substances that deliver these disease-preventing benefits are probably dietary fiber, various nutrients (including potassium, magnesium, folate, and vitamin C), and phytochemicals. Because phytochemicals are probably important for health, it is recommended that everyone consume a variety of fruits and vegetables (dark green vegetables, orange fruit, berries, etc.). Potatoes are the least favored of the vegetables, mainly because of their minimal content of phytochemicals.

An important benefit of fruits and vegetables is that they have a low energy density (energy per 100 g). As a result, they satisfy the appetite after only a relatively small quantity of energy has been consumed. No one ever got fat by eating too many apples or carrots or consuming too much tomato soup!

Whole fruit is superior to fruit juice because of its fiber content (and likewise for vegetables and vegetable juice). Fruits and vegetables may also have a higher content of some vitamins than is found in juices. But juices are a convenient way to boost the intake of fruits and vegetables. We live in a world where sugar-rich soft drinks are consumed in large quantities, especially by young people. Almost anything that displaces them is a big improvement. For that reason, juices can play a valuable role in the diet. But we must bear in mind that fruit juices are similar to soft drinks in terms of carbohydrate concentration. Their ease of consumption (low satiety) means they can contribute to excessive energy intake. Intake of fruit juices should therefore not exceed one or two servings per day. Vegetable juices are preferable as they have a lower carbohydrate (and energy) content than fruit juice.

It is important to avoid being confused by pseudo-juice products. Drinks labeled as "fruit nectar," "fruit beverage," or "fruit punch" contain a lot of sugar but little or no actual fruit juice. Despite the pictures of fruit that often appear prominently on the labels, these products are little more than fruit-flavored sugar water.

Fruits and vegetables have a high content of nutrients combined with a low content of energy. For this reason, they are described as having a high nutrient density. This also applies to whole grains. Sugar lies at the opposite end of the spectrum. This leads to the concept that the diet should consist mainly of foods with a high nutrient density.

Coffee and Tea

Considering the vast quantities that are consumed, tea and coffee are surprisingly free of evidence of harmfulness. Indeed, there is evidence that both beverages may offer some modest protection against heart disease and diabetes. Coffee may also provide limited protection against cancer. The source of this health benefit is almost certainly the rich content of phytochemicals; these survive being mixed with hot water. The one black mark against coffee, and to a lesser extent against tea, is their interference with sleep.

Alcohol

Alcohol in excess creates many problems, especially violence and accidents. It is also a significant factor in cancer. However, in moderation alcohol can be beneficial for the health. It reduces the risk of heart disease and also appears to help prevent hypertension and several other chronic conditions. The balance between risks and benefits of moderate consumption of alcohol are strongly age related: alcohol has a net benefit with people over age 50 or 60, whereas with people below age 40 the harm caused by alcohol dominates the picture. Arguably, the most prudent policy is one that explains that alcohol in moderation—up to two drinks a day for men and one drink a day for women—will likely have several health benefits for people in middle age and older, while also stressing the hazards of abuse. Quite apart from the total alcohol intake, an important factor is drinking pattern. Occasional heavy drinking (binge drinking) can lead to an increased risk of death.

Dietary Patterns and the Mediterranean Diet

Concepts of what constitutes the best advice on achieving the healthiest diet have been in much flux in recent years. There has been a marked shift among nutrition scientists away from a focus on nutrients (vitamins, minerals, and fat); today's focus is on foods and dietary patterns.

There are two dietary patterns that dominate the picture. One is the Western diet, as eaten by the majority of Americans. This was briefly described at the start of the chapter. This dietary pattern contains much meat, refined grains, and sugar and is relatively low in fruit while vegetables are often eaten as French fries. As a result, this diet inevitably means that most Americans have a poor intake of dietary fiber and of several key nutrients, including potassium, magnesium, and folate. This dietary pattern is associated with chronic diseases. In stark contrast there is the Mediterranean diet, which is typically low in red meat and has a generous content of fruits, vegetables, and grains. Other common foods include nuts and legumes. The version of the diet often eaten in southern Europe also contains much olive oil and often includes red wine. Many studies have shown that this dietary patterns is consistently associated with a relatively low risk of chronic diseases.

The Problem with Salt

Increasing the salt content of a food is a common way to improve the palatability and the sales of a processed food product. This may benefit some sectors of the food industry. However, there is rock

solid evidence that lowering the salt content of the diet must be a priority issue. The average American consumes around 9 g/day of salt. Current recommendations call for this to be reduced to below 6 g (or 2300 mg sodium). However, an intake of about 1500 mg/day sodium may be closer to optimal. This could have a major public health benefit as it would significantly lower the prevalence of both hypertension and of mildly elevated levels of blood pressure. This would, in turn, prevent a great many cases of heart disease and stroke.

Supplements: There Is No Shortcut to a Balanced Diet

An important question concerns the use of supplements. Dietary supplements are not a substitute for fruits, vegetables, and other healthy foods; a major reason is that supplements contain, at most, only one or two phytochemicals whereas fruits and vegetables contain hundreds of different phytochemicals.

A multivitamin—meaning pills containing a broad spectrum of vitamins and minerals—are the most popular type of dietary supplement. Are they advisable for the general population? This question has been hotly debated. Our best evidence is that multivitamins have essentially no value for those who eat a reasonably nutritious diet. However, multivitamins are advisable for people at risk of malnutrition as may be the case with people who habitually consume a low-calorie diet as is often the case with elderly people and those with such conditions as anorexia, drug addiction, or advanced cancer. A multivitamin is also advisable for women who could become pregnant and those who are pregnant or breastfeeding. A major reason for this is to ensure sufficient intake of folic acid and of iron.

There is now strong evidence for the benefit of vitamin D, especially for those aged over 50. It appears to reduce the risk of cancer (especially colon cancer) and of cardiovascular disease. The most often claimed benefit for the vitamin is for enhancing bone health helping to reduce the risk of fractures but here the evidence is much weaker and inconsistent. The problem of insufficient vitamin D gets steadily more prevalent the further north one lives; for example, everyone living in the northern states will be unable to synthesize the vitamin in their bodies for around 5 months, from Fall to Spring. Other at-risk groups are the elderly, people with dark skin, and those who expose little skin to the sun. People in these groups are likely to benefit from a supplement of vitamin D that supplies 1000 IU (25 mcg) per day.

Organic Foods

“Doctor. Should I buy organic food?” Organic foods are grown without synthetic pesticides. It is almost certainly preferable to reduce one’s intake of pesticides. But the quantities consumed from conventionally grown food are extremely small. Organic foods are usually much more expensive than regular supermarket food, typically by 50% or more. This extra cost is hard to justify for most of the population.

Don’t Forget the Environment

No account of a healthy diet is complete without also considering how to design it in a manner that is environmentally friendly. Here are some good rules to follow. The single biggest dietary change that we should aim for is the reduction in consumption of meat. This is because meat production requires huge amounts of land, energy, and water. In this regard, four-legged meat is twice as bad as chicken. By contrast, beans and lentils are much more environmentally friendly, quite apart from their

nutritional advantages. In order to reduce transportation people should, where feasible, buy food grown as near as possible to where they live. Another important factor is that people should buy food with minimal packaging and this should be recycled. If food is packaged, then a large size is preferable. Bottled water is an awful product with regard to its harmful environmental footprint, especially brands transported from distant locations.

Dietary Guidelines for Americans

Several major health-related organizations in the United States have published summaries of what, in their expert opinion, are the most appropriate dietary guidelines. One of the most well-known—and authoritative—is published by the American Heart Association [11]. The focus is on reducing the risk of cardiovascular disease.

The US federal government publishes the Dietary Guidelines for Americans [12]. This is a collaboration between the Department of Health and Human Services (HHS) and the U.S. Department of Agriculture (USDA). A thoroughly revised version is published every 5 years, with the most recent one appearing in 2015. This new version made several notable changes from the 2010 version. It now places a strong emphasis on the importance of healthful, food-based dietary patterns. At the same time, it ceased making a recommendation for intake of cholesterol, and there is no longer a focus on lowering the intake of dietary fat.

Food Guides

An Overview of Food Guides

There are several food guides available. These provide advice for the general public on how to select a diet that enhances health and helps to prevent disease. The challenge in constructing a food guide is to translate nutrition knowledge into a format that is easy for people to understand and to apply to their everyday lives.

While the details vary from country to country, there is broad agreement as to the key message. Themes commonly found in different food guides are as follows:

- eat plenty of whole grains, fruits, and vegetables
- consume an appropriate amount of meat, fish, or protein-rich alternatives (such as beans and lentils), and milk (or milk products)
- limit the intake of fat (especially saturated fat), alcohol, and sugar.

If there is one place where "the devil is in the detail,", it is in food guides. Beyond the key themes above, there are a multitude of differences over such things as where to place potatoes (with or separate from other vegetables), where to put legumes (with vegetables or as an alternative to meat), and whether or not to keep fruits and vegetables together in the same group. Quite apart from these issues, there are major differences around the world in the visual design of food guides. The intention in all cases is to convey to the general population how much of the diet should come from each food group. Many countries use a dinner plate design while others have opted for a pyramid design.

Deciding on the "right" answer to each of these questions and then designing the "best" diet goes far beyond questions of the nutrient content of various foods and describing a healthy diet; we must

also consider the vital matter of how best to educate people as to the fundamentals of a healthy diet and how to persuade them to actually eat that diet. Fail to do that and everything is a waste of time! For that reason, a vital consideration in designing food guides is to make them user friendly. In the next section, attention is turned to some of the food guides that are available.

MyPyramid and MyPlate

Until 2005, the guide disseminated to the general public in the United States was the Food Guide Pyramid. The pyramid had a large base that depicted grains. This clearly conveyed the message that grains should be the food group eaten in largest amount. Fats, oils, and sweets were placed at the top of the pyramid and covered a much smaller area than the other food groups. It was a simple matter to look at this one-page document and find out how many servings should be eaten from each food group. But this all changed with the launch of MyPyramid. Unlike all other food guides around the world, this one required the use of the internet. The user entered his or her profile (age, sex, and physical activity) and then received a personalized set of dietary recommendations. The obvious challenge with this food guide is the matter of user accessibility. It seems highly probable that there are millions of people who were willing to read a simple, printed food guide, much as one reads a TV guide, but simply could not be bothered to use a website for this purpose.

In most countries, Canada for example, the folks who write the food guide belong to the health department of the government, but in the United States they work for the Department of Agriculture. That department therefore has a serious conflict of interest: it must help make farming and food production profitable (which often means boosting the sale of less than healthy foods) while at the same time advising people how to eat for health. As a result, there is a strong suspicion that both the old and new pyramids are compromises between these two opposing forces. Marion Nestle of New York University described MyPyramid as “a disaster” [13]. This is how nutrition experts from Harvard School of Public Health described MyPyramid and the Food Guide Pyramid [14]: “The problem was that these efforts, while generally good intentioned, have been quite flawed at actually showing people what makes up a healthy diet. Why? Their recommendations have often been based on out-of-date science and influenced by people with business interests in their messages.”

It seems that the USDA listened to the criticism. In 2011, they abandoned MyPyramid. In its place, they went over to a simple pictorial design called MyPlate (http://www.choosemyplate.gov). The food guide is depicted as a plate with food sectors. For the first time, it is recommended that more of the diet should come from fruits and vegetables than from grains. Unlike MyPyramid, it places little emphasis on how many servings should be eaten from each food group. This new food guide is much easier to understand. It is also available in Spanish.

Harvard’s Healthy Eating Pyramid and Healthy Eating Plate

In view of the criticisms leveled against MyPyramid (and its predecessor), it should come as little surprise that alternative food guides have been developed in the United States. A well-known one is the Healthy Eating Pyramid, produced by the Department of Nutrition of the Harvard School of Public Health (http://www.thenutritionsource.org). Its visual design is similar to the Food Guide Pyramid but with one notable exception: it does not specify the number of servings from each food group. Instead, it tells users to: “Forget about numbers and focus on quality.” In 2011, after the USDA switched from MyPyramid to MyPlate, Harvard also developed their own plate design, called the

Healthy Eating Plate (http://www.thenutritionsource.org). However, they have retained their pyramid food guide as a complement to their plate food guide.

The key difference between the Harvard food guides and those from the USDA is that the Harvard guides place a much stronger emphasis on selecting healthier foods, such as whole grains (rather than refined grains) and fish, poultry, and beans (rather than red meat and processed meat).

DASH Eating Plan

This food guide grew out of the DASH trial (Dietary Approaches to Stop Hypertension). That intervention tested a diet that emphasizes fruits, 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 [15]. The National Heart, Lung, and Blood Institute (NHLBI) then turned the DASH diet into a diet for the general population. This is known as the DASH Eating Plan (dashdiet.org).

Compared with MyPlate, the DASH Eating Plan recommends a greater emphasis on lean meat, poultry, and fish (rather than red meat) and also on nuts, seeds, and beans. This food guide recommends a large cut in oils (only two to three teaspoons per day). The diet supplies more fiber than MyPlate, but much less fat, saturated fat, and polyunsaturated fat.

It is instructive now to compare MyPlate, the Healthy Eating Plate (from Harvard), and the DASH Eating Plan. The most striking differences between the three food guides are as follows. Compared with MyPlate, the other two guides provide about one-third more fiber and about one-third less saturated fat. Whereas the Healthy Eating Plate provides a generous amount of polyunsaturated fat (both n-6 and n-3 fats), the DASH Eating Plan is essentially a low-fat diet with a much reduced intake of all classes of unsaturated fat (but with significantly more protein and carbohydrate). Another notable difference is that while the DASH Eating Plan includes two or three servings per day of low-fat or nonfat dairy foods, the Healthy Eating Plate is dubious as to the value of dairy foods and recommends "no more than one to two servings per day.". The Healthy Eating Plate and the DASH Eating Plan are both excellent diet guides. However, the Healthy Eating Plate is superior with respect to its more generous content of polyunsaturated fat, the importance of which was emphasized earlier. These dietary plans have much in common with the Mediterranean diet which was discussed earlier.

Canada's Food Guide

This food guide is similar to the old Food Guide Pyramid with respect to the number of servings from each food group. And like that food guide it is easy to understand, though the presentation is quite different (available via http://www.hc-sc.gc.ca). There are several notable features. The recommended number of servings of fruits and vegetables (which are lumped together in one food group) has now overtaken grains. This follows the trend we see with the American food guides. Supplements are specifically recommended for particular groups: 400 IU of vitamin D per day for men and women over age 50 (remember this is for people living in Canada) and a multivitamin containing folic acid for women who could become pregnant and those who are pregnant or breastfeeding. Anyone wishing to use this food guide should request a printed copy as this makes using it much easier than reading it via the internet.

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Part V
Sources of Nutritional Information

Chapter 29
Dietary Reference Intakes: Cutting Through the Confusion

Jennifer J. Francis and Carol J. Klitzke

Key Points

- The Dietary Reference Intakes (DRIs) are a set of reference values for nutrients for assessing and planning diets for individuals and groups.
- The DRIs include values for
  - Estimated Average Requirement (EAR)
  - Recommended Dietary Allowance (RDA)
  - Adequate Intake (AI)
  - Tolerable Upper Intake Level (UL)
- The purpose of the DRI is to describe a nutrient intake that will promote health and prevent or delay chronic diet-related diseases.
- The DRIs form the scientific foundation for federal food programs, including nutrition labeling, requirements for school meals, and design of supplemental food packages for the Women, Infants, and Children Program.
- The Dietary Guidelines for Americans and ChooseMyPlate translate the DRI into recommendations and guides for food selection by consumers.

Keywords Dietary Reference Intakes • Recommended Dietary Allowances • Deficiency • Energy balance • ChooseMyPlate

J.J. Francis, M.P.H., R.D.
Dietetics Program, Southern Maine Community College, South Portland, ME, USA

C.J. Klitzke, Ph.D., R.D. (✉)
Department of Nutrition and Dietetics, Viterbo University, 900 Viterbo Drive, La Crosse, WI, USA
e-mail: cjklitzke@viterbo.edu

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Introduction

The Dietary Reference Intakes (DRIs) include four sets of nutrient reference values created by the Institute of Medicine to be used for assessing and planning diets of individuals and groups. These values reflect the optimal amount of select nutrients needed to promote health and prevent disease, while also avoiding their overconsumption. The DRI replaces the Recommended Dietary Allowances (RDA), in use in the United States since 1941, and the Recommended Nutrient Intakes (RNI) in Canada. The DRI was first published in a series of reports between 1997 and 2005, and in 2006 a definitive summary and practitioner's guide was issued [1]. The Netherlands, Japan, and South Korea adapted the concept of the DRI for use in their countries [2–4].

The Dietary Reference Intakes

The DRI consists of four sets of values: Estimated Average Requirement (EAR), Recommended Dietary Allowance (RDA), Adequate Intake (AI), and Tolerable Upper Intake Level (UL). DRIs are provided for 12 life-stage groups, based on age and gender, with additional categories for pregnant and lactating women. The DRI provides either an RDA or an AI for 29 micronutrients as well as for macronutrients, fiber, and water. Additionally, there are separate recommendations for the Estimated Energy Requirement (EER) and Acceptable Macronutrient Distribution Ranges (AMDR).

Estimated Average Requirement

The EAR represents the average daily intake that is likely to meet the nutritional requirements of approximately half of the healthy individuals in a group. Nutrient needs vary from individual to individual. The EAR is set at the point that would meet or exceed the nutrient needs for half of the individuals in a group, but falls short for the half of the group with higher than average requirements. As such, it is not to be used as a recommendation or goal for nutrient intake for individuals. Rather, it is used as a tool for statistical analysis of adequacy and for setting the RDA, as described below. It is important to note that when the EAR for nutrients were determined, the estimations were based on indicators of adequacy, such as urinary excretion, tissue saturation, and blood levels, rather than merely the amounts required to prevent deficiency diseases.

Recommended Dietary Allowance

The RDA is set at a level which exceeds the nutrient needs of nearly all healthy individuals in a population. When the requirement for a nutrient in a population follows a normal distribution pattern, the RDA is based on the EAR plus two standard deviations. If the distribution is skewed, the RDA is set at a level between the 97th and 98th percentile for the nutrient requirement. By this definition, the RDA will exceed the nutrient requirements for the great majority of people in the population; therefore, intakes below the RDA do not necessarily denote a deficiency. However, the RDA can serve as a goal or recommendation for the nutrient intake of individuals.

Adequate Intake

When there is insufficient scientific evidence to set an EAR, no RDA can be determined. In such cases, an AI is set based on the levels of nutrients consumed by apparently healthy individuals. The AI, though a less exact measure than the RDA, is assumed to be adequate for nearly all healthy individuals in a population. Like the RDA, the AI can serve as a goal or recommendation for the nutrient intake of individuals.

Tolerable Upper Intake Level

The UL represents the highest average level of nutrient intake that poses no risk of adverse health effects. Intakes above the UL increase risk of toxicity.

Estimated Energy Requirement

The EER represents the average intake of energy necessary to maintain energy balance for healthy individuals. Values for EER are calculated using equations that factor in age, gender, weight, height, and physical activity. Although EER may be calculated for four different activity levels (sedentary, low active, active, and very active), optimal health is consistent with "active" level or higher of physical activity. Like the EAR, the EER represents the average estimated need for individuals. This is done, rather making a generous recommendation, in order to avoid intakes that are excessive for most individuals.

Acceptable Macronutrient Distribution Ranges

The AMDR represents the range of healthful intakes for carbohydrate, fat, and protein, expressed as a percentage of total energy intake. These ranges were set at amounts determined to reduce the risk of chronic diseases, such as obesity, heart disease, diabetes, and cancer, while providing adequate nutrients. Additional recommendations are given for cholesterol, saturated fats trans fats, and added sugar.

Limits and Uses of the DRI

Limits

Careful use of the DRI as a tool for diet assessment and planning must take several limiting factors into consideration. First, the DRI applies to healthy individuals; it is not intended for people who are malnourished or who have disease conditions that alter nutrient needs. Second, the values represent the average intake over several days. The intakes of individuals vary from day to day, and minor deviations from the DRI are not cause for concern. Third, the DRI represents recommended intake of

nutrients from food rather than from supplements. Food delivers a mix of nutrients and non-nutrients that are consistent with health. Attempting to meet the DRI recommendations through use of supplements rather than food is likely to result in a loss of balance in the diet. Fourth, the DRIs should be considered a benchmark against which to assess adequacy, not a minimum requirement. Lastly, it must be understood that the true nutrient needs of any one individual cannot be known, and, therefore, comparing intake to the DRI should be only one part of the assessment process.

Statistical Analysis

Because of the statistical basis used to develop the DRI, it is possible to use statistical equations to calculate the probability that an individual's diet is inadequate, adequate, or excessive in a particular nutrient. The *Dietary Reference Intakes, the Essential Guide to Nutrient Requirements* [1] explains these assessment techniques.

General Guidelines for Diet Assessment of Individuals

For general purposes, the following guidelines may apply.

- For nutrient intakes below the EAR, the probability of adequacy is less than 50%, so intake likely needs to be increased.
- For nutrient intakes above the EAR but below the RDA, intake probably needs to be increased.
- For nutrient intakes at or above the RDA or AI, intake is likely to be adequate, as long as it reflects long-term intake.
- For nutrient intakes below the AI, it cannot be stated with confidence that intake is deficient; however, intake should probably be increased to the level of the AI in order to ensure adequacy.
- For intakes below the UL, there is little or no risk of adverse effects.
- For intakes above the UL, there is increased risk for adverse effects, so intake should be decreased.
- For energy nutrients, intakes between the lower and upper levels set by the AMDR are acceptable. Intakes below or above the AMDR probably need to be adjusted.
- The EER is not an appropriate tool for nutrition assessment. Body mass index (BMI) is a better tool for assessing energy intake over the long term.

In sum, intakes above the RDA or AI and below the UL are most likely to be adequate without risk of adverse effects. Appendix C presents a simplified table of DRI values (RDA and AI).

DRI and the Consumer

The DRI forms the scientific basis for public policy, including nutrition labeling, fortification of foods, menu-planning requirements for school meals, and composition of supplemental food packages given to low-income women participating in the Women, Infants, and Children Program [5].

Because of the complexity of the DRI and using the tables to help formulate actual diets, the *Dietary Guidelines for Americans* was created and published by the US Department of Health and Human Services and the US Department of Agriculture (USDA) [6]. It provides dietary guidance in the form of recommendations to promote health and reduce the risk of chronic disease. The Dietary Guidelines Advisory Committee used the DRI when creating the Guidelines [6].

ChooseMyPlate (the American food guide) is a graphic representation of the advice provided by the Dietary Guidelines. The DRI is used in the design of ChooseMyPlate so as to ensure nutritional adequacy. A person who follows the advice provided by ChooseMyPlate will receive nutrient intakes at or above the DRI recommendations for nearly all nutrients [6].

The *Dietary Guidelines for Americans* and ChooseMyPlate are further described in Chap. 28.

Summary

The DRI replaces and expands upon the RDAs used in the United States and the RNIs used in Canada. The four sets of DRI reference values can be used to assess and plan the diets of individuals and groups. For individuals, the EAR can be used to statistically assess the probability that the diet is adequate in particular nutrients over the long term. For general consumer purposes, a diet that provides nutrients above the RDA or AI and below the UL is likely to provide adequate nutrients without risk of adverse effects. A diet chosen in accordance with ChooseMyPlate can be confidently expected to provide nutrients within those limits.

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Chapter 30
Food Labels and Sources of Nutrients: Sorting the Wheat from the Chaff

Karen M. Gibson, Norman J. Temple, and Asima R. Anwar

Key Points

- Food labels provide the information needed to guide the selection of foods that will help individuals meet nutrition and health goals.
- Continual changes in food label format necessitate continual reinterpretation of food label information and importance.
- Food labels health claims are tightly regulated by the FDA.
- This chapter explains how to best utilize the information contained on food labels.

Keywords Nutrition labeling • Daily value • Health claims

The Nutrition Facts Label

Many consumers read food labels to help them make healthy choices. But labels are only useful if one knows 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 [1, 2]. A typical Nutrition Facts Label is shown in Fig. 30.1. The label addresses nutrients that are associated with certain chronic diseases or with nutrient deficiencies. By law, a food label must contain the following information:

- 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, sugars, protein, vitamins A and C, calcium, and iron.

K.M. Gibson, D.C.N., R.D.N., C.D., C.S.S.D. (✉)
Department of Nutrition and Dietetics, Viterbo University, 900 Viterbo Drive, La Crosse, WI 54601, USA
e-mail: kmgibson@viterbo.edu

N.J. Temple, Ph.D.
Centre for Science, Athabasca University, Athabasca, AB, Canada

A.R. Anwar, B.Sc.
Recreation and Parks Department, Mississauga, ON, Canada

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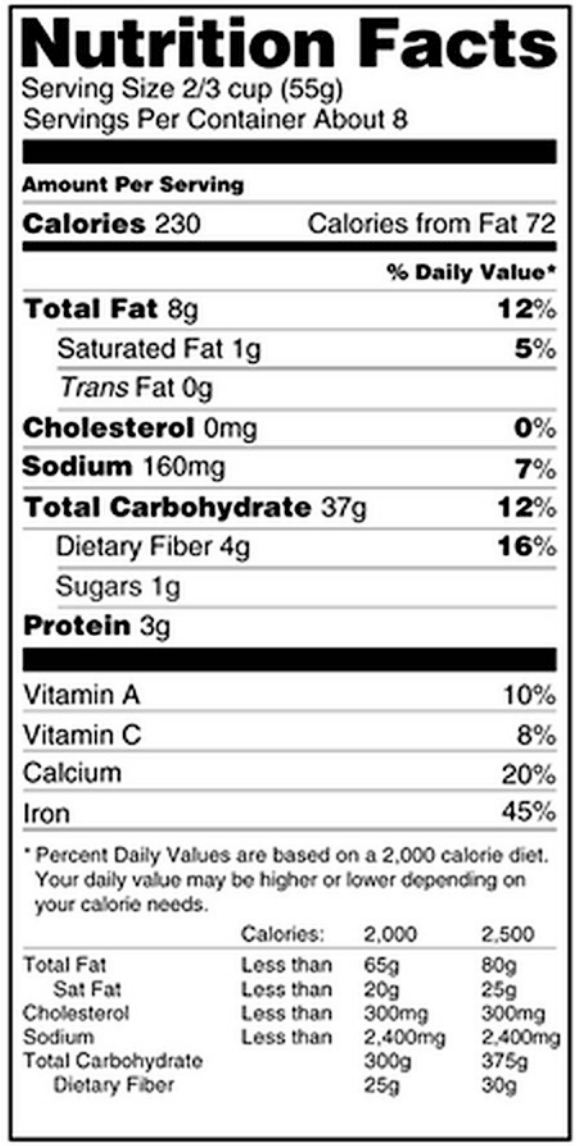

Nutrition Facts

Serving Size 2/3 cup (55g)
Servings Per Container About 8

Amount Per Serving

Calories 230	Calories from Fat 72
	% 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

Fig. 30.1 Sample nutrition facts label

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.

Serving size is one of the most important items of 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 half a cup and all beverages are 8 oz. It is important to be aware that the serving size indicated on a food label may not represent the amount a person actually eats on one occasion. In addition, the serving sizes on food labels are not always the same as those of the USDA Food Guide or the diabetic exchange plan. For example, a serving of rice on a food label is one cup, whereas in the USDA Food Guide and exchange list, it is half a cup.

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 above, for example, one serving of this food equals one cup. But if the consumer eats the whole package (i.e., two cups), that obviously doubles the calories and other nutrient amounts. A serving in a restaurant might easily be considerably more 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 (right and bottom of Fig. 30.1). 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 cholesterol, sodium, and potassium as well as the macronutrients that are sources of energy, namely carbohydrate (including fiber) 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 fat and sugars 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 g
Saturated fat: maximum of 20 g
Carbohydrates: minimum of 300 g
Protein: no daily value is expressed
Fiber: 25 g; 12.5 g per 1000 calories
Cholesterol: maximum of 300 mg
Sodium: maximum of 2400 mg

Food labels list the amount of a nutrient in a serving of the food as a percentage of its DV (Fig. 30.1). 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 desirable for total fat, saturated fat, cholesterol, and sodium; a DV of 5% or less is a good indicator. A higher DV is desirable for total carbohydrates, dietary fiber, iron, calcium, vitamins A and C, and other vitamins and minerals that may be listed, with 10% or more representing a good source, while a DV of 20% is considered high.

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's now put the above information to use by examining the labels from two containers of yogurt (Fig. 30.2). For this purpose, we will assume that the subject, Harry, is an active man. This means his energy intake is around 2500 calories. Which is the healthier choice for Harry?

In each case, the whole container is one serving. Examination of the labels reveals the following notable facts:

- The fruit yogurt has 3 g of fat. Half of this (1.5 g) is saturated fat. This represents 9% of the DV in a 2000 calorie diet. As Harry's energy intake is higher, the percentage in his case will be lower. If Harry has concerns about his blood cholesterol, then the plain yogurt is preferable.
- The plain yogurt has much lower energy content (110 vs. 240 calories). This is because it contains much less fat and sugar. If Harry is watching his weight, then this is an important consideration.
- Being a milk product, yogurt is a rich source of calcium. We see that both types of yogurt have a high percentage for this nutrient.
- Sodium is a vital number to look at as many processed foods contain excessive amounts. The plain yogurt contains 160 mg. This is similar to the amount in a cup of milk.
- The plain yogurt contains more protein (13 vs. 9 g). This is of little importance as protein excess or deficiency is seldom a problem. Appendix C informs us that Harry's recommended intake (RDA) is 56 g, an amount that is readily obtainable from the diet.
- The supermarket customer might be tempted to buy the yogurt marked "Fruit Yogurt" in large letters on the front of the container, making the assumption that it contains significant amounts of fruit. The container might even have large colored images of fruits. But a closer inspection of the Nutrition Facts Label reveals that this yogurt has no more vitamin C and barely any more fiber than the plain yogurt.

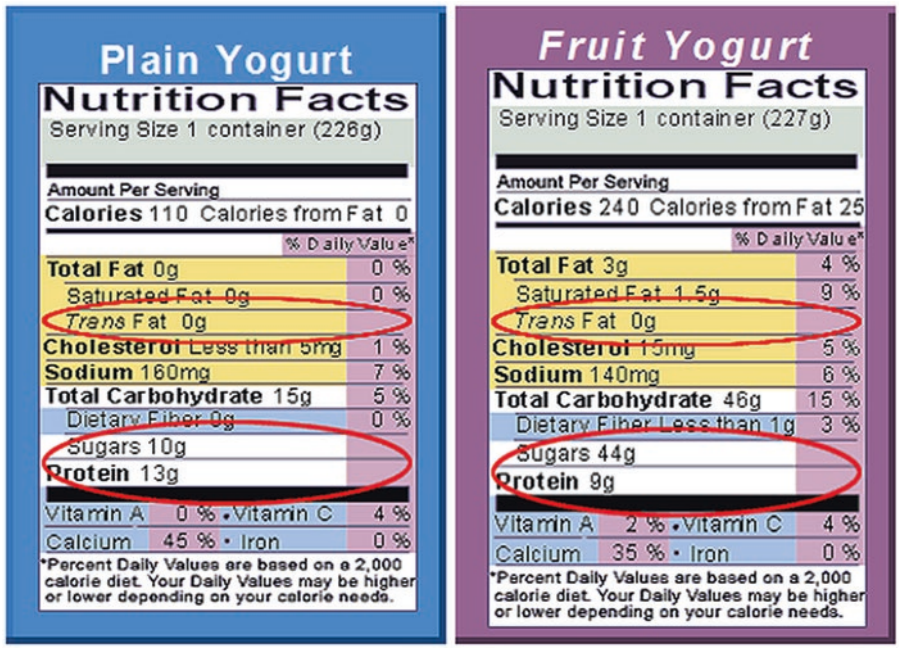

Fig. 30.2 Labels from containers of yogurt

Let's now summarize the key rules for reading labels:

- Read the list of ingredients. Always remember that the large print on the front of the container may be misleading.
- 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 fiber. Start by figuring out reasonable targets for each of these. For Harry, in the above example, he may be well motivated to keep himself healthy and will set his targets at 2500 calories, 1800 mg sodium, 20 g saturated fat, and 32 g fiber.
- 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.

Lastly, we will look at how the calorie content of food is calculated. Fat contains 9 calories/g, while carbohydrate and protein each have 4. So fruit yogurt has 27 calories as fat (3 × 9), 184 as carbohydrate (46 × 4), and 36 as protein (9 × 4). This adds up to 257 calories. The discrepancies with the numbers on the label are 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, for example, 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 web sites that allow this to be done at no cost.

The Nutrition Facts Label was introduced approximately 20 years ago with very few changes since that time. The Food and Drug Administration (FDA) is proposing to update the Nutrition Facts Panel in order to provide a greater understanding of nutrition science, update serving sizes, and provide new labeling requirements for certain package sizes [3]. An example of the proposed format and an alternate format are shown in Fig. 30.3. Once the final rules are released, companies will have up to 2 years to comply, so the consumer might not see the revised Nutrition Facts Panel for some time.

The proposed changes as a result of greater understanding of nutrition science include:

- Information on added sugars as many experts agree that consuming fewer calories from added sugar as they may decrease the intake of more nutrient rich foods while also increasing calorie intake. On average, Americans consume 16% of their daily calories from sugars added during food production.
- Update the daily values for nutrients like sodium, dietary fiber, and vitamin D as this will help the consumer to better evaluate the nutritional contribution that a food makes to the diet.
- Require manufacturers to state the amount of potassium and vitamin D as they are the new "nutrients of public health significance." Calcium and iron would continue to be required, but vitamins A and C would be included on a voluntary basis.
- Remove "Calories from Fat" section as research shows the type of fat is more important than the amount. "Total Fat," "Saturated Fat," and "Trans Fat" would remain on the label.

Serving sizes on the label would also be altered to better reflect how people eat and drink today, rather than 20 years ago. In addition, the proposed rule change would require packaged foods (including drinks) that are typically eaten in one sitting be labeled as a single serving so that calorie and nutrient information be declared for the entire package. For those somewhat larger packages that could be consumed either in one or multiple sittings, manufacturers would have to provide both "per serving" and "per package" calorie and nutrient information in a dual column format (see image).

Fig. 30.3 Proposed food label format. The label on the *left* shows the proposed format while the label on the *right* is an example of an alternate proposed format

The proposed design would make calories and serving sizes more prominent on the label to emphasize their importance in addressing public health concerns such as obesity, cardiovascular disease, and diabetes. The Percent Daily Value (%DV) would be shifted to the left so that information would come first.

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: folate, niacin, riboflavin, thiamin, iron, magnesium, selenium, and fiber. Grains are available as either the refined or whole grain. Although refined grains such as white flour and white bread may be enriched with several vitamins (such as thiamin, riboflavin, and niacin), they are poor sources of various nutrients including vitamins B6 and K, magnesium, and fiber. Whole grains such as oats, Shredded Wheat, and foods made from whole grain flour such as whole grain bread have a much higher content of these nutrients.

Meat, fish, poultry, and eggs: protein, niacin, thiamin, vitamins B6 and B12, 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 B12, calcium, magnesium, and potassium. In addition, vitamins A and D are present if the food is fortified.

Oils: vitamin E and polyunsaturated fats. Vegetable oils, such as corn oil, sunflower oil, and most brands of soft margarine, are rich sources of n-6 polyunsaturated fats. Oils rich in n-3 polyunsaturated fats include flaxseed oil (a rich source), followed by soybean oil and then canola oil.

Food Sources of Select Nutrients

Lipids

Polyunsaturated fat: See above information on oils. The n-3 fats in plant oils are mainly linolenic acid. Rich source of n-3 fats include fatty fish, such as sardines, mackerel, salmon, trout, and herring. Fish oils are particularly rich in the long-chain n-3 fats (DHA and EPA).

Saturated fat: Most animal fats including whole milk, cream, butter, and cheese; fatty cuts of beef and pork, poultry and lamb products, tropical oils including palm, palm kernel, and coconut oils.

Trans fat: Hard margarine (made with hydrogenated oils), deep-fried foods, cakes, cookies, donuts, pastry, crackers, snack chips, and imitation cheese. Some meat and dairy products are minor sources. Due to concerns with the relationship of trans fats to cardiovascular disease, food manufacturers have dramatically reduced the amount of trans fats found in processed food.

Cholesterol: Eggs, liver, milk products (if high in fat), meat, poultry, and shellfish.

Dietary Fiber

Whole grain products such as barley, oats, oat bran, and rye; fruits, legumes, seeds and husks, and vegetables.

Vitamins and Minerals

Food sources of vitamins are shown in Table 25.1 of Chap. 25. Food sources of minerals are shown in Table 26.1 of Chap. 26.

Health Claims

Certain health claims may be stated on food labels. These are authorized by the Food and Drug Administration (FDA) and are meant to inform shoppers that certain foods, nutrients, or ingredients—as part of an overall healthy diet—may reduce the risk of a specific disease. The FDA authorizes these types of health claims based on an extensive review of the scientific literature. The science behind some health claims is stronger than for others. The examples listed below are based on the standard of significant scientific agreement (SSA). Other allowed claims are termed "qualified" health claims as they must be "qualified" in such a way as to not mislead consumers. These health claims are authorized based on an Authoritative Statement by Federal Scientific Bodies. For example, the link between heart disease risk and saturated fat and cholesterol is solid, according to the FDA. The agency therefore allows the following statement: "Diets low in saturated fat and cholesterol may reduce the risk of heart disease." In comparison, the evidence relating folic acid, vitamin B_6, and vitamin B_{12} to reduced risk of cardiovascular disease is rather weak. Therefore, the language allowed by the FDA must include the "qualifier": "As part of a well-balanced diet that is low in saturated fat and cholesterol, folic acid, vitamin B_6 and vitamin B_{12} may reduce the risk of vascular disease."
There are currently 12 approved health claims for food labels and these are listed below:

- Calcium, vitamin D, and osteoporosis
- Sodium and hypertension
- *Dietary lipids (fat) and cancer
- *Dietary saturated fat and cholesterol and risk of coronary heart disease (CHD)
- Fiber-containing grain products, fruits, and vegetables and cancer
- Fruits, vegetables, and grain products that contain fiber, particularly soluble fiber, and risk of CHD
- Fruits and vegetables and cancer
- Folic acid and neural tube defects
- Dietary noncariogenic carbohydrate sweeteners and dental caries
- Soluble fiber from certain foods and risk of CHD
- Soy protein and risk of CHD
- Plant sterol/stanol esters and risk of CHD

The two claims marked with * are based on evidence that is now widely seen as questionable. As new evidence emerges, the FDA will review these and all claims and update the approved list as necessary.
Health Claims Authorized Based on an Authoritative Statement by Federal Scientific Bodies:

- 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
- Saturated fat, cholesterol, and trans fat, and reduced risk of heart disease
- Substitution of saturated fat in the diet with unsaturated fatty acids and reduced risk of heart disease.

If we go back to the example used above with Harry and the yogurt containers, both food items may use the health claim "foods high in calcium, along with a healthy diet and regular exercise, may help reduce the incidence of osteoporosis."
In addition to "health claims," food labels may also contain nutrient content claims. These words now have strict definitions as listed below:

- Free: synonyms include "zero," "no," "without," "trivial source of," "dietarily insignificant source of"
- Low: synonyms include "little," "few" (for calories), "contain a small amount of," "low source of"
- Reduced/less: synonyms include "lower" ("fewer" for calories)

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Suggested Further Reading

FDA. This website provides an explanation of how to understand and use the Nutrition Facts Label. http://www.fda.gov/Food/IngredientsPackagingLabeling/LabelingNutrition/default.htm.

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.

Chapter 31
Achieving Dietary Change: The Role of the Physician

Joanne M. Spahn

Key Points

- The worldwide obesity epidemic has increased the impetus for development of clinic-based strategies targeting delivery of nutrition advice and counseling in the primary-care setting.
- Nutrition counseling is most effective when the intensity of therapy is aligned with the severity of disease risk and supported by counseling and referral of clients to appropriate nutrition intervention programs.
- Client-centered counseling strategies engage the patient in development and implementation of an action plan designed to enhance self-management practices.
- The 5As-counseling model is a recognized evidence-based method for conducting minimal contact behavior change interventions.
- Application of a combination of motivational interviewing and cognitive–behavioral strategies is effective in precipitating nutrition-related behavior change.

Keywords Client-centered counseling • Clinical care guidelines • Behavior change • Motivational interviewing • Evidence-based counseling methods • Stages of change • Cognitive–behavioral theory • Physician interventions

Introduction

Healthy People 2020 established a national goal of increasing the proportion of physician office visits that include nutrition counseling or education for patients with a diagnosis of cardiovascular disease, diabetes, or hyperlipidemia, and to increase the proportion of primary-care physicians who regularly measure the body mass index of their patients [1]. Early intervention by medical providers has the potential to have an enormous impact on disease prevention, mitigation of disease progression, improving the quality of life of patients, and decreasing healthcare expenditures. Inclusion of nutritional status as a routine component of care heightens patients' awareness of the critical link between

J.M. Spahn, M.S., R.D., F.A.D.A. (✉)
J. Spahn Consulting, LLC, Fairfax Station, VA, USA
e-mail: eatforfitness@aol.com

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diet and health and enhances the credibility of the healthcare professional in addressing nutrition-related issues. Engagement of health professionals, government and the community sectors is necessary to support individuals and families in making healthy diet and physical activity choices [2].

This chapter provides guidance on techniques and tools for optimizing the delivery of nutrition assessment, counseling, and referral in a busy primary-care practice setting.

Efficacy of Nutrition Counseling by Physicians

Nutrition and lifestyle counseling is an important component of routine prenatal and pediatric care, and a cornerstone of disease prevention and management. Screening and assessment are the critical first steps to identify opportunities for prevention and treatment. Evidence-based guidelines recommend a step-care approach, aligning of treatment intensity with health risk [3–5]. Patient-centered counseling is an effective means to enhance dietary change through assessment of patient needs and readiness to change, tailoring interventions to meet realistic goals, and encouraging patients to engage appropriate medical and social resources for more intense support [6]. Numerous studies describe effective clinic-based strategies for delivering nutrition advice and counseling in the primary-care setting targeted to patients with diabetes, hyperlipidemia, hypertension, who need weight control, or general diet improvement [7–15]. These multidisciplinary interventions involve a client-centered approach, supported by a variety of office-based systems (office prompts, algorithms, and diet assessment tools).

Physician advice is an important catalyst for diet-related behavior change. Patient retention of nutrition advice is significantly better (95% vs. 27%, $p < 0.01$, related to specific foods; 90% vs. 20%, related to food preparation methods) when received by providers trained in nutrition counseling [16]. Advice provided by trained providers was more extensive, specific, and culturally relevant; communication skills were used to enhance rapport and ensure that patients understood the advice. Multiple studies recommend that primary-care providers receive training in the use of motivational interviewing techniques, goal setting, and use of evidence-based tools for facilitating behavior change [17–20]. Referrals to a registered dietitian or community-based nutrition intervention program are excellent strategies to increase the intensity of interventions, but cannot substitute for ongoing involvement of the patient's primary physician.

Physicians are ideally positioned to influence patients to seriously consider dietary change to improve health, especially when they make referrals to dietitians and comprehensive lifestyle intervention programs. A listing of dietitians available in all geographic areas can be found on the Academy of Nutrition and Dietetics web site (http://www.eatright.org). Group interventions, such as behavioral therapy or self-management education programs, are efficacious and cost-effective strategies for supporting diet and physical activity lifestyle change [21–30]. Lifestyle change curriculum, materials, training information, and a program locator can be found on the Centers for Disease Control web site (http://www.cdc.gov/diabetes/prevention/lifestyle-program/index.html).

Medical Office System Support

In busy medical practices, an explicitly planned and coordinated team approach, knowledgeable staff, and supportive office systems facilitate rapid assessment, sensitive conversations, patient-centered counseling, and referrals. Modifications to medical office systems and electronic health record systems aid delivery of care consistent with algorithms that align intensity of treatment with level of

health risk. Innovations in health technology facilitate timely screening and assessment (e.g., automating BMI determination and risk classification), enhance access to appropriate educational materials, improve communication among healthcare providers and patients, and enhance the referral process [31, 32]. For example, weight is routinely screened during routine prenatal visits, but an electronic health record system facilitates rapid assessment of weight change, prompts timely counseling, and provides instant access to appropriate educational material or a referral.

New primary-care delivery models, such as the patient-centered medical home (http://www.pcmh.ahrq.gov), suggest practice organization which leverages healthcare teams that utilize new technologies (in-house or virtual) and healthcare reforms, such as the Affordable Care Act [33], to expand the capacity of primary-care providers to improve access to high-quality nutrition counseling and intensive lifestyle interventions. Primary-care providers screen, assess, motivate, and coordinate care with dietitians, other healthcare team members, or community organizations, all based on patient readiness and care guidelines. Future enhancements of electronic health record systems will support the use of mobile technology and wi-fi-enabled glucometers, scales, blood pressure monitors, and activity trackers which automatically transmit data to a server or smartphone applications. Studies indicate that services delivered remotely are effective [34]. These emerging technologies simplify the monitoring of food intake, physical activity, weight, blood pressure, and blood sugar, and facilitate timely feedback via text-messaging, telephone, and e-mail.

Modification of office systems to streamline office-based prevention, standardize the approach to less intensive care, and to coordinate with nutrition professionals and programs outside the office for more intensive interventions have been effective strategies for the implementation of current evidence-based guidelines [15, 35, 36]. A well-designed office system facilitates an evidence-based approach, ensuring efficient and consistent data collection, assessment and documentation of counseling, simplified tracking of care through the use of flowcharts, electronic prompts, or chart reminders, reminder messaging for patients, and coordinated educational materials and strategies [37].

The principles for organizing an office system to support delivery of nutrition care advice and counseling include [19, 38]:

1. Policy and procedure for the delivery of nutrition advice and counseling to target populations.
2. Determining baseline rates for target populations (e.g., patients with diabetes, hyperlipidemia, hypertension, obesity).
3. Defining staff roles and identifying a process champion to support coordination, training and acquisition of resources.
4. Identifying and adapting screening, assessment, and intervention tools, and developing referral procedures appropriate for various patient populations (e.g., pediatrics, prenatal, weight management, self-management of diabetes). Utilization of office information technology to aid screening, assessment, and decision support which aligns with clinical care guidelines is helpful. Identify and cultivate relationships with nutrition professionals, multidisciplinary clinics, and community resources to link patients with appropriate medium-intensity and high-intensity behavioral interventions.
5. Training of healthcare providers.
6. Setting a start date; planning periodic communication to assess implementation and chart reviews.

Routine documentation of a core set of nutrition-related data—such as height, weight (electronic medical records can flag at-risk patients), waist circumference, and activity level—sets the stage for the provider to address diet related to clinical care. Patients may complete assessment forms while waiting to see the provider. A recent review provides a description of brief assessment tools suitable for clinic use to support the dietary management of cardiovascular disease, diabetes, or obesity [39]. The WAVE (Weight, Activity, Variety, and Excess) and REAP (Rapid Eating and Activity Assessment for Patients) are two such tools designed to target healthy eating and cholesterol reduction [40]. Each

Table 31.1 Web-based nutrition education resources

Source of information	Internet site
Academy of Nutrition and Dietetics	http://www.eatright.org/
Centers for Disease Control and Prevention	http://www.cdc.gov/diabetes/prevention/lifestyle-program/curriculum.html http://www.cdc.gov/cholesterol/educational_materials.htm
Canadian Obesity Network	http://www.obesitynetwork.ca/5As_evidence
Dietary Guidelines Tools & Resources	http://health.gov/dietaryguidelines/2015/resources.asp
Joslin Diabetes Center	http://www.joslin.org/info/diabetes-and-nutrition.html
NHLBI Health Information for the Patient, Public, and Professional	http://www.nhlbi.nih.gov
NIH Office of Dietary Supplements, Dietary Supplement Fact Sheets	http://dietary-supplements.info.nih.gov (then click on "Health Information")
National Institute of Diabetes and Digestive and Kidney Diseases, The Weight-control Information Network (WIN)	http://win.niddk.nih.gov/
University of Virginia School of Medicine	https://med.virginia.edu/ginutrition/patient-education/
USDA ChooseMyPlate resources and online tools	http://www.choosemyplate.gov/health-professionals

assessment tool provides a brief diet assessment and facilitates meaningful counseling in 1–9 min. Table 31.1 identifies sources of high-quality education literature, interactive media, and self-monitoring tools (provided in a variety of languages and suitable for low-literacy clients) which target a wide variety of nutrition-related issues.

Client-Centered Counseling

Client-centered counseling is designed to place much of the responsibility for the intervention process on the client. By adopting a facilitation role, the counselor fosters a greater openness and trust. Use of informal clarifying questions increases the client's insight and self-understanding. Establishing client rapport is a prerequisite for free expression of thoughts and feelings that, particularly in the unmotivated client, may not be "politically correct." The goal is to move from the traditional hierarchical relationship to one of partnership.

This approach toward counseling is particularly useful in diet counseling as it is the client who ultimately determines what change he or she is willing and able to make and sustain. The physician brings a depth of medical knowledge to objectively assess and communicate assessment results, help to frame the problem, and motivate and guide the client to set realistic goals. The client knows best what lifestyle changes can be made and can identify barriers and solutions relevant to their situation. The client-centered approach takes the pressure off the provider to have all the answers and represents a shift in the typical relationship between physician and client, which may be somewhat unfamiliar to both parties. The ultimate goal of counseling is to actively engage the patient in self-management practices necessary to change and maintain a healthy diet. The traditional doctor–patient approach (e.g., "I want you to walk for 45 minutes every day and lose 10 pounds") is likely to antagonize many patients. They may well give the impression to the doctor that they agree with the plan, but will then go and find a doctor who will give them a pill to fix the problem.

The 5As Counseling Model

The 5As is an evidence-based method for conducting minimal contact interventions targeting behavior change [31, 41]. It is a framework for sensitive, realistic, measurable, and sustainable nutrition change strategies that focus on improving health and well-being. Adoption of this approach for physician-provided nutrition counseling allows others to collaborate in developing tools and materials to support the process. The 5As include:

- *Ask*: ask permission to discuss diet and/or weight and explore readiness to change.
- *Assess*: assess diet-related risk factors, diet, diet history, and physical activity patterns.
- *Advise*: give clear, specific, and personalized lifestyle change advice, including tailored information about personal health risks/benefits.
- *Agree*: collaborate with the patient to identify nutrition-related health and behavioral goals and strategies that the patient is willing to implement.
- *Assist*: assist the patient in achieving agreed-upon goals by acquiring knowledge, confidence, and social/environmental support for behavior change. Refer high-risk patients to more intensive counseling in accordance with evidence-based guidelines. Arrange follow-up contact to provide ongoing support.

The Canadian Obesity Network provides 5As toolkits to support integration of evidence-based counseling techniques in pediatrics, healthy pregnancy, and adult practice. Primary-care team training and implementation resources are available to support each step in the process (http://www.obesitynetwork.ca/5As_Team).

Models for Inducing Change

Transtheoretical Model and Stages of Change

This model attempts to describe a sequence of cognitive and behavioral stages people use over time to achieve intentional behavior change. The core concept, known as Stages of Change, reflects an individual's attitudes, intentions, and behavior related to change of a specific behavior. Stages of change are identified as precontemplation, contemplation, preparation, action, and maintenance. Table 31.2 outlines treatment strategies endorsed by the transtheoretical model [42]. Strategies targeted to the early stages of change target motivation, and those used in the later stages are more consistent with strategies used in behavioral therapy.

Motivational Interviewing

Motivational interviewing integrates well within the transtheoretical model. It facilitates the client in exploring and resolving their own uncertainty and building confidence and enhancing commitment to change. The four guiding principles of the technique include expression of empathy, development of discrepancy, roll with resistance, and support self-efficacy (client confidence in their ability to

Table 31.2 Stages of change and stage appropriate treatment strategies

Stage of change	Treatment strategies
Precontemplation	Personalize assessment information, educate about risk, acknowledge patient's emotions related to condition
Contemplation	Increase patient's confidence (self-efficacy), discuss ambivalence and barriers to change, reinforce past accomplishments, encourage a support network, emphasize expected benefits
Preparation	Facilitate client setting of small, specific, realistic goals to build confidence; reinforce small accomplishments
Action	Provide tailored self-help materials; refer to a behavioral program or self-management program
Maintenance	Help patient anticipate and prepare for high-risk situations, link patient with community support groups, encourage continued self-monitoring and goal setting, if patient ready to continue

accomplish a specific task). The tone of the counseling session is totally nonjudgmental and the counselor uses open-ended questions and reflective listening to frame discrepancies between client goals and actions. Conflict and confrontation are avoided by rolling with resistance—verbalizing the understanding that the client is in the best position to determine when change can occur. The process stresses the use of reflective listening skills rather than the drive to provide information; it supports enhancement of self-efficacy and optimism for change [43]. This is a major paradigm change from the counseling that is frequently employed in a busy clinic setting, which is oriented around problem solving. Further resources and training information on this technique can be found at http://motivationalinterviewing.org.

Cognitive–Behavioral Theory

Cognitive–behavioral theory is based on the assumption that all behavior is learned and is directly related to internal factors (e.g., thoughts and thinking patterns) and external factors (e.g., environmental stimuli and feedback) that are related to the problem behavior. Patients are taught to utilize a variety of behavioral and cognitive strategies to recognize behaviors that lead to inappropriate eating and replace them with more rational thoughts and actions. The behavioral strategies most suited to minimal contact interventions are outlined in Table 31.3 and include self-monitoring, goal setting, and problem solving.

Incorporation of Behavioral Theory Tenets to the 5As Model

The 5As model provides specific guidance on how to integrate motivational interviewing, the transtheoretical model, and cognitive–behavioral therapy principles into a minimal contact dietary intervention. A quick assessment allows for tailoring of counseling goals. For those patients not ready to make dietary changes, the goal of the intervention is to enhance readiness/motivation. The

Table 31.3 Behavioral strategies useful to support dietary change

Strategy	Application
Self-monitoring	Cornerstone of therapy, used in goal setting/progress assessment
	Provide rationale and instruction for self-monitoring
	Assist patient in reviewing log and identifying patterns
	Assist with goal setting and problem solving
	Celebrate successes
Goal setting	Collaborative activity
	Identify goal that client is willing to expend effort to achieve
	Discuss pros and cons of goal
	Document and track progress toward long- and short-term goal
	May need to provide information/skill development
	Encourage strategies to build confidence
	Celebrate successes
Problem solving	Define the problem
	Brainstorm solutions
	Weigh pros and cons of potential solutions
	Patient selects/implements strategy
	Evaluate outcomes/adjust strategy

intervention addresses the client's ambivalence about change; motivational interviewing is an appropriate strategy. Clients ready to change will be more open to utilize behavior therapy strategies such as self-monitoring, goal setting, and problem solving. The 5As model outlined in Table 31.4 guides the content of the brief nutrition encounter.

Summary

A growing body of literature has emerged that describes brief and effective clinic-based strategies for delivering nutrition advice and counseling in the primary-care setting to motivate patients to take action to improve their health. The 5As model for minimal contact interventions targeting behavior change is one such starting point. Numerous organizations have developed nutrition-specific tools and counseling guides to support this intervention model. Physician knowledge of behavior change models relevant to individual-level interventions facilitates tailoring of nutrition counseling to meet patient needs. Tailoring of nutrition education materials and referral to nutrition experts, behavior therapy, self-management education programs, or community programs can enhance counseling intensity and support patients' development of self-management practices necessary to achieve and maintain healthy diets. Routine use of patient-centered counseling strategies, innovations in information technology, and increased availability of moderate- and high-intensity lifestyle change programs in the clinical or community setting will further enhance delivery of nutrition advice and counseling in the primary-care setting.

Table 31.4 Incorporation of behavioral theory tenets to the 5As model

Ask	To address the topic you might say: "What you eat is very important for your health and for the management of your [blood cholesterol, blood pressure, etc.]. May I discuss your diet with you today?" This invitation gives the client some control over the encounter. If the answer is "no," end the discussion. If the patient is uncertain or says "yes," avoid giving advice, but continue the assessment.
Assess	
Diet	Age, condition, and disease-specific assessment criteria should be addressed.
Diet readiness	Diet: Recommend use of a brief nutrition assessment tool such as the WAVE or REAP (good waiting-room activity).
Diet history	Diet readiness to change: You may ask the client to rate on a scale of 1–10 (10 being fully ready to take action) how ready they feel to take action to improve their diet right now. The focus of the intervention will vary based upon the readiness score:
Anthropometric and disease-specific criteria	• If score is low [1–4], inform, raise awareness, explore beliefs/attitudes, and encourage change. • If score is moderate [5–7], explore patient's ambivalence and, if willing, negotiate a small, specific behavior change goal. • If score is high [8–10], focus on goal setting/problem solving.
Advise	You might say: "Based upon your health risk [specify] and current diet assessment, I recommend we focus on _____ [excess saturated fat intake, excess carbohydrate intake, low fruit/vegetable intake]." Aim for a strong, succinct, clear, personalized message about what you think the patient should do, delivered with concern and conviction, and related to the benefits to be derived from this change. For patients not ready to change, but open to a discussion about diet change, rather than giving specific advice, you could briefly explore the patient's ambivalence to change by asking: "Why did you rate yourself a—on the scale from 1 to 10?" "What would need to happen for you to be more ready to change?" "What would be some advantages to making a diet change?" "What are the disadvantages to making a diet change?" "Have you attempted to change your diet? What worked or didn't?" "Would family/friends help you to change your diet?" You might end the intervention here by saying: "I respect your decision to not make a change right now. You are the best judge of what is right for you, but when you are ready, I will be willing to assist you."
Agree	For patients ready to make diet change, you might ask: "What do you think needs to change in your diet?" "What are your ideas for making that change?" • Negotiate behavior change goals • Encourage self-monitoring • Briefly discuss barriers and guide use of problem solving
Assist	Provide handouts and web resources based upon patient goals/interests. Provide lists and recommendations for community resources. Follow up by phone, e-mail, or an office visit in 2–4 weeks, if specific behavior change goals are set. If patient is at high risk or has a chronic disease diagnosis, consider a referral to a registered dietitian or for more intensive lifestyle counseling.

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Part VI
Other Selected Topics

Chapter 32
Dietary Supplements: Navigating a Minefield

Norman J. Temple

Key Points

- Use of dietary supplements has increased rapidly in recent years and around half of people in North America regularly use supplements.
- A wide variety of supplements are sold. In some cases, there is firm evidence supporting their efficacy but in many other cases there is little or no supporting evidence.
- Many 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, and infomercials on TV.
- Many marketing practices are unscrupulous; these involve giving unreliable or dishonest information that is not supported by scientific studies.
- The marketing of supplements in the United States is only weakly regulated and thus permits many products with misleading claims.
- Suggestions are given on counseling patients so that they can better evaluate claims made for supplements.

Keywords Dietary supplements • Dietary Supplement and Health Education Act • Herbal preparations • Marketing of dietary supplements • Multivitamin supplements

Introduction

> Hope springs eternal in the human breast
> A. Pope, Essay on man, Epistle i.

Dietary supplements refer to any substance taken in addition to regular food. Supplements include vitamins, minerals, amino acids, herbs, enzymes, and various substances extracted from plants and animals. They are sold as liquids, tablets, capsules, and powders. By definition these products are not

N.J. Temple, Ph.D. (✉)
Centre for Science, Athabasca University, Athabasca, AB, Canada, T9S 3A3
e-mail: normant@athabascau.ca

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conventional foods but are intended to supplement the diet, generally with the intent of improving health and body functioning, and of preventing or treating disease.

There has been a rapid increase in recent 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 United States doubled after the passing of this law to almost $18 billion in 2000 [1] and have been steadily increasing since. Sales in the USA now total roughly $32 billion per year. Surveys reveal that around half of adults in the USA take supplements regularly [2, 3]. Canadian surveys are broadly similar [4]. The profiles of 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 receive very little training in this area.

Common Supplements

Many types of supplements are sold. The quality of the evidence supporting their efficacy covers a wide spectrum: some are based on solid science and are recommended in other chapters, whereas at the other end the marketing claims are blatantly dishonest.

Vitamins and Minerals

Evidence has accumulated in recent years suggesting that supplements of vitamin D may be protective against several diseases including cardiovascular disease and cancer (especially colon cancer) [5, 6]. Supplements may also reduce all-cause mortality [7]. Most interest has focused on whether vitamin D can enhance resistance to bone fractures but here the evidence is mixed and inconclusive [7, 8]. Though still the subject of ongoing research, the weight of evidence indicates that many people would benefit from a daily supplement that provides at least 1000 IU (25 μg) per day [6]. People most likely to benefit from a supplement are the elderly, people with dark skin, those who expose little skin to the sun, and for inhabitants of northern latitudes, including the northern states of the USA.

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—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 as is often the case with elderly people and those with anorexia, drug addiction, or advanced cancer.

There has been ongoing debate regarding whether healthy adults should take such a multivitamin supplement. 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 5–15 years. Findings consistently reveal that people who choose to consume a multivitamin supplement gain no benefit in terms of a reduced all-cause mortality [9–11]. These findings are supported by the results of randomized controlled trials. Several such trials have taken place in order to determine whether multivitamins have any value in the areas of all-cause mortality, 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 [12]. 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 such products will improve health or prevent disease. This can sound very impressive. In support of this it has been firmly established that antioxidants are important for the body's defenses. However, nutritional studies do not categorically support a blanket claim that all antioxidants generally promote health. In fact, the reverse may also be true.

Several large RCTs have been conducted in which β-carotene, vitamin C, or vitamin E has been given, either for primary or secondary prevention. These are the three major antioxidant vitamins. The dose has typically been several times higher than the RDA. A recent major meta-analysis concluded that supplementing with these vitamins leads to an *increase* of about 2–5% in all-cause mortality [13].

As was discussed in Chap. 11 on coronary heart disease, the consensus among nutrition scientists is that, first, foods naturally rich in antioxidants, such as fruit and vegetables, are excellent for health, but, secondly, these benefits are unlikely to be obtained from purified antioxidants. The reasons for this are complex and not universally understood. Therefore, when sellers of supplements state in their advertisements that a product is "rich in antioxidants," that is weak evidence that it will improve health or prevent disease.

Herbs

A great many different herbal preparations are used in North America and around the world. They are employed for both prevention and the treatment of a wide variety of disorders. Supporting evidence for the value of herbal supplements is highly contentious. Unlike conventional drugs, herbal supplements 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 this problem, many herbal products sold in North America do not contain the herbal product stated on the label. This was shown in a recent study where about half the samples of herbal products that were purchased did not contain the species indicated on the label [14]. For these reasons even if a carefully conducted trial indicates that a particular herbal treatment is effective, one cannot be confident that patients treated with a product labeled as the same herb will see the same benefit.

Here we look at two examples of herbal treatments that have been much researched and are widely used.

- Echinacea. This herb is widely used in North America and Europe for the prevention and treatment of the common cold. A detailed review concluded that: "The overall evidence for clinically relevant treatment effects is weak." [15]
- St John's Wort. Evidence suggests that it may be effective in the treatment of mild to moderate depression [16]. 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 sold at health food stores will have the same amounts of the same constituents or will be as effective.

These two 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.

Many supplements consist of a mixture of herbs. Often the label will give the ingredient list as a dozen or so herbs, each with a Latin name. Little research has been conducted on mixtures of herbs. Moreover, such herbal cocktails may induce harmful side effects.

Detoxification and Stimulation of 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 the 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 some other organs as well—so that detoxification is accelerated and the body is cleansed. This will then lead to all sorts of benefits, such as more energy. 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. For some herbs there is supporting evidence, Echinacea for example. But in most cases the claims come minus credibility.

Glucosamine and Chondroitin

Supplements of these substances have become 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 [17].

Exotic Fruit Juices

In recent years, several exotic fruit juices (or “super fruits”) have appeared on the market. The main ones are acai, goji, mangosteen, and noni. They are sold by multilevel marketing and through health food stores. They invariably come with promises of wonderful benefits, but at an exorbitant price. A health food store in Edmonton, Canada, visited by the author charges about $50–$60 per liter for these juices. By contrast, the local supermarket sells fruit and vegetable juices for less than $3 per liter.

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. New products appear with bewildering regularity. 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. Some of the more commonly sold ingredients of supplements sold for purposes of weight loss are described in Table 32.1.

Table 32.1 Features of common ingredients found in weight-loss supplements[a]

Supplement	Claimed action	Effectiveness	Safety	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

[a]Sources of information: Medline Plus http://medlineplus.gov and National Center for Complementary and Alternative Medicine http://nccam.nih.gov
[b]All products are potentially hazardous if taken in excess

A Repeating Story

What we see, time and time again, is weak evidence dressed up as solid science. The marketers of supplements often use scientific evidence the way a drunk uses a lamp post: more for support than illumination.

The following are the major types of claim made in support of the efficacy of supplements: (1) mere speculation (e.g., that detoxification will improve health or that an exotic fruit juice is rich in antioxidants and will therefore improve health); (2) a change in functioning of the body (e.g., a change in one parameter of the immune system, and based on that it is claimed that the body will be less likely to develop infections); (3) weak clinical evidence (e.g., a particular herb has been used by many herbalists for decades and they claim it is effective); and (4) anecdotal evidence, often from an unqualified person with a serious conflict of interest ("Many of my customers have tried [the product] and it works very well."). A slight variation of anecdotal evidence is the use of testimonials ("Jim from Miami says: 'Thanks to Speedy Fat Burn I have lost 25 pounds in one month.'"). But what is lacking, in the great majority of cases, in the claims of those marketing supplements is consistent evidence from well-conducted RCTs, with clinical endpoints, showing real health benefits, and published in peer-reviewed journals.

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 [18].

Potential Hazards from Supplements

One of the most common mantras of 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 [19]. The true figure likely runs into the thousands as most cases are probably never reported.

A recent study estimated that 23,000 visits occur each year to emergency departments in the USA as a result of harm caused by supplements [20]. 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 use of supplements. The type of supplements most often linked to this problem are those recommended for energy and weight loss.

Supplements can be hazardous in a variety of ways. Many herbal supplements have toxic effects. Some supplements sold with the claim that they enhance sexual function have been shown to be adulterated with drugs [21]. 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 [22]. Recent studies carried out in the USA and Canada have reported that many supplements contain high levels of fillers or contaminants [14, 23]. Again, this problem is most often associated with herbal products. Quite apart from toxic contaminants, many herbs interact with various drugs. Another problem that is probably quite common, though hard numbers on this seem to be lacking, is that many people with a health problem that could be helped by a conventional medical treatment turn instead to useless supplements. Looked as a whole this evidence compels the conclusion that dietary supplements, especially herbal preparations, should only be used with much caution.

This problem is not limited to herbal preparations: micronutrients can also be hazardous. Evidence has emerged in recent years linking calcium supplements with harmful side effects, most notably a 20–40% increased risk of myocardial infarction [24]. As a result it has been proposed that any benefit delivered by calcium supplements in reducing the risk of fractures is outweighed by harm to other parts of the body. However, this suggestion has not been confirmed.

How Dietary Supplements Are Marketed

Dietary supplements are marketed in diverse ways [25]. 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, bulk mail, spam e-mails and internet websites, as well as by infomercials on TV.

Direct Contact with Consumers

HFS are a popular source of dietary supplements. HFS staff seldom have any proper scientific knowledge regarding the topics on which they freely dispense advice. But what they do have is a strong economic incentive to sell products. As a result, 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. In addition, 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 [25].

It's 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 visits made to 260 HFS and pharmacies across Canada [26]. The results reveal that on 90% of times that questions were asked in HFS, the recommendations made 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 get a commission for their sales.

The people who control this form of marketing often engage in unscrupulous activities. 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." In another case, the mastermind was referred to as "Widely regarded as the world's #1 nutritionist" and the product as "The biggest discovery in nutrition in the last 40 years!"

How Supplements Are Advertised

The advertising of dietary supplements is carried out by a variety of means. Newspapers are one common method (sometimes as multipage supplements). Infomercials are another method. They are TV programs produced and paid for by commercial companies. They resemble regular TV programs but are, in reality, a form of advertising. 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 [27].

The Object of the Exercise

The purpose of all this huge marketing enterprise is, of course, to maximize sales. As mentioned earlier, there are some supplements for which reasonably solid evidence exists justifying their value. Each of these cost around $3 or $4 per month. But go into a HFS, tell the salesperson that you don't have enough energy, you have an ache in your knee, and your mother died of cancer and you will likely be advised to take a handful of supplements, each costing between $20 and $60 per month. This might easily add up to $100–$200 per month. And it is quite likely that the recommended supplements would have little or no beneficial effect on health.

Regulations on the Marketing of Supplements

United States

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 regulations [28]. Whereas under the former law manufacturers were required to prove that a dietary supplement is *safe*, now, under DSHEA, the onus is 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.

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.

DSHEA was passed by Congress after heavy lobbying that was orchestrated by the supplement industry [28]. Whatever the intent may have been, there is no doubt that over the years following passage of DSHEA, there were 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* [29] 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* [30] with a focus on herbal supplements. These comments are as true today as when they were written more than a dozen years ago.

Canada

Canada provides an object lesson for the USA on how not to reform the system for the production and marketing supplements. In 1999, Health 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 types of scientific evidence. When these regulations were announced, the clear impression was given that the marketing of supplements was to be made much more honest. The supplement industry was given several years to implement the regulations, which came into force in 2004. The evidence referred to in this chapter indicates that little improvement has taken place [31]. In that respect the situation in Canada is still every bit as bad as that in the USA. 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 toxicity 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 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 and impartial source of information. Moreover, every year millions of people talk to a physician.

Physicians can offer the following simple rules to help their patients 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 physicians 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. A healthy dose of skepticism is a consumer's best protection against fraudulent and misleading marketing.
- For further information check credible sources of information. Several health-related organizations supply information on supplements at their websites. These include:

  Mayo Clinic http://www.mayoclinic.org/drugs-supplements
  National Center for Complementary and Alternative Medicine (NCCAM) http://nccam.nih.gov
  Medline Plus http://medlineplus.gov/

  The National Cancer Institute's website gives reliable information about various supplements claimed to be effective in the prevention or treatment of cancer http://www.cancer.gov/cancertopics/treatment/cam

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Chapter 33
A Plague of False and Misleading Information

Norman J. Temple

Key Points

- False and misleading information is widespread across many areas of nutrition.
- This chapter briefly examines some examples including Dr Oz and his TV show, unscientific weight-loss treatments, diet and exercise programs that are based on their blood type, and detoxification.
- The chapter also looks at training programs for nutritionists that lack scientific credibility.
- Problems of conflict of interest in research are discussed.

Keywords Blood groups • Conflict of interest • Detoxification • Dr Oz • False information • Misleading information • Nutritionist training program

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 present chapter continues the subject of how the problem of false and misleading information is widespread across many areas of nutrition. This problem has a long history across many areas of 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 always 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). The scope of the problem of false and misleading information is enormous and is continuously changing. It is clearly impossible, therefore, to cover all aspects of this problem. This chapter is intended only to present some illustrative examples of the problem.

N.J. Temple, Ph.D. (✉)
Centre for Science, Athabasca University, Athabasca, AB, Canada, T9S 3A3
e-mail: normant@athabascau.ca

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Physicians and other healthcare professionals need to be cognizant of this problem. This is because out of any random group of a dozen patients several will believe some of the false ideas that are being continually disseminated.

The Case of Dr Oz

Dr Mehmet Oz is a highly accomplished heart surgeon whose TV show is 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, recently 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."

Weight-Loss Treatments

If diet books worked, then the obesity epidemic would have been vanquished years ago. But for the past two decades, the diet book industry has been growing at the same rate as 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, 140 books were published in 2014 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 256 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 cover.

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 a person should select their diet and exercise program based on their ABO blood type. Over the years several other authors jumped on the publishing bandwagon with books making similar claims. These books claim that a person's blood type is the basis for treating 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 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 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% reported using detoxification therapies [6]. Detoxification is often advocated to enhance weight loss. The treatment at the center of detoxification is fasting, often accompanied with juices. As noted above and in the previous chapter the supplement industry has also 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.

The Vitamin Summit

The USA has a very large number of people who are highly active in promoting the distorted nutrition science referred to above. Sometimes they come together. Here is an example. In May 2016, a free online conference took place called the "Vitamin Summit." In their promotion of this conference the organizers claim that the speakers are: "The most distinguished and diverse group of vitamin experts ever assembled for one event!" Let's take a closer look. Here are some of the illustrious speakers:

- Andrew Saul. This person advocates megadoses of vitamins, including vitamin C. This idea was popularized in the 1970s but has largely been abandoned by conventional physicians and nutritionists as clinical studies rarely provide supporting evidence.
- Dr Joseph Mercola. According to an article on him in Wikipedia, he dismisses medical concerns over avian influenza pandemics. He asserts that the government, big business, and the mainstream media have conspired to promote the threat of avian flu in order to accrue money and power. Furthermore, he has been highly critical of vaccines and vaccination policy, and questions whether HIV is the cause of AIDS [10].
- Ty Bollinger. This person promotes heavily distorted and grossly unscientific information about medicine and cancer.

Training Programs for Nutritionists

The usual training program in North America for a person who wishes to be recognized as a nutritionist is a 4-year degree in nutrition. To become a dietitian also requires an internship. But do a Google search using the term "nutritionist training program" and many programs pop up, most of which are seriously lacking in scientific credibility. Here is one example.

The American School of Natural Health (http://www.americanschoolofnaturalhealth.com) offers a training course to become a "nutrition consultant." According to the website, "[the] course stresses the use of whole and organic foods—an integral concept in many indigenous societies. Today we see that a return to chemical free foods along with other dietary measures is an effective answer to many health complaints and common conditions. The course also focuses on the importance of Detoxification & Cleansing, as only fully functioning organs are able to absorb and utilize nutrients optimally."

Programs of this type typically take about 1 or 2 years to complete which is considerably less than conventional nutrition programs. But many people are in a rush to become a qualified nutritionist. The American Fitness Professionals & Associates (www.afpafitness.com/nutrition-certification-programs) caters to those people. They will train a person to become a "Certified Nutrition & Wellness Consultant" in only 100 h.

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." Some indications of what students will learn during the program are indicated by a description of books from the approved reading list:

1. "The 4-Week Ultimate Body Detox Plan shows you how to get rid of toxins using a simple and effective step-by-step approach."
2. "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."This is OK
3. "The only Self-Help Guide to make alterative cancer therapies work for YOU. A bold revelation of what this 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 Conflict of Interest in Research

Commercial organizations have a long history of meddling in the scientific process so as to distort the outcomes of research in ways that are favorable to the particular industry. The tobacco industry and Big Pharma have been playing this game for decades. Here we look at how this takes place in the area of food and nutrition.

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. An analysis was made of studies conducted between 1999 and 2003 on soft drinks, juice, and milk [11]. The findings of each study were classified as being favorable or unfavorable to the industry that sponsored the study. For interventional studies none of the studies with industry financing reported a finding that was unfavorable whereas 37% of studies with no industry funding did so. For all types of study, including observational studies and reviews, those with industry financing were 7.6 times more likely to report a finding favorable to industry than studies with no industry financing. Much the same has been reported concerning research on olestra, a fat substitute [12]. By contrast, an analysis of papers in the area of obesity or nutrition saw no evidence of a relationship between the source of funding and the results [13]; however, that study focused only on studies published in four of the leading medical journals. Those journals may have higher standards and may therefore routinely reject papers where the results may not be kosher.

These findings, taken as a whole, do not necessarily indicate that actual fraud 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 want 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 recently published in a nutrition journal that reviewed the value of vitamin supplements [14]. 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.

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 public generally has no formal training and no ability to discriminate between nutritional facts, fancies, and fantasies. This places the onus on health professionals to be aware of this never-ending problem. They also have a responsibility to explain the problem to their clients and to provide sound information.

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Chapter 34
Drug Interactions with Food and Beverages

Garvan C. Kane, Sheila M. Wicks, Temitope O. Lawal, and Gail B. Mahady

Key Points

- Vitamin K-rich foods impair anticoagulant effects of warfarin
- Acidic beverages aid absorption of antifungal drugs
- Grapefruit juice, alcohol, and caffeine may interfere with drug metabolism
- Garlic enhances anticoagulant effects and reduces protease inhibitor levels
- Cranberry supplements may enhance the effects of warfarin.

Keywords Drug metabolism • Tyramine • CYP3A4 • Cranberry • Grapefruit • HMG-CoA reductase inhibitor • Alcohol • Caffeine • Garlic • Ginger

Introduction

In general, for proper administration of medications, patients should follow the label instructions carefully. 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. Yet for many reasons, patients rarely ask about which foods should be avoided. 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. However, importantly, there are many incidences when the consumption of specific foods

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

S.M. Wicks
Department of Clinical Anatomy and Cell Biology, Rush University, Chicago, IL, USA

T.O. Lawal
Department of Pharmacy Practice, University of Illinois at Chicago, 833 South Wood Street, Chicago, IL, USA

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

G.B. Mahady (✉)
Department of Pharmacy Practice, University of Illinois at Chicago, 833 South Wood Street, Chicago, IL, USA
e-mail: g.b.mahady@gmail.com

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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. 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

In general, as a result of simple dilution food will slow absorption by reducing the drug's concentration; 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 certain 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 will typically cut in half the amount of iron absorbed, it may be needed to minimize gastric irritation.

Specific Examples of Food–Drug Interactions

Here, we look at examples of food–drug interactions (see Table 34.1).

Effects of Vitamin K on Warfarin Anticoagulation

The anticoagulant effect of warfarin is mediated through inhibition of the vitamin K-dependent coagulation factors II, VII, IX, and X. A key feature in the stability of the warfarin anticoagulant effect is week-to-week differences in the content of vitamin K in the diet. Foods particularly 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 can 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/day) may help in achieving a more stable warfarin effect.

Monoamine Oxidase Inhibitors and Tyramine

Monoamine oxidase (MAO) inhibitors, used in the treatment of depression and phobic anxiety disorders, 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,

Table 34.1 Drug–food interactions[a]

Drug	Food interaction	References
Acetaminophen	Alcohol ↑ AE	[5]
Artemether	Grapefruit ↑ DE	[6]
Atorvastatin	Grapefruit ↑ DE	[5, 6]
	Alcohol ↑ AE	
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 ↑ DE	[5, 8]
	Alcohol ↑ AE	
Cyclosporine	Grapefruit ↑ DE	[6, 9]
Diazepam	Grapefruit ↑ DE	[5, 6]
	Alcohol ↑ AE	
Doxycycline	Dairy, Ca, Mg, Fe ↓ DE	[1]
Ebastine	Grapefruit ↑ DE	[6]
Felodipine	Grapefruit ↑ DE	[6, 9]
Griseofulvin	Alcohol ↑ AE	[5]
Fe supplements	Food ↓ effect	[10]
Isocarboxazid	Tyramine ↑ AE	[10]
Isoniazid	Alcohol ↑ AE	[5]
	Tyramine ↑ AE	
Isosorbide dinitrate	Alcohol ↑ DE	[5]
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]
Methadone	Grapefruit ↑ DE	[6]
Metronidazole	Alcohol, ↑ AE	[5]
Midazolam	Grapefruit ↑ DE	[6]
Minocycline	Dairy, Ca, Mg, Fe ↓ DE	[1]
Nimodipine	Grapefruit ↑ DE	[6, 7]
Nisoldipine	Grapefruit ↑ DE	[6]
Nitrofurantoin	Alcohol ↑ AE	[5]
Phenelzine	Tyramine ↑ AE	[5]
Pranidipine	Grapefruit ↑ DE	[6]
Saquinavir	Grapefruit ↑ DE	[3, 4, 6]
	Garlic ↓ DE	
Sertraline	Grapefruit ↑ DE	[5, 6]
	Alcohol ↑ AE	
Sildenafil	Grapefruit ↑ DE	[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]

(continued)

Table 34.1 (continued)

Drug	Food interaction	References
Tranylcypromine	Tyramine ↑ AE	[10]
Triazolam	Grapefruit ↑ DE	[6]
Warfarin	Vitamin K-rich foods ↓ DE	[2, 3, 11, 12]
	Garlic ↑ 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

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. However, when MAO is inhibited, tyramine reaches the circulation where it leads to a sudden and significant release of norepinephrine, leading to severe systemic hypertension.

Calcium Impairs Absorption of Certain Antibiotics

Calcium-rich foods, such as dairy products and tofu, even milk added to tea or coffee, are sufficient to significantly impede the absorption of several antibiotics, including tetracycline, minocycline, doxycycline, levofloxacin, and ciprofloxacin [1]. To improve their absorption, these medications should be taken 1 h before or 2 h after calcium, magnesium, and iron supplements or dairy products.

Ginger Enhances Anticoagulant Effects

Ginger is a widely used condiment, food, and herbal medicine. It is used as a digestive aid, to treat inflammation, for morning sickness, but 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 [2]. 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 in the case of 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 [2]. In addition, it has been shown that ginger and/or its chemical components inhibit cytochrome P450 (CYP450) isoenzymes. 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.

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 effects are well documented because of its beneficial effects on health [3, 4]. Garlic contains phytochemicals that may influence the pharmacokinetic and pharmacodynamic behaviors of prescription drugs. However, the compounds contained in garlic have shown inconsistent effects on the cytochrome P450 isoenzymes. Clinical reports show a possible interaction with garlic (primarily as a dietary supplement) and warfarin. Some case reports show that the ingestion of garlic with warfarin may increase the INR, but other reports showed no effect. However, since garlic decreases platelet aggregation, there may be a chance 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 pharmacodynamics 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 coadministration 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 (*Glycine max*) 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, soymilk, or other soy products may decrease the INR in patients [2].

Specific Examples of Food–Beverage Interactions

Use of Acidic Beverages to Aid Drug Absorption

The oral broad-spectrum antifungal drugs, ketoconazole and itraconazole, are dependent on an acidic environment for absorption. 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 [13]. 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 34.2) [14].

Citrus Juice Inhibits Drug Metabolism

The discovery of the significant effect of grapefruit juice on drug metabolism occurred over 20 year ago [9]. Both grapefruit and grapefruit juice, as well as *Citrus auranitum* (Seville oranges) and *C. grandis* (pomelo), interact with a number of prescription drugs, interfering with their metabolism

Table 34.2 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
Pepsi	2.5	Diet Pepsi	3.2
Cranberry juice	2.8	Mountain Dew	3.3
Canada Dry ginger ale	2.7	Tropicana grapefruit juice	3.4
Dr. Pepper	2.9	7-Up	3.4
Sprite	2.9	Tropicana orange juice	3.8

[a]Those medications in the left column tend to aid in ketoconazole absorption

and increasing the risk of dose-dependent side effects [6, 9]. The compounds responsible for these interactions include the flavonoids and furanocoumarins. These compounds are present in sufficient quantity in a typical glass of grapefruit juice (and which are also present in the whole fruit, the pulp, and the peel) to irreversibly inhibit a key-metabolizing enzyme (CYP3A4) in the intestinal wall, although no effects are seen on the similar enzyme in the liver [7]. The extent to which an individual is affected by grapefruit juice is largely genetically determined and is related to the extent and relative distribution of isoforms of this enzyme in the intestine. While there are broad ethnic differences (African Americans affected more than Caucasians), prediction of the scope of the effect in a particular individual is impossible in the clinic.

Recent studies suggest that grapefruit and grapefruit juice inhibit CYP3A4, an enzyme that metabolizes >65% of drugs, as well as P-glycoprotein and a number of other metabolic enzymes and transporters. Responses are typically quite variable between individuals, with patients with the highest intestinal expression of CYP3A4 experiencing the greatest grapefruit juice interaction. With this comes a range of dose-dependent effects, and both desirable and undesirable clinical effects can be observed.

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 (statins, such as lovastatin and simvastatin, and to a lesser extent atorvastatin) can all undergo significant interaction with grapefruit juice, as they are all substrates for the CYP3A4 and P-glycoprotein (P-gp). Fluvastatin and pravastatin are unaffected. Other medications undergoing a significant interaction with grapefruit juice include the immunosuppressants (cyclosporine 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.

In a recent review, Lee et al. [15] have challenged the validity of medical advice suggesting that grapefruit juice should not be used with statins. In their review of the clinical trials of grapefruit juice combined with statins, they conclude 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 h apart, and grapefruit juice increases atorvastatin blood concentrations by ~80% (whenever taken). They point out that 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. They conclude that drinking grapefruit juice in moderation (one glass per day) may therefore be beneficial and not adverse to health [15]. They further suggest that 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 [15]*;* 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.

Interestingly, orange juice is also now known 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 appear to be 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].

In summary, grapefruit and other citrus juices can inhibit the metabolism of many medications spanning a variety of clinical fields. 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 are the most difficult to identify, and this inhibition of metabolism can lead to many-fold 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 above-mentioned medications, particularly when they are taking them for the first time or in high doses.

Effect of Alcohol on Drug Action

Alcohol imparts many effects on drug therapy, both acutely and with chronic excessive consumption [5]. Alcohol 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. Like caffeine and grapefruit juice, concomitant alcohol can also acutely and directly affect drug metabolism. CYP2E1 is one of the enzymes that is responsible for alcohol metabolism. 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). The opposite may also occur: chronic alcohol consumption, by inducing a five- to tenfold increase in CYP2E1 levels, may increase metabolism of these drugs over time [5].

The CYP-P450 isozyme, CYP2E1, is 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 using 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 widely consumed through coffee, tea, soda energy drinks, and many other carbonated beverages. Acting as a central nervous system stimulant, caffeine leads to elevation in mood, a reduction in fatigue, and an increased facility for work. In addition to these stimulant effects and its effects on the cardiovascular system, caffeine has specific actions on drug metabolism, interacting with the CYP1A2 enzyme system responsible for the metabolism of specific drugs [8]. However, it is likely that there are only a few medications that undergo a clinically significant interaction with usual doses of dietary caffeine; these are particularly medications with a narrow margin between when they are therapeutic and toxic (e.g., clozapine, lithium, and theophylline). The consumption of dietary 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 side effects in patients consuming large quantities of caffeine (5–10 cups of coffee per day). It should be noted that this psychiatric population is one in which caffeine consumption is frequently high. 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.

Cranberry Increases Anticoagulant Effects

Cranberries (*Vaccinium macrocarpon*) are very popular worldwide as a food and 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 [9, 11]. In one case report, when cranberry was administered together with warfarin, there was an increase in the international normalized ratio (INR) and significant bleeding. There is also one report of a very serious interaction in which a patient taking approximately 2 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. [16] investigated the effects of cranberry juice on simultaneous administration of R–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 day. On day 5, they ingested 10 mg racemic R–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 day 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. 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.

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 is much lower, thus only large amounts (1500–3500 mL/day) are reported to decrease the INR [2, 9].

Conclusion

This chapter has reviewed some of the most common drug interactions with food and beverages. 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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Chapter 35
Nutritional Status: An Overview of Methods for Assessment

Catherine M. Champagne and George A. Bray

Key Points

- Obesity is increasing and should be assessed in the healthcare setting and plans made to reduce energy intake and/or to increase physical activity so as to encourage weight loss.
- 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.
- Poor diets are observed at various ages, particularly in adolescents and the elderly, often for very different reasons due to the aging process.
- Poor diets are observed at various ages, particularly in adolescents and the elderly, though for different reasons.

Keywords Nutrition assessment • Obesity • Body mass index • Dietary intake

Introduction

This chapter focuses on the whole area of nutritional assessment and explores the wide spectrum of testing available that can aid in determining the health of an individual. This 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. A nutritional 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.

C.M. Champagne, PhD (RDN, LDN, FADA, FAND, FTOS) (✉)
Department of Nutritional Epidemiology, Pennington Biomedical Research Center, Louisiana State University, 6400 Perkins Road, Baton Rouge, LA 70808, USA
e-mail: catherine.champagne@pbrc.edu

G.A. Bray, M.D.
Pennington Biomedical Research Center, Louisiana State University, Baton Rouge, LA, USA

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With comprehensive data on diet and biological information, the physician can make an accurate estimate of that person's nutritional status. Decisions can then be made on an appropriate plan of action to either maintain current health status or referral to counseling or other interventions that may enable the individual to reach a more healthy state. Only with sufficient anthropometric, biochemical, clinical, and dietary information can a plan be drafted.

One part of nutritional assessment is to determine nutritional needs of malnourished individuals suffering from protein and micronutrient deficiencies, in addition to caloric deficiencies. This often requires the use of nutrient-dense diets. But with the advent of the "obesity epidemic" and the epidemic of noncommunicable diseases, we have to deal with dietary composition as a contributing factor.

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 and its risks. Overweight is commonly defined as a BMI of 25 or higher, and obesity as a BMI of 30 or higher. Measurement of the waist circumference to gauge the degree of central adiposity is also recommended.

The epidemic of obesity in the USA started around 1980 and developed rapidly. However, the epidemic appears to have stabilized as there were no significant changes in the prevalence of obesity in youth or adults between 2003–2004 and 2011–2012 [1], but those with a BMI $\geq$40 is still rising. Data from NHANES in 2013–2014 indicate that the overall obesity prevalence among adults aged 20 and over (age-adjusted) is now at 37.3%, and among youth aged 2–19 years it has plateaued at 17.2% [2]. The prevalence of obesity is higher in women than in men (36.5% vs 33.7%) [1]. Obesity enhances the risk of diabetes, heart disease, and cancer among others. A recent report by Flegal et al. [3] quantified the health burden of obesity and reported estimates ranged from 5 to 15% for all-cause mortality, −0.2 to 8% for all-cancer incidence, 7–44% for cardiovascular disease incidence, and 3–83% for diabetes incidence; the variability is due to methods used for the population attributable fraction.

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 required for health.

Food Frequency Questionnaires

Currently, there are very extensive validated diet history questionnaires available from the National Cancer Institute, but they are long and burdensome. Shorter dietary questionnaires focused on targeted intakes (fruits, vegetables, dietary fats) are less burdensome. The food frequency questionnaire—often referred to simply as FFQ—is one means of establishing usual food intakes, 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.

Diet and Lifestyle History

An example of a basic nutrition and lifestyle history is shown in Box 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.

Box 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 ____
Has your weight changed in the past 5 years? Yes ___ No ___ How? _____
Are you trying to lose (or gain) weight? Yes ___ No ___ How? _____ Why? _____
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 information on 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. Currently, the methodology promoted in this type of assessment is best described as a multiple-pass method [4]. 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; omitted food probes are used for foods eaten 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 NHANES to track what Americans are eating and eventually to inform public policy [5].

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 [HFCS]) may enable the physician to counsel the patient more effectively. This recall is most efficiently collected by a registered dietitian who may also counsel the patient due to limited time a physician has for this intervention.

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 to keep 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 physician. A number of problems with dietary intake information have been observed: the patient may not accurately report foods consumed or portion sizes, they may choose to modify intakes knowing that the dietitian and/or physician will review the diary, or they may simply fail to disclose everything they consume.

Underreporting of Dietary Intake

It is important to realize that underreporting of food eaten is one of the major sources of error [6]. Misreporting of energy intake has been routinely observed in surveys of the US population. Men and women with obesity under-report more than normal weight individuals, despite improvements in measurement protocols [7]. Misreporting of energy intake may be common in elderly low-socioeconomic status populations [8], in Middle Eastern countries [9], and in developing nations [10].

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 35.1). For practical information on BMI and the treatment of overweight and obesity in adults the physician can refer to the guidelines of the National Heart, Lung, and Blood Institute (http://www.nhlbi.nih.gov/files/docs/guidelines/prctgd_c.pdf) and those released in 2013 by the Obesity Society, the American Heart Association, and the American College of Cardiology (http://www.obesity.org/news/press-releases/tos-aha). Guidelines are also available for the children and adolescents from the Endocrine Society (https://www.endocrine.org) and for adults from the American Association of Clinical Endocrinologists (https://www.aace.com).

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 35.1).

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 normal BMI is considered to be <23, a BMI cut-off point for risks varies from 22 to 25, and for high risk it varies from 26 to 31. 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]/year is high) and level of physical activity are additional criteria for determining the risk from 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. The challenge for clinicians is to estimate fat distribution with reasonable accuracy while also doing this in a time-efficient manner and at a reasonable 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

Table 35.1 Classification of overweight and obesity by BMI, waist circumference, and associated disease risks (https://www.nhlbi.nih.gov/health/educational/lose_wt/BMI/bmi_dis.htm)

			Disease risk[a] relative to normal weight and waist circumference	
			Men 102 cm (40 in.) or less	Men >102 cm (40 in.)
	BMI (kg/m^2)	Obesity class	Women 88 cm (35 in.) or less	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[b]	III	Extremely high	Extremely high

[a]Disease risk for type 2 diabetes, hypertension, and cardiovascular disease (CVD)

[b]Increased waist circumference can also be a marker for increased risk, even in persons of normal weight

indicated in Table 35.1, a waist circumference greater than 88 cm (35 in.) in women or 102 cm (40 in.) in men signifies an elevated risk. These waist circumferences are also the defining levels for diagnosis of the metabolic syndrome. A very large international trial, the International Day for the Evaluation of Abdominal Obesity (IDEA) study, reported that waist circumference is 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 indicate that waist circumference is associated with CVD, independently of the relationship that BMI has with CVD risk, and regardless of age or geography [11].

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. This is valuable information to collect on a routine office visit with a physician [12].

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 be overweight but not overfat.

Body Composition Analyses

Dual x-ray absorptiometry (DXA) has replaced underwater weighing as the gold standard for determining body fat and lean body mass. DXA's advantages are that it is safe, easy to use, and very accurate with the use of appropriate standards. The disadvantages are the generally high cost and the need for regular cross-standardization of the instrument, as well as the weight limits of the table (e.g., for assessment of very obese people) [12]. However, iDXA (GE Lunar) scans can provide closely comparable data to whole-body analysis with a half-body analysis in obese subjects [13].

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 [12].

Lazzer and colleagues [14] found that DXA and BIA were not interchangeable for the assessment of percent fat mass in severely obese children and adolescents; they offered a new predictive equation for estimation of body composition for use in such subjects. Some researchers have claimed that DXA has not achieved the reliability in children to be considered the "gold standard" for body composition assessment in pediatric studies [15]. Nichols and coworkers [16] 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 [17] 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 an important consideration when identifying people with excess fat mass. DXA was found to be a reliable tool in assessing skeletal muscle mass in older women [18]. 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 [19].

Laboratory Tests

Routine blood testing is necessary for the evaluation of nutrient status. Anemia is one of the most frequently detected abnormalities in premenopausal women. 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 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. Blood pressure should also be measured. Measuring HbA1c enables the clinician to determine what average blood glucose levels have been and whether the patient has prediabetes for which lifestyle intervention can be so important.

Special Concerns by Age

Individuals can become overweight at any age, but obesity is more common at certain ages. Several surveys have 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 years, and 50% will do so after age 20.

People can therefore be divided into four subgroups with regard to obesity. The first group includes individuals who will never become overweight although this group can be identified only in retrospect. The second group includes pre-overweight or pre-obese individuals who have a BMI of less than 25. The third group includes "preclinically overweight" individuals, who become overweight without clinically significant problems at the time of evaluation (i.e., the so-called healthy obese). As time passes, however, these individuals age or gain weight, they may show clinical signs of diabetes and develop complications such as hypertension, gallbladder disease, dyslipidemia, or the metabolic syndrome. The fourth group of individuals comprise those that are considered "clinically overweight" and have problems related to obesity.

Adolescents

Obesity is becoming a significant health problem among adolescents. In 2013–2014, 17.2% of US adolescents ages 12–19 years were overweight [2], triple the prevalence of three decades earlier. The prevalence of type 2 diabetes, previously considered an adult disease, has increased substantially in children and adolescents.

Increased weight in childhood becomes a progressively better predictor of weight in early adult life as children move into adolescence. Adolescents who are above the 95th percentile for weight have a 5- to 20-fold greater risk for overweight in adulthood than other adolescents. During adolescence, parental overweight is a less important predictor than it is for children at younger ages. Although 70–80% of overweight adolescents with an overweight parent will be overweight as young adults, the numbers are only modestly lower (54–60%) for overweight adolescents without overweight parents. Despite the importance of childhood and adolescent weight status, most overweight adults develop the disease only after they become adults.

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. Many establish lifelong eating habits during this period. Although young people from low-socioeconomic backgrounds are at greatest risk for poor dietary patterns, many adolescents rely on high-fat, high-sugar foods for much of their diet. Others skip meals as a method of weight control. The diets of adolescents often lack adequate fruits and vegetables and sufficient amounts of vitamins A and C, folate, calcium, iron, and fiber.

Because most bone deposition occurs during adolescence, adequate intake of calcium and vitamin D is important. Many teenagers consume less than the adequate intake (AI) for calcium (1300 mg).

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. For more details regarding nutrition and adolescence, see Chap. 4.

Elderly

Elderly individuals often have poor dietary intakes 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 that their senses of taste and smell have declined. They may have lost their sense of smell, which tends to make food seem tasteless. 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 older individuals to lack vitamins A and C, folate, and potassium. Inadequate consumption of protein-rich foods leads to 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, perhaps secondary to lactose intolerance, and also to a low intake of leafy green vegetables. Many elderly people spend a considerable amount of time indoors, and vitamin D synthesis and activation decrease with age, often resulting in inadequate vitamin D. This depends on geography, with those living in northern locales at greater risk. Although clinical zinc deficiencies are uncommon, older individuals often have marginal zinc levels because of low intake of protein-rich foods. See also Chap. 6 on aging.

Reduced physical activity and a decrease in metabolic rate with aging require that older people should often choose foods that have a high nutrient density and a low energy density. If the caloric intake for an elderly person is <1600 kcal/day, he/she is at risk of inadequate intake of vitamins and minerals. A multiple vitamin and 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.

Walking and weight training can improve an older person's balance, muscle mass, and endurance and should be encouraged. A full exercise regimen allows older individuals to feel more independent and lessens the likelihood of falls and injuries. Exercise also has a positive effect on mental attitude and helps control weight and maintain bone health.

Food Access and/or Food Security

As mentioned briefly, an energy-dense diet does not necessarily equate to a nutrient-dense diet. However, energy-dense, nutrient-poor foods are the cheapest sources of calories. As a result of this, findings from both America and France have indicated that economic factors may be pressuring poor people to select an unhealthy diet. However, other factors may also be at work. Taste and convenience of added sugar and fats may be more appealing and further influence the consumer into selecting less healthy foods [20, 21].

Another factor that pressures poorer people to eat an unhealthy diet is that for millions of Americans there is limited availability locally of healthy foods (i.e., with a low energy density and a high nutrient density). Poorer people are often faced with barriers regarding both the available choices in their local stores combined with a lack of transportation which limits their access to foods that are healthier. This is common in rural areas of America where foods may oftentimes not be classified as healthy [22, 23].

Other Areas of Concern

In addition to the issues of obesity, it is still important to remember that specific areas of concern need to be addressed that do not pertain as much to overweight as they do to essential nutrients. Indeed much of the population suffers from specific deficiencies. Key to women and, in particular those who are vegetarian, is iron deficiency. Obviously in all women, it is necessary to test for iron status and address the problem if there is a diagnosis of anemia.

Dietary fiber is an issue in practically all American diets since the reported intake of fiber falls short of the recommended adequate intake or AI which is 30–38 g/day for men and 21–25 g/day for women. NHANES 2009–2010 found that adult males consumed between 18 and 20 g/day and women between 15 and 16 g/day [24]. Focusing on increasing fruit and vegetable intake and switching away from 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 from the physician to his/her patient population. Because these are common dietary concerns, iron, calcium, fiber, vitamin D, and *n*-3 fatty acids should be considered in conversations between the physician and the patient.

Healthy Eating Index

In assessing the adequacy of the patient's diet, it may be helpful to utilize a tool such as the Healthy Eating Index or HEI [25]. This tool measures diet quality based on conformance to federal dietary guidance. The HEI-2010 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 physician's office. Scores are given for 12 dietary components then expressed on a 1000-kcal basis. In order to complete the evaluation, there needs to be an analysis of dietary intake of the individual, either by a 24-h recall, food frequency, or analyzed food records. Nine components receive high scores based on adequacy, while components of concern (i.e., refined grains, sodium, and empty calories) receive high scores based on lower consumption. The HEI-2010 assesses diet quality as specified by the Dietary Guidelines for Americans.

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 the diet and environmental factors that weigh in on 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 overweight individual begin a program to lose weight, especially if this occurs at an early age. A routine office visit presents an opportunity to encourage proper diet and weight control and to help manage underlying organic disorders that cause obesity. Research continues to elucidate the pathologic process of obesity. However, because of the increase in obesity in the USA, 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, obesity will be difficult to prevent.

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Chapter 36
Nutritional Considerations Following Bariatric Surgery

Christopher Larson

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.

Keywords Bariatric surgery • Roux-en-Y gastric bypass • Sleeve gastrectomy • 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 USA will be obese (BMI >30 kg/m^2) and 11% will be considered severely obese (BMI >40 kg/m^2) [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. 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. 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].

C. Larson, P.A.-C., R.D.N. (✉)
Department of Minimally Invasive Bariatric Surgery, Gundersen Health System,
1900 South Ave. NC3-004, La Crosse, WI 54601, USA
e-mail: CJLarson@gundersenhealth.org

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The 1991 National Institutes of Health criteria for consideration of bariatric surgery includes patients with a BMI of ≥35 with associated medical problems or a BMI of ≥40 kg/m^2. The American Society for Metabolic and Bariatric Surgery (ASMBS) has recommended that bariatric surgery be considered for patients with a BMI of 30–35 kg/m^2 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 are well established and underscore the need for lifelong surveillance. This chapter provides clinical guidance on nutritional considerations following bariatric surgery.

Bariatric Surgical Procedures

In 2014, it was estimated that 193,000 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 51.7% and 26.8%, respectively [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. 36.1). 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.

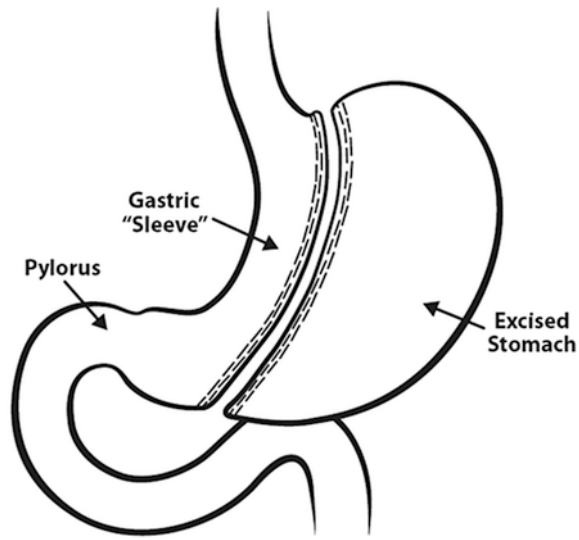

Fig. 36.1 Sleeve gastrectomy

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. 36.2).

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 puts patients at risk of nutritional deficiencies described later in this chapter.

Postoperative Dietary Recommendations

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

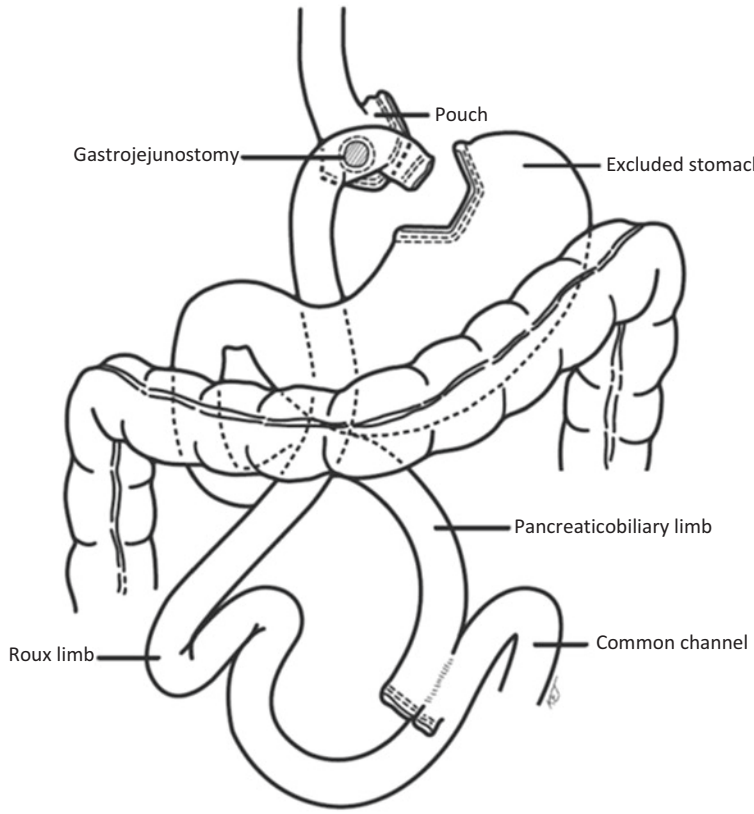

Fig. 36.2 Roux-en-Y gastric bypass

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 36.1 [5]. Moize et al. have developed a bariatric food pyramid to represent the dietary and lifestyle recommendations for the post-RYGB patient (Table 36.2) [6].

General Guidelines

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 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 36.1 Postoperative bariatric diet

Diet stage	Postoperative timing	Fluids/food	Guidelines
I	1–2 days	• Clear liquids • Non-carbonated; no calories • No sugar, no caffeine	Gastrografin swallow test for leaks on postoperative day 1; once tested, begin sips of clear liquids
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 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	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
	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 post-operative	Avoid rice, bread, and pasta until patient is comfortably consuming 60 g/day protein plus fruits and vegetables
IV *Vitamin and mineral supplementation daily.*[b] *May switch to pull form if <11 mm in width and length after 2* months *post-operative*	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

Adapted with permission from: Mechanick JI, Kushner RF, Sugerman HJ, et al. American Association of Clinical Endocrinologists, The Obesity Society, and American Society for Metabolic & Bariatric Surgery Medical guidelines for clinical practice for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient. Surg Obes Relat Dis. 2008;4:S109–84

[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 post-operative

Table 36.2 Nutritional recommendations for post-gastric bypass patients

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
Every day 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 from Moizé VL, Pi-Sunyer X, Mochari H, Vidal J. Nutritional pyramid for post-gastric bypass patients. Obes Surg. 2010;20:1133–41

Carbohydrates

At present there is no consensus regarding carbohydrate intake for patients following weight-loss surgery. Adequate carbohydrate is necessary to prevent ketosis. The dietary reference 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 but a minimum of 60 g/day or up to 1.5 g/kg of ideal body weight 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 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.

Micronutrient Recommendations

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 supplementation and laboratory testing.

Following bariatric surgery supplementation should consist of a minimum of two adult multivitamins with minerals daily, 400–800 mg of elemental calcium, preferably as calcium citrate three times daily, a minimum of 3000 international units (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.

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

Low iron stores (hypoferritinemia) and iron deficiency anemia may occur in up to 50% of RYGB patients and less commonly in SG patients [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 oral supplementation, alternative treatment, such as IV iron infusion, should be considered.

Zinc, copper, and selenium deficiencies have been reported in post-RYGB patients though the incidence is lower than that seen with iron. Routine screening for zinc deficiency has been suggested after RYGB. Screening for copper and selenium should also be considered based on symptoms such as poor wound healing and unexplained anemia [8].

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} (500–1000 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.

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].

Vitamin D deficiency or insufficiency should be treated with increased oral doses of vitamin D_3. Significant deficiency (<20 ng/mL) may require treatment with 50,000 IU once a week for 8 weeks.

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.

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_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. Clinicians should be aware of early symptoms of deficiency such as muscle cramping, paresthesia, gait abnormalities, and potential Wernicke encephalopathy or beriberi. Early symptoms may resolve with oral doses of 20–30 mg/day; however, IV doses up to 100 mg 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 one 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

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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Suggested Further Reading

American Society for Metabolic and Bariatric Surgery. www.asmbs.org.

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Appendix A: Aids to Calculations

Weight

1 g = 0.035 oz
1 kg = 2.20 lb
1 oz = 28.35 g
1 lb = 454 g

Length

1 cm = 0.393 in.
1 m = 39.37 in.
1 in. = 2.54 cm
1 ft = 30.4 cm

Volume

1 pt (US) = 0.473 L = 16 oz
1 qt (US) = 0.946 L = 32 oz
1 fl oz = 29.57 mL
1 L = 2.11 pt (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
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

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Carbohydrate: 4
Protein: 4
Alcohol: 7

Body Mass Index (BMI)

BMI = weight (kg) divided by height $(m)^2$ *or* [weight (lb) × 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. 8th 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 U.S. 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 more than ten million articles published in thousands of scholarly journals in all areas of the biomedical sciences.

http://www.eatright.org

American Dietetic Association. Resource for nutrition information. (Also in Spanish)

http://www.nhlbi.nih.gov

National Heart, Lung, and Blood Institute. Provides much valuable information on heart disease and related subjects. (Also in Spanish)

http://www.heart.org/HEARTORG

American Heart Association. Another resource on heart disease. (Also in Spanish)

http://www.cancer.gov

National Cancer Institute. This provides extensive information on all aspects of cancer. (Also in Spanish)

http://www.diabetes.org

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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
The Weight-control Information Network (WIN). Information on all aspects of weight control. (Also in Spanish)
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.choosemyplate.gov. This is provided by MyPlate (the American food guide).
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 food.

Appendix C: Dietary Reference Intakes (DRI)

Dietary Reference Intakes (DRI) consists of four tables, as explained in Chap. 29. 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.

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: http://fnic.nal.usda.gov, then click on "Dietary Guidance".

		Male	Female				
		>18 years	19–50 years	51–70 years	>70 years	Pregnancy	Lactation
Dietary fiber	g	38[a]	25	21	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

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