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Nutrition in Clinical Practice

FOURTH EDITION

David L Katz
Kofi D. Essel
Rachel S.C. Friedman
Shivam Joshi
Joshua Levitt
Ming-Chin Yeh

Wolters Kluwer

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To my patients over the years, my greatest teachers; and to Dr. Ather Ali—friend, colleague, trailblazer—in loving memory.

—DLK

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ABOUT THE AUTHORS

David L. Katz, MD, MPH, FACPM, FACP, FACLM, is a world-renowned expert in Preventive Medicine and Lifestyle Medicine, with particular expertise in nutrition. He earned his BA at Dartmouth College (1984), his MD at the Albert Einstein College of Medicine (1988), and his MPH from the Yale University School of Public Health (1993). He completed sequential residency training and board certification in Internal Medicine (1991) and Preventive Medicine/Public Health (1993).

Katz is the founder and former director of Yale University's *Yale-Griffin Prevention Research Center* (1998–2019); Past President of the *American College of Lifestyle Medicine*; President and Founder of the nonprofit True Health Initiative; and Founder and CEO of Diet ID, Inc. He is a Fellow of the *American College of Preventive Medicine*; the *American College of Physicians*; the *American College of Lifestyle Medicine*; and Morse College, Yale University.

The recipient of numerous awards for teaching, writing, and contributions to public health, Katz was a 2019 *James Beard Foundation* Award nominee in health journalism, has been a widely supported nominee for the position of US Surgeon General, and has received three honorary doctorates. He is a recipient of the *Lenna Frances Cooper Award* from the *Academy of Nutrition and Dietetics*, and the 2021 recipient of *Rundle-Lister Award* for transformative nutrition medical education from the University of Toronto.

He has more than 200 peer-reviewed publications; has published many hundreds of online and newspaper columns; and has authored/coauthored 19 books to date, including the three prior editions of *Nutrition in Clinical Practice*, multiple editions of a leading textbook in preventive medicine and epidemiology, and a textbook on clinical epidemiology and evidence-based medicine. Katz holds multiple US patents and is the principal inventor of the overall nutritional quality index™; inventor of diet quality photo navigation™, the first fundamentally new method for comprehensive assessment of dietary intake introduced in decades; and inventor of several innovations in research methodology and biomedical evidence synthesis including the multisite translational community trial; evidence mapping; and evidence threshold pathway mapping.

Katz has held faculty positions at the Yale University schools of Medicine, Public Health, and Nursing, and served as Director of Medical Studies in Public Health at the Yale School of Medicine for roughly a decade. He was awarded an adjunct professorship at the University of Washington School of Medicine. He practiced primary care Internal Medicine and evidence-based Integrative Medicine for a combined total of nearly 30 years.

Katz has given presentations on disease prevention at conferences in all 50 US states and in multiple countries on six continents. He has been recognized by peers as the "poet laureate of health promotion."

He and his wife, Catherine, live in Connecticut. They have five grown children.

Kofi D. Essel, MD, MPH, FAAP, is a board-certified community pediatrician at Children's National Hospital in Washington, DC, and Assistant Professor of Pediatrics at the George Washington University (GW) School of Medicine and Health Sciences with over a decade of experience in nutrition and obesity education. As an alumnus of the GW School of Medicine, Dr. Essel initially trained in the Community/Urban Health Scholarly Concentration. Since then, he has spent the last several years working closely with a variety of community organizations throughout Washington, DC, on a diverse set of health initiatives. He has dedicated his career to advocacy and research around healthcare training, health

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disparities, and community engagement, with a special interest and national recognition in the areas of addressing obesity and food insecurity in families.

Dr. Essel serves as the Director of the GWU Community/Urban Health Scholarly Concentration. He also serves as a Clinical Public Health Mentor in the GW School of Medicine's innovative Patient, Populations, and Systems (PPS) Course, in addition to being the Director of the Clinical Public Health Summit on Obesity, "How Physicians Can Engage Obesity With Tools of Health Equity & Empathy in Washington, D.C." He was nationally recognized by the Alliance for a Healthier Generation for helping to create an innovative curriculum to enhance pediatric resident trainee skills on obesity management. He also coauthored a national toolkit for pediatric providers to better identify and screen for food insecurity in their clinical settings with the American Academy of Pediatrics and the Food Research & Action Center (FRAC). He is the Principal Investigator for a large family centered community-clinical collaboration focused on addressing diet-related chronic diseases in marginalized settings in Washington, DC.

Dr. Essel serves on several local and national committees, including sitting on the Board for FRAC. He is actively engaged in improving the pipeline for the recruitment and maintenance of underrepresented minorities into varying fields of medicine.

Dr. Essel grew up in Little Rock, Arkansas, and attended the infamous Little Rock Central High School. He earned a BS from Emory University with a focus on Human Biology/Anthropology. While there, he was named to the College Hall of Fame, received the Universities Humanitarian Award, and later was recognized as one of the top 20 champions of health promotion in the last two decades. Dr. Essel earned his MD and MPH in Epidemiology from the GW School of Medicine and Health Sciences and was inducted into the Golden Humanism Honor Society, and bestowed with the Benjamin Manchester Humanitarian Award and Leonard Humanism in Medicine Award. He completed pediatric residency training in a select community advocacy track and completed further academic training in a specialized General Academic Pediatric fellowship at Children's National Hospital. Dr. Essel has received numerous local and national awards for his professional practice, most recently being selected for the Top 40 Under 40 Leaders in Health Award by the National Minority Quality Forum.

In his free time, you can find Dr. Essel with his family and friends, cooking flavorful meals, playing on the basketball court, or volunteering and mentoring in his church and community. He is happily married to his wonderful and beautiful wife, Candace, and has two young children that keep him very active and busy.

Rachel S.C. Friedman, MD, MHS, is Associate Program Director at Kaiser Permanente Santa Rosa Family Medicine Residency and a board-certified practicing family physician in Santa Rosa, California, caring for a diverse patient population with a strong focus on preventive care and lifestyle medicine. Dr. Friedman received a BA in History of Medicine from Harvard University (2001; magna cum laude, Phi Beta Kappa) and MD and MHS degrees from Yale School of Medicine (2008). While in medical school, she worked with Dr. Katz on the 2nd edition of this textbook and taught his innovative Nutrition Detectives curriculum to more than 600 school children in Connecticut. She subsequently completed both family medicine residency and an Integrative Medicine Fellowship at the UCSF-affiliated Sutter Santa Rosa Family Medicine Residency, where she coauthored a full-length educational rock opera *Diabetes: The Musical*, which was featured at local and national medical conferences from 2010–2012. Dr. Friedman was part of the founding faculty of the KP Santa Rosa Family Medicine Residency; has conducted clinical research on food insecurity; and has given talks to physicians across Northern California about nutrition, integrative medicine, and racial justice. She serves as an editor of *STFM PRiMER*, an online peer-reviewed family medicine journal, and was selected to be on the board of the

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national AFMRD Diversity and Health Equity Taskforce. Dr. Friedman lives in Sonoma County with her husband, Marc, and their two children.

Shivam Joshi, MD, is an internist, nephrologist, and plant-based physician practicing at NYC Health + Hospitals/Bellevue in New York City. He received his BS from Duke University and his MD from the University of Miami. He completed his residency at Jackson Memorial Hospital/University of Miami and his nephrology fellowship at the Hospital of the University of Pennsylvania. He is also a clinical assistant professor at the New York University Grossman School of Medicine with research interests in plant-based diets, fad diets, and nephrology. He has written numerous scientific articles and speaks nationally on these subjects. He is the youngest nephrologist to receive the NKF's Joel D. Kopple Award, the highest award in renal nutrition. You can follow him on Twitter (@sjoshiMD).

Joshua Levitt, ND, is a naturopathic physician who is known for his exceptional clinical skills, his depth of knowledge and his casual charismatic style. It is this unique combination that underlies his clinical expertise and provides comfort and reassurance to his patients with complex medical problems. In practice, Dr. Levitt draws on a deep understanding of the science of both conventional and natural medicine and the art of combining the two into a "best of both worlds" treatment strategy. He has over 20 years of direct clinical experience, using a unique blend of nutritional therapy, herbal medicine, and physical medicine to treat a wide range of common and complex diseases and conditions.

Dr. Levitt's education includes an undergraduate degree in physiology from UCLA, a doctorate in naturopathic medicine from Bastyr University, formal integrative medicine residency training, and an ever-growing, humbling list of lessons learned from the lives of patients.

In addition to his clinical work, Dr. Levitt is an author, advisor, product formulator, and consultant in the health and wellness industry. He is the author and creator of many popular books, programs, products, articles, and videos, all of which demonstrate his passion and commitment to nutrition and natural health.

He lives in Connecticut with his wife, Amanda; their three children, Sircia, Callie, and Zaiah; and a Hungarian Vizsla named Raya.

Ming-Chin Yeh, PhD, MEd, MS, is a Professor in the Nutrition Program at Hunter College, City University of New York. Dr. Yeh's research involves developing innovative intervention strategies to promote a healthy lifestyle for health promotion and disease prevention. His primary research interests focus on obesity and diabetes prevention and management, as well as cancer health disparities in multi-ethnic populations. Dr. Yeh is also experienced in qualitative research methods and has conducted studies using mixed-methods approaches. Specifically, he has conducted NIH-funded translational research on cultural and linguistic adaption of the Diabetes Prevention Program (DPP) for diabetes prevention in Chinese Americans. In addition, Dr. Yeh's recent research aims to reduce cancer health disparities by engaging community residents in liver, colorectal, and lung cancer prevention using social media campaigns and community-based participatory research. Other prior projects include investigating factors contributing to obesity in immigrant populations; examining the relationship between parenting style, home environment, and childhood obesity; reviewing the role of gut microbiota toward promoting health in vegan diets; and qualitative research in nutrition such as understanding barriers to fruit and vegetable consumption.

Dr. Yeh is actively involved in community services. For example, he has engaged community-based organizations in disseminating current health and nutrition-related information to residents. Over the years, he has developed a strong relationship with many key organizations in NYC and regularly delivers nutrition-related seminars at health fairs organized by local organizations. Dr. Yeh teaches a graduate-level nutrition research course and undergraduate-level courses in community nutrition and lifecycle nutrition. He also serves as a capstone advisor for graduating MS nutrition students.

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His degrees and training include the following: PhD in Public Health Nutrition, University of North Carolina—Chapel Hill; MEd, Teachers College, Columbia University; MS, New York University; BS, Taipei Medical College, Taiwan; postdoctoral training at the Yale University Prevention Research Center.

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PREFACE

In the 20 years since the first edition of *Nutrition in Clinical Practice*, dietary intake patterns have gone from a leading predictor of morbidity and mortality in the United States and industrialized countries around the world to the leading predictor. As protean as the direct effects of nutrition on human health are, the impact of dietary patterns at the scale of nearly 8 billion hungry *Homo sapiens* on planetary health is arguably even more profound. Nor can it be overlooked that this book will publish as the greatest pandemic in a century runs its course, and the origins of that pandemic—and the next if we fail to learn the lessons of this unfolding history—are rooted in our global food demand and corresponding modes of supply.

Addressing nutrition in clinical practice, in other words, was indisputably important those 20 years ago, but is all the more so now. The House of Medicine is embracing this reality. Culinary Medicine reverberates through ever more medical school curricula, and the American College of Cardiology has formally adopted the position that dietary intake should be assessed with every patient.

It is a new day. And to greet it, we offer a new edition of *Nutrition in Clinical Practice*.

I am personally gratified and honored to be involved in the production of a fourth edition. The publication of a textbook with one's name on it is rather worse than the famous nightmare of standing stark naked in front of a large crowd. This is exposure of a daunting kind, while awaiting a verdict from a jury of peers. Editions follow favorable verdicts only, and I am proud of that, and, quite frankly, relieved!

This edition represents a comprehensive update to every chapter and entry. That exacting effort is the beneficiary of a bounty of diverse expertise, as am I. My fellow editors—Drs. Essel, Friedman, Joshi, Levitt, and Yeh—deserve special recognition. All of us, in turn, are grateful to the very diverse group of chapter authors who ensured our collective attention to all relevant and timely details. I wrote the first edition of *Nutrition in Clinical Practice* on my own those 20-some-odd years ago. This edition was a team effort and is, we believe, more vigorous for those hybrid inputs. Our intent has been to preserve all that earned favorable verdicts for the three prior editions, while enhancing the breadth and depth of content with more targeted expertise.

We commend our collective effort to you in the service of adding years to lives; adding life to years; and doing those in a manner that preserves the natural beauty, vital resources, and biodiversity of this planet we all call home. The rest of the team joins me in the hope that you find this a valuable, actionable resource.

The verdict, as ever, is yours to render.

—David L. Katz

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PREFACE TO THE FIRST EDITION

While compiling this text, I have been as committed to what it excludes as to what it includes. Excellent, comprehensive textbooks, even encyclopedias, of nutrition have been written. I have made use of a good many of them in this effort. But as it may, in fact, be considered true that we "are" what we eat, such books cover a vast array of topics in agonizing details. Agonizing, that is, for the clinician seeking the answers to clinical questions but quite appropriate for the nutritional biochemist.

First among the principles to which this text is devoted is *clinical relevance*. If material seemed likely to be of use to the clinician interacting with a patient, even occasionally, it was included. If such an application seemed far-fetched, or if the material did not support an understanding that would enhance such an exchange, it was left out. The range of nutrition topics germane to clinical care is quite expansive. Thus, a fairly selective inclusion process resulted in leaving quite a lot still to be said.

The second principle governing the compilation of this text is *consistency of application*. Only in books do states of health and disease, and the underlying factors that promote them, stay neatly in their own columns and rows. In reality, these states coexist in single patients, often in complex abundance. Therefore, mutually exclusive, disease-specific nutrition recommendations are apt to be of limited clinical utility. Conversely, if dietary recommendations never change in accommodation to varying states of health and clinical objectives, a book of many chapters seems an excessive effort to portray this set of uniform guidelines. I have sought the middle ground between the subtle applications of nutritional management that pertain to the occasional disease or risk factor and the unifying features of diet that may be universally applied to promote health.

The third principle governing this effort is that to be of use, material intended for clinical application must be described in terms of the extent, consistency, and quality, of *the underlying evidence*. This may be considered a text of evidence-based medicine, with the literature reviewed for each chapter considered to represent preliminary, suggestive, or definitive evidence of any association described.

I strove to be consistent in the application of such terms, but found myself sometimes using, for example, "conclusive" rather than "definitive." Despite such variation, the character of the evidence base should generally be clear. Associations supported by animal or in vitro or observational evidence only were considered *preliminary*; associations supported by a combination of basic science studies as well as observational studies in humans, or by limited interventional studies in humans, were considered *suggestive*; and associations subtended by the results of either large-scale human intervention trials (particularly randomized, controlled trials), or the aggregation of consistent results from numerous less rigorous studies, were considered *definitive*.

The fourth principle, related to the third, is that for a subject of scrutiny to be well understood, it must be *viewed in its entirety* (or some approximation thereof). There is a risk (although certainly, too, a benefit) when each of many experts elaborates one particular aspect of nutrition as it pertains to health. That risk was perhaps never better expressed than in the allegorical poem, *The Blind Men and the Elephant*, by John Godfrey Saxe. I in no way wish to suggest that the expert authors of detailed chapters in the standard nutrition texts suffer any semblance of blindness, but rather that something of the overall character of nutrition and health is missed when only a small part is examined in great detail. I have become convinced, for example, that nominal n-3 fatty acid deficiency is likely widespread in the United States and contributing to adverse health outcomes. This conclusion is reached less on the basis of

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definitive evidence in any one area and more on the basis of remarkably consistent and voluminous evidence in the aggregate, across the expanse of many subjects. Only one author, struggling through each of many chapters in turn, may infuse the characterization of each topic with understanding derived from the others. As I cannot dispute the potential disadvantages of solo authorship, I have sought instead to capitalize fully on any potential advantages. I have therefore freely shared what insights I have gained in the sequential review of so many topics, endeavoring at all times to be clear about the sources of my opinion and the nature of the evidence.

The final principle to which this text is devoted is the notion that there should be a *theoretical model* in which the complex interplay of human behavior, food, and health outcomes is decipherable. In much the same way that unifying threads of evidence have led me to specific recommendations for nutrition management, I have come through this labor convinced of the utility of the *evolutionary biology model* of human dietary behavior. This argument is elaborated in Chapter 39. The behavior and physiology of all animals are largely governed by the environments to which they adapted; there is both reason and evidence to suggest that, with regard to nutrition, the same is true of us.

While there is some interpretation offered in this text, it is only that which a devotee and teacher of evidence-based principles of medicine could abide and not avoid. In the inescapable need to convey to you my interpretations, I have endeavored to cleave as close and consistently to fact as possible. In the time-honored medical tradition of blending the best of available science with just the requisite art, I submit this work to you as a platform for the clinical practice of nutrition.

Following the introduction, a concise but comprehensive overview of dietary influences on the organ system or pathology under discussion is provided. The overview is generally divided into the influence of the overall dietary pattern (*Diet*) and the influence of specific nutrient (*Nutrients/Nutriceuticals*). As indicated, other topics are included in the overview, such as pathophysiology, epidemiology, and other issues of clinical relevance and/or general interest. The overview section uses the scheme provided earlier to rate the available evidence for each practice. Unpublished and non–peer-reviewed literature has been accessed as required to facilitate preparation of this text, but the assessment of evidence is based only on the peer-reviewed literature; references are to be found at the end of each chapter. Following the overview, other *Topics of Interest* not related directly to dietary management are provided as indicated (e.g., surgical management of severe obesity). Chapters conclude with *Clinical Highlights*, a summary of those nutritional interventions of greatest clinical utility and for which the evidence is decisive, convincing, or suggestive. Each chapter is cross-referenced with other chapters and with pertinent *Nutrient/Nutriceutical Reference Tables* and other *Nutrition Resource Materials* in Section III.

CLAIMS, DISCLAIMERS, AND ACKNOWLEDGMENTS

Solo authorship of a text on nutrition may seem an act of either brash imprudence or unpardonable hubris. At times, poring over references and painstakingly compiling chapters, I have been tempted to think it both. But, please accept my assurances that it is neither. There is very definitely method in the potential madness of this project.

I am a clinician with an active practice in primary care internal medicine. Every day in the office I am confronted by the abiding interest of my patients in their own nutritional practices and by the innumerable attendant questions. And to be of use to my patients, to offer guidance when guidance is needed, I must have the answers at hand. I can certainly refer to a dietitian for counseling in support of clinical goals, but hardly as a means of answering each question that comes along.

So, the clinician in practice, encountering what I encounter in my practice every day, must be able to

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answer a range of questions about nutrition and health, and nutrition and disease. If unable to do so, the clinician misses a crucial opportunity to influence favorably the role of dietary behavior in the mitigation of chronic disease. On the list of the leading causes of death in the United States, dietary practices rank number 2, just behind smoking.

My nutrition expertise, cultivated by training, research, and teaching over the past 15 years, is appropriate for this project. But I certainly cannot claim to have the consummate knowledge in each of the diverse content areas of this text that is owned by that field's luminaries. To those experts, far too numerous to mention here, I owe a monumental debt. I have endeavored to make their work accessible to an audience of clinicians, but, in doing so, I have traveled the many trails they so painstakingly blazed.

My legitimacy, or perhaps my excuse, then, is not so much my claim to expertise in everything from lipid metabolism to ergogenic aids, but rather my dual devotion to nutrition and to clinical practice. The experts to whom I am indebted have made their contributions to the literature, yet the accessibility of that literature to the busy practitioner is suspect. This text is as much translation as original work, the translation of current nutrition knowledge into a form useful to the clinician. This text of nutrition is both by, and for, the practicing clinician. If any one practitioner is to access all of this information and apply it to clinical practice, it is only reasonable that one clinician has been able to write it.

And so that is why I have written this text and justified the interminable hours of effort to myself. To those whose work has guided me, I offer thanks. For any omissions, or worse still, misrepresentations, I accept full responsibility (who else could I blame?). Yet, even this solo effort has depended, and greatly benefited, from the direct and indirect contributions of many individuals. I owe debts of gratitude; I have little hope to repay to those who made this book possible.

—David L. Katz

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—David L. Katz

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—Kofi D. Essel

To my mom, for introducing me to a plant-based diet back in the day and for believing in me, always.

—Rachel S.C. Friedman

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—Shivam Joshi

A project of this magnitude can only come to exist by the collective effort of a community. I'm so grateful for mine. To our leader, my colleague, my mentor, my friend, and the best hiking partner one could ever have, Dr. David L. Katz—it's an honor and a privilege to know you. To my author colleagues: Dr. Lise Alschuler, Dr. Jenna Blasi, Dr. Jill Deutch, Dr. Xinyin Jiang, Dr. Shireen Kassam, Dr. Laurie Mischley, Dr. John Nowicki, Dr. Erica Oberg—fine work by all of you. To the blessed memory of Dr. Ather Ali, who will always be an inspiration. And to innermost circle—Amanda, Sircia, Callie, Zaiah, Eliana, and Rags—you all know that I'll never give you up, never let you down.

—Joshua Levitt

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—Ming-Chin Yeh

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Clinically Relevant Nutrient Metabolism

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Chapter 1

Clinically Relevant Carbohydrate Metabolism

Kristen Dammeyer, David L. Katz, and Jennie Brand-Miller

INTRODUCTION

Carbohydrate represents the predominant form of all plant matter and is thus a principal dietary source of energy for humans in nearly every culture. Food plants are composed principally of sugars, starches—the carbohydrate energy reserve in plants—cellulose, and other components. Generally, between 40% and 70% of calories are derived from carbohydrate among human populations, with higher amounts prevailing in less developed countries. In contrast, Arctic peoples derive most of their food from animals and eat little carbohydrate.

The main metabolic function of dietary carbohydrate is to provide energy. Carbohydrate metabolism is principally directed toward the maintenance, utilization, and storage of carbohydrate energy reserves, in the form of circulating glucose and tissue-bound glycogen. Glucose in plasma is the most readily available energy source for most cells in the human body, and thus homeostatic mechanisms for the maintenance of relatively stable blood glucose levels must be robust, absent pathology (see Chapter 6). Indeed, the brain, red blood cells, and renal medulla rely on glucose almost exclusively to fuel their activity. Glycogen acts as a storage carbohydrate in animal cells, analogous to the role of starch in plants. From culinary and gustatory perspectives, carbohydrates contribute significantly to the palatability of food, most notably when conferring sweetness. Unlike protein, which provides essential amino acids, and fat, which provides essential fatty acids, the carbohydrate nutrient class does not, a priori, denote a specific group of essential nutrients; however, high-carbohydrate foods serve as the principal dietary source of protein, fat, and micronutrients for many people. Furthermore, because fiber is classified as carbohydrate (see Appendix E), dietary fiber intake is derived primarily from carbohydrate-rich foods. Dietary fiber can be classified as viscous (pectin, beta-glucan, guar gum) and nonviscous (cellulose, lignin, hemicellulose). Carbohydrates are so named because their chemical structure, $C_n(H_2O)_n$, consists of carbon and water molecules in a 1:1 ratio. Digestible carbohydrates include polysaccharides and the sugars of the monosaccharide and disaccharide classes (see Table 1.1). In structural terms, the polysaccharide macromolecules are “complex” carbohydrates and the mono- and disaccharides are “simple” carbohydrates. Polysaccharides include cellulose and starches, of which only starch is digestible. The starches that predominate in the human diet, amylose and amylopectin, are glucose polymers. Starch is sequestered in plant cells behind a robust cell wall, rendering it relatively resistant to digestion until it absorbs water and swells (gelatinizes) during cooking. Highly gelatinized starches can be digested rapidly, but other starches by virtue of their structure or the presence of a physical barrier, are digested slowly. There are several categories of “resistant starch,” which remain inaccessible to digestion despite exposure to heat and water (1). In the typical Western diet, approximately 2% to 5% of ingested starch is resistant. Resistant starches stimulate the growth of colonic bacteria that in turn ferment the starches into short-chain fatty acids.

TABLE 1.1

The Classification of Carbohydrate as Simple or Complex, Based on Structural and Functional Properties[a]

	Structure	Function	Representative Foods
Simple	Monosaccharides – glucose – galactose – fructose	Added to foods or beverages in processing	Table sugar Sugar-sweetened beverages Sugar-sweetened breakfast cereals
	Disaccharides – maltose – sucrose – lactose	or Naturally-occurring in foods that taste sweet	or Fruits, vegetables Milk, yogurt Honey, maple syrup
Complex	Starches Amylopectin starch Amylose starch Resistant starch Modified starches Glycogen	Energy storage in plants Energy storage in animal tissues	Whole grain wheat, beans, lentils Present in wheat, rice, corn, oats and potatoes
	Cellulose Hemicellulose	Components of cell walls and dietary fiber	Cell walls of plants Wheat bran, oat bran
	Gums Beta-glucans Pectins	Added to increase fiber content or to increase viscosity or form gel	Confectionery Fiber supplements Fruit

[a]*See pages 8–10 for further discussion.*

Disaccharides include sucrose, a molecule composed of glucose and fructose; lactose, a molecule composed of glucose and galactose; and maltose, two molecules of glucose. Short-chain glucose polymers are collectively known as oligosaccharides and often confer sweetness. Monosaccharides of dietary importance include glucose (which is derived principally from the hydrolysis of dietary starch along with sucrose, lactose, and maltose), fructose, and galactose. The five-carbon monosaccharides, ribose, and deoxyribose, are synthesized endogenously for the production of nucleic acids. Sorbitol is the alcohol of glucose. The alcohol of xylose, xylitol, is used as a sweetener in the food industry.

Carbohydrates can only be absorbed in the form of monosaccharides. Therefore, disaccharides and starches must undergo hydrolysis in the gut. This process begins in the mouth with the release of salivary amylase, which disrupts the alpha-1,4-glucosidic bonds of amylose, a straight-chain glucose polymer, and amylopectin, a branched polymer, breaking them down to maltose, isomaltose, and oligosaccharides. At branching points, amylopectin contains an alpha-1,6-glucosidic bond that is finally hydrolyzed in the intestinal brush border. Chemical and physical differences between amylose and amylopectin influence their cooking characteristics and their rate of digestion in vivo. The straight chains of amylose strongly attract each other and therefore require more water and heat to gelatinize. As a consequence, high amylose starches are more slowly digested than branched-chain amylopectin.

The glucose linkages in cellulose are derived from a beta-1,4 bond for which no human enzyme is available, accounting for the indigestibility of cellulose. The products of the action of salivary and pancreatic amylase are maltose and maltotriose from amylose and maltose, maltotriose, alpha-limit

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dextrins (a composite of 1,4-alpha and 1,6-alpha glucose molecules), and glucose from amylopectin. The final stage of digestion takes place on the luminal side of the mucosal microvilli that line the small intestine.

Starches in intact seeds or kernels, such as grains and legumes, are packaged tightly together with proteins and fiber that can slow digestion by acting as a physical barrier to water and amylase. Thus, the efficiency with which starch is converted to glucose depends not only on the structure of the starch itself but also on the overall composition of the food of which it is a part (2).

When carbohydrate intake is excess of immediate energy needs, the glucose load can be handled in one of two ways. Under the influence of insulin, excess glucose is stored as glycogen or fat, as occurs in healthy, nondiabetic individuals. If the glucose uptake into the cell is slow or inhibited, excess glucose builds up in the bloodstream, resulting in the signs and symptoms of diabetes mellitus (see Chapter 6). The liver and muscle are the primary depots for glucose, where it is stored in the form of glycogen. However, once glycogen stores are full, additional glucose is converted to fat in the process known as *de novo* lipogenesis.

In healthy individuals, increasing plasma glucose levels result in energy release and oxidative phosphorylation-generating adenosine triphosphate (ATP) and citrate via the citric acid cycle, an enzymatic cascade used by all aerobic organisms to generate ATP from the products of glycolysis. The citric acid cycle is initiated via the action of pyruvate dehydrogenase and citrate synthase, which initiate entry of pyruvate into the citric acid cycle. High levels of ATP provide negative feedback on the enzyme phosphofructokinase to decrease glycolysis, resulting in accumulation of the intermediate product fructose-6-phosphate. Fructose-6-phosphate is converted to fructose-2, 6-biphosphate, which reactivates phosphofructokinase.

When carbohydrate intake is excess of immediate energy needs, marked rises in ATP and citrate produced by aerobic metabolism result in buildup of citric acid cycle substrates, including oxaloacetic acid and acetyl CoA, which act as potent stimulators of fatty acid synthesis. Consequently, a very large dietary carbohydrate load results in secretion of triglycerides and very low-density lipoprotein (VLDL) molecules into the systemic circulation. Calories in excess of need, from any macronutrient source, are stored as body fat once glycogen stores are filled. The prototypical 70 kg adult can store approximately 500 g of glycogen for a total carbohydrate energy reserve of approximately 2,000 kcal. When that reserve is filled, surplus calories from any macronutrient source are preferentially stored as fat (3).

The rate of glycolysis can be altered by as much as 90 fold in response to the metabolic needs of working muscle. Abundant carbohydrate intake induces glycolysis and inhibits gluconeogenesis, whereas fasting stimulates the reverse. Energy stores within the cell are carefully monitored by proteins that can send signals to influence metabolism in response to changes in energy levels. When ATP levels are high, the tricarboxylic acid cycle is slowed, and glycolysis is inhibited. Conversely, high levels of adenosine diphosphate (ADP) and adenosine monophosphate (AMP) induce glycolysis to produce regeneration of ATP.

Anaerobic glucose metabolism in muscle leads to the production of pyruvate, which can be further metabolized to CO_2 in muscle or transported to the liver. During vigorous physical activity, oxygen levels decrease, and the muscle tissue is unable to support the metabolism of pyruvate to CO_2. Anaerobic metabolism ensues to reoxidize nicotinamide adenine dinucleotide (NADH) formed during glycolysis, resulting in the production of lactate. The accumulation of lactic acid during vigorous activity is potentially responsible for the muscle pain that often develops, although this theory has been contested (4).

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Carbohydrate in the cytosol plays an essential role in protein glycosylation and is tightly regulated by cellular enzymes. When blood glucose levels are abnormally high, however, abnormal glycosylation, or glycation, can occur outside the cell. Proteins in tissues continuously exposed to the high levels of circulating glucose are particularly vulnerable, including the glomerular basement membrane, the vascular endothelium, and the lens of the eye. Glucose and galactose are metabolized in the lens of the eye, and elevated serum levels of either are associated with cataract formation and retinopathy. Thus, both diabetes mellitus and galactosemia are risk factors for cataract formation and blindness.

Glycation constitutes an important cumulative injury to cells that is associated with aging (see Chapter 31). Fructose glycates nearly 10 times as efficiently as glucose. However, even at high intake, the fructose level in blood is only about 1% that of glucose. At usual levels of intake, fructose is converted to glucose in the mucosal enterocyte and absorbed into the portal bloodstream (5). If fructose intake is excessively high (> 95th percentile), this pathway is saturated and fructose reaches the liver, where it stimulates de novo lipogenesis and secretion of very-low-density lipoprotein - triglyceride and TG.

Replacement nutritive sweeteners are available, including the disaccharide isomaltulose and the monosaccharide sugar D-tagatose (6). Starch is digested by salivary and pancreatic amylase and intestinal brush border enzymes in the upper and middle portions of the jejunum. Brush border enzymes include isomaltase, sucrase, and lactase (in some adults; see Chapter 24). An excess of enzyme is available for most oligosaccharide digestion, with the exception of lactose. Lactase availability limits the rate at which lactose is cleaved to glucose and galactose. Brush border enzymes are inhibited as levels of monosaccharides rise in the intestinal lumen, preventing an accumulation of sugars that could result in osmotic diarrhea. Dietary sucrose induces the enzymes sucrase and maltase. Lactase levels, however, are not influenced by the quantity of dietary lactose.

Starches resistant to human enzymatic digestion are fermented by bacteria in the large bowel, which liberate 50% to 80% of the available energy in the form of fatty acids and release carbon dioxide, hydrogen, and methane as byproducts. The fatty acids produced in the large bowel include butyric, isobutyric, propionic, and acetic acids. Cells of the large bowel derive energy from butyric acid and isobutyric acid in particular, and these molecules may play an important role in protecting the bowel mucosa from carcinogenesis.

Monosaccharides are absorbed by simple diffusion, facilitated diffusion, and active transport. Ingestion of a 50-g load of some sugars can exceed the rate of absorption, resulting in gastrointestinal (GI) discomfort. Passive diffusion is slowed by the movement of water into the gut lumen produced by the osmotic effect of ingested sugars. The typical D-stereoisomers of glucose and galactose are absorbed through protein channels by active transport, facilitating more rapid uptake into the blood than passive diffusion. Fructose, a monosaccharide derived from fruits and vegetables, as well as sucrose and high-fructose corn syrup (HFCS), is absorbed via facilitated diffusion. Osmotic diarrhea is induced by the acute ingestion of approximately 50 to 100 g of fructose; more fructose is tolerated if ingested as sucrose because digestion of the disaccharide slows the rate of absorption.

Lactase deficiency, the most common enzyme deficiency affecting carbohydrate metabolism, is present in approximately half of all adults worldwide. Besides humans, milk ingestion is typically limited to infancy in most mammals; therefore, the lactase gene is expressed predominantly in infancy and down regulated by genetic control thereafter. Lactose ingestion in adulthood favored the selection of genetic mutations that preserved lactase production into adulthood in northern Europeans (and their descendants) and smaller populations in Asia and Africa. Variation in adult lactose tolerance by ethnic background correlates with the practice of dairying over millennia. Lactose-intolerant adults can generally tolerate about 5 g of lactose (equal to approximately 100 mL [3.4 oz] of milk) without symptoms (see Chapter 24).

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Higher amounts are tolerated in dairy foods containing live *lactobacilli*, such as yogurt. Hard cheese products contain little residual lactose. Lactose tolerance can be assessed by administering 50 g of lactose and measuring the serum glucose or the rise in breath hydrogen. If glucose rises more than 1.4 mmol/L, the lactose has been efficiently hydrolyzed. Conversely, if breath hydrogen rises by more than 20 ppm, this indicates lactose has reached the colon and undergone fermentation, that is, low lactase levels in the small intestine.

Glucose from dietary carbohydrates and fatty acids from dietary fats are the principal sources of nutrient energy. Both are metabolized to carbon dioxide and water via the tricarboxylic acid cycle. Only when oxidative enzyme pathways are saturated is glucose stored as glycogen. If glycogen synthetic pathways are also saturated, excess glucose is converted to fatty acids for deposition in various tissues, including the liver and adipose tissue. Approximately 5% of the available energy from oxidation is lost when glucose is converted to glycogen, and more than 25% is lost when glucose is stored as fat. Glycogen stores in muscle can only be used by the muscle, while liver glycogen is sufficient to meet the energy needs of a fasting adult on a 2,000-kcal diet for approximately 14 hours. Nearly 100 times as much energy, or 120,000 kcal, is stored in the adipose tissue of a lean adult. However, only a small portion of this energy is readily available, generally enough to support energy needs for several weeks. Once glycogen stores are full, excess dietary carbohydrate is converted to fatty acids and stored in adipose tissue. The efficiency with which different sugars are converted to fat is variable.

As an energy source, carbohydrate is intermediate between fat and protein with regard to both energy density and satiety induction. Carbohydrate provides roughly 4 kcal/g, which is approximately the same as that of protein. The satiety index of carbohydrate—meaning the degree to which a given “dose,” measured in calories, induces a sense of fullness—is higher than that of fat but lower than that of protein (see Chapter 38). Fiber content can enhance the satiety index of carbohydrates. Viscous fibers have been shown to reduce appetite more readily than nonviscous fibers by slowing the emptying of the stomach and acting as a physical barrier that shields carbohydrates from digestive enzymes (7). Fiber adds volume but relatively few calories to food, and soluble fiber may contribute to satiety by other mechanisms as well (see Chapter 38 and Appendix E).

After carbohydrate ingestion, most of the glucose in the circulation escapes hepatic first-pass removal, whereas excess fructose is absorbed by the liver, where it is converted to glucose, lipid, or lactate. Fructose ingestion raises serum levels of both lactic acid and uric acid. Galactose is metabolized principally in the liver, and the rate of metabolism can serve as a marker of liver function. Galactose rises in serum in proportion to the dose ingested, although serum levels of galactose are blunted by concomitant administration of glucose, either orally or intravenously. In infants, galactose derived from the lactose in milk is used for the synthesis of brain gangliosides.

Most tissues utilize a variety of nutrients for fuel, including glucose, free fatty acids, lactic acid, or short-chain fatty acids. However, the brain and red blood cells rely solely on glucose, except in periods of prolonged fasting, when they switch to ketone-body metabolism. Congenital deficiency of the enzyme glucose-6-phosphate dehydrogenase principally affects the red blood cells, occurring in populations with historical exposure to malaria. These individuals are susceptible to hemolytic anemia in the presence of drugs that disrupt glutathione reduction, such as sulfonamides.

The adult brain uses approximately 140 g of glucose/day, accounting for 560 kcal. Glucose needs are higher during pregnancy and lactation, when glucose is required for fetal growth and the production of lactose in milk. At peak lactation, human milk contains ~70 g lactose/L, the highest of any mammal. During fasting or absence of dietary carbohydrate, about 130 g of glucose can be synthesized daily from noncarbohydrate precursors in the process called gluconeogenesis. The main precursors are lactic acid,

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amino acids (from the diet or muscle protein breakdown), and glycerol from fat breakdown. While animals are unable to convert fatty acids into glucose, they can convert them into ketones, which gradually take the place of glucose to fuel the brain. Nonetheless, other tissues still depend on glucose, and a minimal intake of ~50 g a day is obligatory. The recognition that a balanced diet requires carbohydrate has resulted in the establishment of a recommended dietary allowance (RDA) for adults of 130 g of sugars or starch daily (8).

A diet rich in fructose (>95th percentile, or 20% to 25% of total energy intake) results in elevated serum triglycerides and low-density lipoproteins, although levels tend to normalize over a period of weeks in lean individuals. A diet rich in glucose or starch has the opposite effect (9). Conversely, a high-glucose diet can result in elevated serum glucose and insulin levels, which are unaffected by a high-fructose diet (10). High-carbohydrate diets reduce levels of high-density lipoproteins, especially when compounded with high fructose intake. Consequently, a diet high in sucrose or HFCS has deleterious effects on the lipid profile, whereas these effects are partially mitigated in a diet containing predominantly starchy carbohydrates (11). Polyunsaturated fat in the diet also blunts the fasting triglyceride rise induced by sucrose or fructose, and decreases LDL (12,13). Individuals with hypertriglyceridemia tend to have a particularly brisk rise in triglycerides in response to high carbohydrate intake.

CARBOHYDRATE METABOLISM AND THE ENDOCRINE SYSTEM

Glucose levels in the blood are primarily regulated by the action of insulin and glucagon, released from the beta cells of the pancreas. The main role of insulin is to promote energy entry and storage in cells when blood glucose levels are high, which is accomplished via several mechanisms: translocation of GLUT-4 glucose transporters to the plasma membrane, which facilitates glucose entry into liver, skeletal muscle, and adipose tissues; stimulation of glycogen and fat formation; inhibition of fat utilization for energy via suppression of glucagon release; and inhibition of gluconeogenesis by the liver. Glucagon is released when blood glucose levels fall, and its actions are directly opposite of those produced by insulin, promoting glycogen breakdown to release glucose and synthesis of new glucose via gluconeogenesis in the liver and kidney.

The gut has emerged as a major regulator of carbohydrate metabolism with discovery of the role of incretins (i.e., peptide hormones released from the intestinal L and K cells in response to the presence of nutrients in the lumen of the small intestine). GLP-1, one of the most well-characterized incretins, acts to lower blood glucose via stimulation of insulin release, increasing insulin sensitivity in the tissues, promoting beta-cell mass, suppressing glucagon secretion, delaying gastric emptying, and increasing satiety in the brain. The other incretin, GIP, secreted by K cells in the upper small intestine can have adverse effects when secreted in excess. It promotes lipogenesis, fatty liver, insulin resistance, and postprandial inflammation and reduces fat oxidation in skeletal muscle (14).

The adrenal gland also plays a role in glucose homeostasis via release of epinephrine, which stimulates glycogenolysis in the liver. Epinephrine also stimulates glycogenolysis in skeletal muscle, whereas glucagon does not.

CLASSIFICATION OF CARBOHYDRATES

Despite widespread use of the terminology, clear definitions of “complex” and “simple” carbohydrate are elusive, rendering the terminology confusing, in part because they rely on both structural and functional

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classifications. Structurally, a simple carbohydrate is composed of mono- or disaccharides, while complex carbohydrates are composed of units containing three or more sugar molecules (see Table 1.1). In the United States, but not other countries, the functional definition of carbohydrate complexity is based on the metabolic fate of ingested items. Foods that engender a brisk rise in blood glucose, and consequently blood insulin, are considered simple carbohydrates. Foods that induce low and slow post-ingestion increases in glucose and insulin are functionally complex carbohydrates.

But a look at fruits and vegetables demonstrates how these definitions are contradictory. All the energy in fruits and some vegetables (carrots, sweet potatoes) comes from mixtures of the monosaccharides glucose and fructose, and the disaccharide sucrose, yet compared to starchy foods like rice and potatoes, they raise glucose modestly. Many experts consider whole fruits and vegetables with the cell walls intact to be sources of complex, rather than simple, carbohydrate.

Another wrinkle in the definition of carbohydrate complexity is the manner in which foods package nutrients. While sugar added to a whole-grain breakfast cereal are structurally similar to that added to a candy bar, the metabolic fate is influenced by the company it keeps. Fiber in grain products, in particular soluble fiber (see Appendix E), slows the entry of glucose (and lipids) from the GI tract into the bloodstream, attenuating postprandial glycemia, lipemia, and insulinemia, even in the presence of sugars (15–19). However, other fibers added to food during processing, including inulin and wheat bran, share some laxative properties with natural fibers; however, they do not reduce blood glucose or cholesterol (20).

A more useful classification system for carbohydrates is the Glycemic Index (GI). The GI, first developed by Dr. David Jenkins et al. (21) at the University of Toronto and initially used for diabetic exchange lists, entered into the popular lexicon with the advent of “low versus slow carbohydrate” dieting in the 1990s (see Chapter 5). The GI is defined as the area under the 2-hour postprandial curve for blood glucose values relative to a reference standard (often glucose but sometimes white bread) and based on a fixed dose of carbohydrate. Over time, the Glycemic Load (GL) has gained increased popularity as a tool for dietary guidance and has been implicated in regulating food reward and cravings (22). The GL is the GI of a food multiplied by the amount of carbohydrate per serving. Thus, while the GI compares foods gram-for-gram of carbohydrate (i.e., carbohydrate exchanges), the GL compares glycemic potential based on a typical serving (see Tables 1.2 and 1.3). Foods with the highest GL are higher in carbohydrate content as well as GI, but some foods that are high in carbohydrate still have a low GL because their GI is very low (e.g., beans and pulses).

As opposed to a low-carbohydrate diet, there is mounting evidence that a low-GL diet can be generally healthful and of particular value in ameliorating insulin resistance or impaired glycemic responses (23). As well, a low-GL diet has been associated with decreased risk of cancer (24,25), cardiovascular disease (26), and hypertension (27). Given these findings, application of the GI and GL can be useful for guiding the diet of not only those with diabetes (type 1, type 2, and gestational diabetes) but also those with obesity, cardiovascular disease, and nonalcoholic fatty liver disease (28–31). Nonetheless, the importance of applying GI or GL measures to the diets of healthy individuals has been questioned (32), and some of the health implications of low versus high GI/GL foods remain unresolved (24,33).

TABLE 1.2

The Glycemic Index of Some Common Foods

Food Group	Food	Glycemic Index
Breads	White bread[a]	100

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	Whole-wheat bread	99
	Pumpernickel	78
Cereal products	Cornflakes	119
	Shredded wheat	97
	Oatmeal	85
	White rice	83
	Spaghetti	66
	Bulgur wheat	65
	Barley	31
Fruit	Raisins	93
	Bananas	79
	Oranges	66
	Grapes	62
	Apples	53
	Cherries	32
Vegetables	Parsnips	141
	Baked potato	135
	Carrots	133
	Corn	87
	Boiled potato	81
	Peas	74
	Yams	74
Legumes	Lima beans	115
	Baked beans	60
	Chickpeas	49
	Red lentils	43
	Peanuts	19
Dairy products	Yogurt	52
	Ice cream	52
	Milk	49
Sugar	Sucrose	86

[a]*Reference standard. In some applications, sucrose rather than white bread is used as the reference standard, and given a value of 100.*

Adapted from Jenkins DJA, Jenkins AL. The glycemic index, fiber, and the dietary treatment of hypertriglyceridemia and diabetes. J Am Coll Nutr. 1987;6:11–17.

TABLE 1.3

The Glycemic Index and Glycemic Load of Some Common Foods[a]

Food/Portiown	Carbohydrate (g)	Glycemic Index	Glycemic Load

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Potato/1 each, 170 g	43	85	37
Carrots/0.5 c, 78 g[b]	8	47	4
Apple/each, 154 g	22	38	8
Apple juice/1 cup	29	40	12
Soft drink/20 fl oz	68	63	43
Milk/1 cup	12	27	3
Lentils/0.5 cup, 99 g	20	29	6
Peanuts/3 T, 30 g	5	14	1
Instant rice/0.75 cup, 124 g	26	91	24
Spaghetti/0.75 cup, 105 g	30	44	13

[a]*For the GI and GL scores for an extensive list of foods, see American Journal of Clinical Nutrition. Revised international table of GI values. Available at* http://www.ajcn.org/cgi/content/full/76/1/5#SEC2; *accessed 9/18/07.*

[b]*Note that although carrots and soft drinks have rather comparable GI scores, their GL scores differ by more than an order of magnitude.*

Adapted from Foster-Powell K, Holt SH, Brand-Miller JC. International table of glycemic index and glycemic load values. Am J Clin Nutr. 2002;76:5–56.

As a practical matter, guiding patients toward a less-processed diet abundant in vegetables, fruits, and whole grains, along with healthful oils from plant sources and high-quality protein sources, is warranted on general principles (see Chapter 45) and will also direct them toward a diet relatively low in overall GL. The converse is likely to be true as well (i.e., guidance toward a low-GL diet will result in increased intake of fruit, dairy, legumes, and, therefore fiber, but pasta and sushi can be included without excess glycemia). Thus, the clinician is encouraged to offer guidance to patients in terms of foods and their place in a health-promoting diet (see Chapters 45 and 47) rather than based on some isolated property of a food (e.g., fat content).

CARBOHYDRATES IN THE DIET

The recommended macronutrient threshold for carbohydrate is 45% to 65% of total calories, although healthful diets with higher carbohydrate content have been recognized (8). When choosing carbohydrates, emphasis should be placed on high-quality sources: unprocessed or minimally processed food with high dietary fiber content. Refined grains and highly processed foods depleted of micronutrients ought to be limited (28,34,35). A metric based on added sugar, fiber content, GI, and ratio of whole grain to total grain has been proposed in order to assess carbohydrate quality (36). Consumption of a diet rich in such high-quality carbohydrate may reduce chronic disease risk (37). However, individuals with diabetes or other chronic diseases may be required to limit or count carbohydrates and place greater importance on using measures such as the GI or GL to guide food choices (28,29,37).

Low and very-low carbohydrate diets have wavered in popularity of carbohydrate restriction as a weight loss aid (38). In general, the wholesale rejection of a macronutrient class may facilitate weight loss in the short term by restricting choice and thus calories but is at odds with the nutrient balance required for optimal health and the dietary balance required for pleasure and behavioral sustainability

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(39). Long-term carbohydrate restriction has not been shown to be superior to other dietary patterns for weight loss and may actually precipitate adverse health outcomes (38). The practice of wholesale carbohydrate restriction is, therefore, not encouraged. The topic of carbohydrate restriction, including sugars, is addressed in greater detail in Chapters 5 and 45.

Added sugars are defined as monosaccharides and disaccharides added to foods and beverages, whereas the term *free sugars* include sugars naturally present in honey, syrups, fruit juices, and fruit juice concentrate. The extent to which added sugars should be restricted is a subject of debate in the literature. The Tolerable Upper Intake Level for calories from added sugar is set by the Institute of Medicine at 25% of calories/day (8). A common recommendation, however, is to limit the intake of calories from added sugar to less than 10% of calories/day. Lower upper limits of 5% to 6% have been suggested based on dietary modeling, but in practice such diets may be less nutritious (40). Meanwhile, the World Health Organization suggests that restricting free sugars to less than 5% of daily calories may confer additional health benefits (41). The evidence basis for this recommendation is in the role of sugar in dental caries, rather than weight control. Restriction of added sugars has been associated with the improvement of conditions such as nonalcoholic fatty liver (42). Yet, other studies have either failed to demonstrate a relationship between added sugar consumption and disease (43) or demonstrate a relationship at higher levels of intake, around 13% of total energy (44). Further, there is evidence that restricting added sugar to less than 5% daily energy is associated with reduced micronutrient intake (40) and higher proportion of energy from alcoholic beverages (45).

While the exact extent to which added sugar should be restricted remains to be determined, experts agree that the 10% level is reasonable. This level allows other food group and nutrient needs to be met within calorie limits. Indeed, it is important to remember that sugars confer sweetness and improve the palatability and enjoyment of many nutritious foods that may otherwise be avoided (e.g., yogurt).

NONNUTRITIVE SWEETENERS

Nonnutritive sweeteners, often referred to as *artificial sweeteners*, have been in use for the past century to confer an appetizing sweet taste without contributing to the caloric content of food. The U.S. Food and Drug Administration has granted approval for five nonnutritive sweeteners: acesulfame potassium, aspartame, neotame, saccharin, and sucralose, and a naturally occurring low-calorie sweetener stevia (46). Nonnutritive sweeteners bind sweet taste receptors by mimicking the structural motifs of natural carbohydrates; however, they elicit an effective sweetness response 200 to 600 times stronger than table sugar. Because of this, they can be added to food in such small quantities as to negate their caloric contribution (47). For decades, nonnutritive sweeteners were considered an effective method of reducing caloric intake without sacrificing palatability of food and drink; however, recent studies have produced evidence that their use may actually contribute to obesity in adults and children via dysregulation of energy balance (48–52).

Several hypotheses have emerged to explain the paradoxical association of nonnutritive sweeteners and weight gain. For example, nonnutritive sweeteners may alter the gut microbiological flora, triggering an inflammatory process that promotes insulin resistance and weight gain (53). Another potential mechanism suggests that the GI tract utilizes sweet taste as a means of predicting a high-calorie meal and will alter its absorptive properties to compensate (54). Finally, the recent discovery of sweet taste receptors in the GI tract has provoked a new hypothesis that nonnutritive sweeteners inappropriately activate sugar receptors in the gut, leading to GLP-1 release and insertion of glucose transporters in intestinal epithelia (55–57). Thus, the jury is still out whether it is safer to consume nutritive sugars in moderation or replace them

with nonnutritive sweeteners.

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SUMMARY

Carbohydrates are the predominant form of energy stored in plants and usually the largest proportion of energy in human diets. While there is no established minimum requirement, many populations have thrived on high carbohydrate diets. Sugars, starches and dietary fiber are all classed as carbohydrates. In normal circumstances, the brain and red cells rely solely on the simple carbohydrate glucose as their source of energy. Within the usual range (45%–65% of energy), the quality and sources of carbohydrate appear to be more important than the precise amount. Rapidly and slowly digested forms of sugars and starches, along with fiber in various forms, influence glycemia, lipid metabolism and the colonic flora. High levels of glucose in the blood derived from dietary carbohydrates increase insulin secretion and protein glycosylation throughout the body, affecting insulin sensitivity, aging and complications of diabetes. The rate of intestinal digestion of dietary carbohydrates also influences levels of the incretin hormones GLP-1 and GIP. In turn, these affect appetite, insulin sensitivity, lipogenesis, liver fat content and inflammation. High glycemic index and glycemic load diets based on rapidly digested carbohydrate foods are associated with increased risk of type 2 diabetes and cardiovascular disease. Conversely, diets rich in cereal fiber and low glycemic index carbohydrates are beneficial for the management and prevention of these diseases. Clinicians should model their own food choices and encourage their patients towards a diet that is abundant in vegetables, fruits and whole grains, along with healthful oils from plant sources and high-quality protein foods.

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Chapter 2

Clinically Relevant Fat Metabolism

Emily Mills and and Penny M. Kris-Etherton

INTRODUCTION

Lipids are categorized broadly as water-insoluble compounds that are soluble in organic solvents and are derived from both plant and animal products. Common lipids include free fatty acids, triglycerides, phospholipids, and cholesterol. Cholesterol is an important constituent of cell membranes and myelin and found exclusively in animal tissues. Cholesterol is utilized in the production of adrenal and gonadal steroid hormones and bile acids.

Dietary fat is a source of energy and essential nutrients (e.g., linoleic acid and alpha-linolenic acid [ALA]). It is a substrate for prostaglandin synthesis and contributes to essential structural components of cells. Polyunsaturated fatty acids (PUFAs) are precursors of eicosanoids, including prostaglandins, thromboxanes, and leukotrienes.

Most of the energy from fat in the diet is derived from triglycerides, molecules formed by three fatty acid molecules that are esterified to a molecule of glycerol. Among the three classes of macronutrients (carbohydrate, protein, and fat), lipids provide the greatest energy density—approximately 9 kcal/g (versus 4 kcal/g for carbohydrate and protein). In addition to being a concentrated source of energy, dietary lipids enhance the absorption of fat-soluble micronutrients (i.e., vitamins A, D, E, and K) and contribute to the flavor profile and palatability of food.

The three major classes of fatty acids are saturated (SFAs), monounsaturated (MUFAs), and PUFAs. Fatty acid molecules containing no double bonds between adjacent carbon atoms are classified as *saturated* because available carbon bonds are maximally occupied by hydrogen atoms, while molecules containing one or more double bonds are *unsaturated*. Trans fats are a clinically significant subset of both MUFAs and PUFAs that are produced by conversion of the carbon double bond to the trans isomer form. There are two major sources of dietary trans fats (or trans fatty acids [TFAs]): iTFAs (industrial TFA), which are produced through partial hydrogenation (i.e., using hydrogen to saturate available carbon binding sites) of naturally occurring MUFAs and PUFAs, and rTFAs (ruminant TFA), which are formed in ruminants by biohydrogenation of vaccenic acid and linoleic acid (1). iTFAs have adverse health effects that exceed those of saturated fat (2) and are a topic of intense interest in public health nutrition and food policy (3). rTFAs are found primarily in dairy products. Further clinical study is necessary to understand the effect of rTFAs on cardiometabolic disease, though as a whole, dairy products have conflicting health effects. They serve as a source of under-consumed nutrients in the U.S. population, such as calcium, potassium, and vitamin D, though they are not an optimal source of fat due to high SFA content (4).

Dietary fat has a low satiety index, meaning that calorie for calorie, it is less filling than the other macronutrients (5,6). This is consistent with a preponderance of evidence linking relatively high-fat diets and foods with a high energy density to weight gain. Although a key factor in satiety is energy density, so higher-fat diets that are also high in fruits and vegetables (e.g., Mediterranean-style diet) are satisfying (7–9) (see Chapter 5). It is important to note this topic remains a matter of some debate (10,11).

Lipases produced by the serous glands on the tongue and by gastric chief cells in the stomach break down triglycerides in the upper gastrointestinal tract and require an acidic environment. Pancreatic lipases secreted into the duodenum also contribute to the breakdown of triglycerides. For the most part, lipases are active at the 1- and 3-ester bonds in the triglyceride molecule but not at the 2 linkage. The transport of hydrophobic lipids in an aqueous medium is accomplished through emulsification, the dispersal of fat into tiny droplets, which is achieved by mechanical churning of stomach contents against a partially closed pylorus. In the duodenum, bile salts contribute to the stabilization of lipid micelles, preventing them from reaggregating. In addition to fatty acids, micelles are rich in 2-monoglycerides because of the resistance of the fatty acid at the 2 position on glycerol to lipolysis.

Emulsification and chemical digestion of fat are accelerated in the duodenum; mechanical digestion in the stomach decreases droplet size and increases exposed surface area. The presence of fatty acids and amino acids and the secretion of hydrochloric acid in the stomach triggers the release of cholecystokinin-pancreozymin as well as secretin. The acidity of the gastric chyme is reversed by the buffering effects of the duodenal mucosa, the secretin-induced release of bicarbonate from the pancreas, and the release of alkaline bile from the gall bladder induced by cholecystokinin.

In the upper small bowel, pancreatic lipase is activated in the alkaline environment and then acts on emulsified fat droplets. Lipase is bound to the droplets by colipase, which is secreted concurrently from the pancreas. Pancreatic lipase also cleaves fatty acids at the 1 and 3 positions of the triglyceride, producing two molecules of free fatty acid and one of monoglyceride (i.e., a fatty acid bound to glycerol in the 2-carbon position). Fat absorption then occurs predominantly in the proximal portion of the small bowel.

Free fatty acids and monoglycerides are readily absorbed in the upper small intestine. Short and medium chain fatty acids are absorbed into portal blood, bound to albumin, and transported to the liver. Longer-chain fatty acids and cholesterol are re-esterified to triglycerides, and then packaged into chylomicrons that are transported via lymph.

Bile salts separate from the lipid droplets at the mucosa and are ultimately reabsorbed in the lower small bowel as part of the enterohepatic circulation. Bile acid sequestrants lower cholesterol by interrupting this circulation, causing bile acids to be lost in stool and depleted; their reconstitution requires consumption of cholesterol. Phytosterols and stanols, cholesterol-like compounds in plants, result in similar cholesterol loss in stool by directly inhibiting absorption in the small bowel (12).

Absorption of ingested triglycerides is facilitated by phospholipids, which are present in the diet in much smaller quantities. Phospholipids act to emulsify triglycerides in the stomach. They are structurally important in separating hydrophobic lipids from water in the cell membrane.

Fatty acids and monoglycerides are absorbed almost completely, whereas only 30% to 70% of dietary cholesterol is absorbed. Fatty acids can be used as an energy source by most cells, with erythrocytes and cells of the central nervous system being notable exceptions. The brain uses glucose exclusively for fuel unless the supply is decreased, at which time ketone bodies produced from the catabolism of fatty acids can serve as an alternative energy source. The mitochondrial transport of long-chain fatty acids requires a carrier, carnitine transferase. The metabolic needs for fat can be met with an intake of as few as 20 to 25 g/day; however, it is important that essential fatty acid (EFA) requirements be met.

Energy consumed in excess of need is stored principally as triglycerides in adipose tissue, predominantly as palmitic (saturated) and oleic (monounsaturated) acids (see Table 2.1). The fatty acid composition of food influences the fatty acid composition of adipose tissue (13). The energy reserves in

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body fat even in lean individuals are generally 100-fold greater than glycogen stores, providing a depot of approximately 120,000 kcal in an average 70-kg male. Often overlooked in discussions of obesity is the important role of body fat as a survival mechanism for a species long subject to cycles of feast and famine (see Chapter 44).

TABLE 2.1

Classes of Fat and Fatty Acids of Dietary Significance

	Class*a*			
Fatty Acid	**Essential**	**Monounsaturated**	**Polyunsaturated**	**Essential**
Myristic acid	C14:0			
Palmitic acid	C16:0			
Stearic acid	C18:0			
Oleic acid		C18:1, omega-9		
Linoleic acid			C18:2, omega-6	√
Gamma-linolenic acid			C18:3, omega-6	
Arachidonic acid			C20:4, omega-6	√
Linolenic acid			C18:3, omega-3	√
Eicosapentaenoic acid			C20:5, omega-3	
Docosahexaenoic acid			C22:6, omega-3	

[a]Fatty acids are designated by "C," followed by the number of carbon atoms per molecule and then a second number to signify the number of double bonds (unsaturated sites). "Omega" is used to signify the position of the first (or only) double bond in an unsaturated fatty acid, relative to the "omega" carbon, which is the carbon farthest from the terminal carboxyl group.

For the most part, longer chain fatty acids, in particular SFA, are less readily absorbed than shorter chain fatty acids. There are virtually no short-chain fatty acids (with 2 to 4 carbons) of nutritional significance. Medium-chain triglycerides, which have 6 to 12 carbons, are absorbed more readily than longer-chain triglycerides because of their more efficient emulsification and greater water solubility. They also tend to be absorbed (i.e., bound to albumin without re-esterification by enterocytes) directly into the portal circulation, whereas the micelles are absorbed via lymphatics. C12 is interesting because studies have shown that some/much of it is absorbed via the lymphatic system (14). There is interest in the use of medium-chain triglycerides, both enterally and parenterally, as an energy source in various clinical states associated with fat malabsorption, including premature birth, AIDS, and pancreatic insufficiency (15–18). Recent evidence suggests that dietary medium-chain triglycerides may contribute a therapeutic advantage of preserving insulin sensitivity in patients with metabolic syndrome (19).

Portal flow is considerably faster than lymphatic flow. Thus, medium-chain triglycerides are relatively unaffected by deficiencies of bile salts, require minimal pancreatic lipase activity, are relatively unaffected by impaired enterocyte function, and are absorbed far faster than long-chain triglycerides (see Chapter 18). Long-chain triglycerides of the omega-3 variety from marine sources are more readily absorbed than saturated or monounsaturated fatty acids of comparable length. Despite some minor differences in fatty acid absorption efficiency between classes, an average healthy person absorbs over 98% of dietary lipid (20). Thus taken in total, fatty acids should be viewed as efficiently absorbed.

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Factors that can affect fatty acid absorption include the intramolecular structure of the lipid, presence of divalent cations in the diet (such as calcium and magnesium), emulsification, the size of lipid droplets, and the composition of the food matrix with which the fats are ingested (21).

Cholesterol in the bowel, whether of endogenous or exogenous origin, is incompletely absorbed. There is debate regarding the upper limit of cholesterol absorption in adults; rates have been shown to vary from 20% to 80%, with typical absorption rates in the range of 30% to 70% (22). Although some scientists believe it to be maximal at approximately 500 mg/day, others believe 40% of up to 2 g of intestinal cholesterol will be absorbed daily. Ingested cholesterol affects serum cholesterol but to a lesser extent compared with SFA, in part because of less absorption and in part because of the importance of endogenous cholesterol biosynthesis, which is under feedback regulation. A high cholesterol intake may raise serum cholesterol by as much as 15%, although accumulating evidence suggests that this may depend on the overall dietary pattern (23–25). Also, differences in cholesterol absorption among individuals contribute to variable serum cholesterol responses to dietary cholesterol. When intake of saturated fat is low, cholesterol in the diet is less clearly linked to serum cholesterol levels or to the risk of coronary heart disease, in large part because a diet that is low in animal products is typically low in both SFA and cholesterol (26). The bacterial degradation of unabsorbed cholesterol in the large bowel may contribute to the increased risk of colon cancer associated with diets high in animal fat (27–29).

Average stool fat in adults is in the range from 4 to 6 g/day. With a very high fat intake, fat absorption continues more distally in the small bowel. Of note, human infants have a similar capacity to absorb fat when fed human milk because of the presence of lipase in human milk. Lipase is absent from bovine milk, and infants that are given bovine milk are subject to some degree of fat malabsorption (see Chapters 27 and 29). Breast milk is recommended by the American Academy of Pediatrics for the first year of life and cow's milk is not recommended until infants are 12 months of age (30). Of note, commercial infant formulas do not contain cow's milk.

Adults have a reserve capacity to absorb as much as twice the amount of fat typically present in even high-fat diets. Although neonates have low levels of bile salts and thus have a limited ability to form micelles, the lipase present in human milk can cleave even the fatty acid at the 2 position on glycerol, producing free fatty acids that are relatively readily absorbed, independent of micelle formation. Capacity for fat absorption tends to decline with age in older adults. Poor vitamin D status is one consequence of clinical importance. This fat-soluble vitamin critical for skeletal health is a nutrient of public health concern due to underconsumption (31).

Partial gastric resections tend to produce some degree of fat malabsorption, with fecal fat increasing from 4 to 6 g/day up to 15 g/day; this effect may contribute to the weight loss observed after gastric bypass surgery (see Chapter 5). Exocrine pancreatic insufficiency results in fat malabsorption. Disease or resection of the ileum may result in bile acid deficiency, which leads to fat malabsorption.

LIPOPROTEIN METABOLISM

Triglycerides are the principal source of fuel from fat and are stored in adipose tissue. Cholesterol and phospholipids act primarily as membrane constituents. In the fasting state, fatty acids for energy production are derived from adipose tissue stores. In the fed state, fatty acids are taken up by adipose tissue from chylomicrons and very-low-density lipoprotein (VLDL); the uptake of triglycerides from these particles is mediated by the enzyme lipoprotein lipase.

Fatty acids with chain lengths shorter than 12 to 14 carbons are bound to albumin and transported directly to the liver via the portal vein. Endothelial cells can take up lipoprotein particles, as well as free

fatty acids bound to albumin; triglyceride from lipoprotein particles is the predominant delivery source.

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Triglycerides are packaged in chylomicrons, which contain unesterified cholesterol in the outer layer and esterified cholesterol in the core. There is some evidence that the ingestion of fat of any type stimulates endogenous production of primarily saturated fatty acids, which are released into the circulation along with the fat from exogenous sources.

Hepatic enterocytes package ingested fat into chylomicrons and VLDL, both of which contain apoprotein B_{48}. High-density lipoprotein (HDL), manufactured in the liver and rich in apoproteins C (apo C) and E (apo E), interacts with the lipoproteins of intestinal origin. HDL transfers apo C and apo E to chylomicrons. Apo C serves as a cofactor to activate lipoprotein lipase, whereas apo E in the chylomicron remnant core facilitates the particle's uptake by hepatocytes.

Lipoprotein lipase activity is stimulated by heparin and insulin. The hypertriglyceridemia, seen in poorly controlled diabetes mellitus, is associated with reduced insulin action, which leads to reduced lipoprotein lipase activity (see Chapter 6). Niacin activates lipoprotein lipase, which explains its utility in treating hypertriglyceridemia. Lipoprotein lipase is inhibited by glucagon, thyroid-stimulating hormone, catecholamines, and adrenocorticotrophic hormone; these hormones generally also stimulate the release of free fatty acids from adipose tissue reserves.

Free fatty acids are used to produce adenosine triphosphate in muscle and adipose tissue; if not used immediately for energy generation, they are reesterified to triglycerides. This process requires the enzyme glycerol-3-phosphate, which necessitates both glucose and insulin for synthesis. Therefore, carbohydrate feeding has the tendency to decrease the concentration of free fatty acids in the circulation by augmenting the availability of glucose and the levels of insulin. Insulin action promotes re-esterification of free fatty acids into triglycerides and opposes lipolysis. Free fatty acids taken up from plasma by the liver are predominantly incorporated into VLDL. High levels of VLDL production in the liver lead to hypertriglyceridemia, a characteristic feature of hyperinsulinemic and insulin-resistant states (32,33) (see Chapter 6).

Fatty acids from chylomicrons and VLDL are used for fuel by the heart, smooth muscle, red muscle fibers, kidneys, and platelets in particular. In addition, they serve as substrate for the formation and function of biomembranes. The fatty acid composition of lipoprotein particles formed by enterocytes influences cellular and subcellular membrane integrity and function, in the synthesis of prostaglandins and leukotrienes (see Chapters 11 and 33). Fatty acids removed from lipoprotein particles of intestinal origin contribute to the energy stored in adipose tissue. The fatty acid composition of VLDL synthesized by the liver is influenced by dietary fat composition, which influences the composition of adipose tissue. Both VLDL and the low-density lipoprotein (LDL) produced when VLDL is acted on by lipoprotein lipase are atherogenic and are taken up by macrophages and subendothelial smooth muscle cells.

HDL uptake by the liver is influenced by the interaction of apo E and its receptor. There are several isoforms of apo E, encoded by various mutations in the apo E allele. Apo EII is associated with the accumulation of chylomicrons and VLDL in blood due to impaired hepatic uptake. Although the concentration of HDL in plasma is lower than that of LDL, HDL particles are present in larger numbers. HDL particles exchange apoproteins and surface lipids with chylomicrons and VLDL. Cholesterol acquired by HDL is esterified by the enzyme lecithin cholesterol acyltransferase. The esterified cholesterol moves to the core of the HDL particle, facilitating additional uptake of cholesterol from other lipoprotein particles. HDL is largely taken up by the liver, as well as other tissues with high cholesterol requirements, including the adrenal glands and ovaries.

Virtually all human tissues can synthesize cholesterol from acetate. The rate-limiting step in cholesterol biosynthesis involves the enzyme beta-hydroxy-beta-methylglutaryl coenzyme A (HMG-CoA) reductase.

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HMG-CoA reductase is stimulated by insulin and inhibited by glucagon. The class of drugs referred to as "statins" comprises HMG-CoA reductase inhibitors, and they work by inhibiting the rate-limiting enzyme in cholesterol biosynthesis. High cholesterol feeding can inhibit endogenous cholesterol synthesis, whereas gastrointestinal loss of cholesterol, such as that induced by bile acid sequestrant drugs, can actually stimulate endogenous production.

When LDL receptors are deficient, as in familial hyperlipidemia type IIA, rising levels of LDL do not inhibit cholesterol biosynthesis, as they do normally. Under conditions of homeostasis, an adult in a Western country may consume a daily average of 335 mg of cholesterol. An additional 800 mg/day is synthesized endogenously. Approximately 400 mg is lost daily in bile acids, another 600 mg in biliary cholesterol, and 50 mg in the production of steroid hormones, and 85 mg is excreted as sterols from skin. Thus, approximately 1,135 mg of cholesterol is exchanged daily. Most cholesterol in circulation is in the esterified form, produced through the action of lecithin cholesterol acyltransferase, which is manufactured by the liver. Esterification of cholesterol is also mediated by acyl-CoA cholesterol acyltransferase, particularly in the liver. The esterifying enzymes have different preferences for fatty acid substrate.

FATTY ACIDS

Fatty acids, carbon chains with the basic formula $CH_3(CH_2)_nCOOH–$, are short, medium, or long chain, and they are saturated, monounsaturated, or polyunsaturated. Short-chain fatty acids have fewer than 6 carbons; medium-chain fatty acids have 6 to 12; and long-chain fatty acids have 12 or more. SFAs contain no carbon-to-carbon double bonds, whereas MUFAs contain one and PUFAs contain more than one. Fatty acids in the saturated class include stearic (18 carbons), palmitic (16 carbons), myristic (14 carbons), lauric (12 carbons), and medium-chain fatty acids (8 to 10 carbons). The principal dietary monounsaturated is oleic acid (18 carbons, cis configuration), whereas the trans stereoisomer elaidic acid is derived primarily from industrial hydrogenation of unsaturated fatty acids. PUFAs include the n-6 linoleic acid (18 carbons) and the n-3 fatty acids linolenic (18 carbons), eicosapentaenoic (20 carbons), and docosahexaenoic (22 carbons). PUFAs are further classified as omega-3 and omega-6 fatty acids. Those with the initial double-bond 3 carbons from the methyl terminus of the molecule are n-3 or omega-3 fatty acids, and those with the initial double-bond 6 carbons from the methyl terminus are n-6 or omega-6 fatty acids). The endogenous synthesis of cholesterol, saturated fatty acids, and unsaturated fatty acids occurs from acetyl coenzyme A, with the exception of linoleic acid and alpha-linolenic acid, the principal omega-6 and omega-3 fatty acids, respectively in the diet. Because of endogenous synthesis of cholesterol and other fatty acids, none of these nutrients is essential in the diet. In contrast, linoleic acid and alpha-linolenic acid are EFAs since they are not synthesized endogenously (see Table 2.1). Naturally occurring fatty acids tend to have even numbers of carbons, to be unbranched, and to be in the cis configuration relative to double bonds. The industrial process of partially hydrogenating vegetable/liquid oils results in the production of a preponderance of now rather notorious trans stereoisomers of monounsaturated fat (34–36), a formulation with adverse effects on health but favorable commercial properties. As of June 2018, the Food and Drug Administration (FDA) banned iTFA in the United States, citing partially hydrogenated oils as unsafe for food (37,38). These actions were based on the evidence that TFAs raise LDL levels, lower HDL levels, and increase the risk of heart disease, stroke, and type 2 diabetes. Since the ban, 98% of iTFA has been removed from the U.S. food market (39). The effect of this on Americans' health remains to be seen; however, 3 years after Denmark banned artificial trans fats, cardiovascular disease mortality in their country decreased on average by 14.2 deaths per 100,000 individuals annually (40). Additionally, 3 years after New York City banned iTFAs in 2007, hospitals where the law went into

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effect saw a 6% decline in myocardial infarctions and stroke admissions compared to those without restrictions (41).

Conjugated linoleic acid (CLA), a family of isomers of an 18-carbon PUFA found in meat and dairy, has generated interest as a potential aid in weight loss. Findings in both animal and human studies have shown promising anti-obesogenic effects. Additional animal studies have shown that CLA is protective against cancer and cardiovascular disease; however, human evidence is at best mixed (42–45). Adverse health effects of this group of fats cannot be excluded with confidence; thus, further human trials are needed to understand their efficacy and safety.

ESSENTIAL FATTY ACIDS

Fatty acids can be synthesized endogenously, and the primary carbon source is glucose-carbon (derived from dietary carbohydrate); those that cannot be synthesized endogenously are essential nutrients (i.e., linoleic acid and alpha-linolenic acid are both EFAs (see Table 2.1 and Appendix E). Fatty acid synthesis occurs primarily in the liver. Enzymes involved in fatty acid synthesis have a high affinity for fatty acids of the n-3 PUFA class, with successively lesser affinity for fatty acids of the n-6, n-9 and n-7 PUFA classes. Affinity in general is greater, the less saturated the fatty acid. Fatty acid composition of cell membranes provides an assessment of EFA status and deficiency. EFAs of the n-3 and n-6 classes are substrates for the lipoxygenase and cyclooxygenase enzymes. The products of EFA metabolism are referred to collectively as eicosanoids.

The eicosanoid products of EFA metabolism clearly vary with the distribution of n-3 and n-6 fatty acids in the diet, with implications for immune function, hemostasis, and metabolism, as discussed in more detail elsewhere (see Chapters 9 and 11). Deficiency of EFAs is associated with impaired growth, abnormal skin (i.e., a dry scaly rash), and infertility.

There are three important n-3 PUFAs: ALA, eicosapentaenoic acid (EPA), and docosahexanenoic acid (DHA). ALA, the essential n-3 fatty acid, is found primarily in plants while EPA and DHA are found in fish, seafood, and certain algae. The importance of omega-3 fatty acids to homeostasis and a variety of physiologic states is discussed throughout the text (see especially Chapters 7, 9, 11, and 20). Linolenic acid can be metabolized to EPA (20 carbons, n-3) or DHA (22 carbons, n-3) (see Table 2.1), both of which are important constituents of cell membranes and are particularly abundant in the retina and brain. The efficiency with which humans convert ALA to EPA, and DHA especially, is low, variable and unpredictable (46).

PUFAs of the n-6 class are particularly important in cell and subcellular membranes throughout the body; both linoleic acid and arachidonic acid are abundant in structural phospholipids. Animals and humans are deficient in an enzyme needed to convert oleic acid to linoleic acid, which is why the omega-6 fatty acid, linoleic acid, is required in the diet. Linoleic acid can be converted to the 20-carbon arachidonic acid, also an omega-6 fatty acid. Therefore, arachidonic acid is essential in the diet only when linoleic acid intake is inadequate. Thus, only one n-6 fatty acid is truly essential, whereas a second is conditionally essential. Additionally, as noted, PUFAs of both n-6 and n-3 classes are important eicosanoid precursors. As discussed in Chapters 9, 11, and 20, the relative abundance of each class of EFA in the diet influences the distribution of prostaglandins and leukotrienes, with important implications for platelet function and inflammatory reactions.

Various lines of evidence support increased health benefits from higher intakes of n-3 fatty acids than the Western diet generally provides (47–49) (see Chapters 7, 11, 29, and 44). Long-chain n-3 PUFAs have been shown to reduce obesity in rodent models via suppression of appetite, enhanced fat oxidation

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and energy expenditure, and reduced fat deposition; however, evidence in humans is limited (50). EPA and DHA have been directly associated with reduced inflammation (51) and cardiac risk (52,53). Their counterpart, ALA, has also been shown to decrease risk of cardiovascular disease (54). The ratio of n-3 to n-6 fatty acids in the diet may be an important determinant of eicosanoid ratios, with implications for immune system function and inflammation (55) (see Chapters 11 and 20). Anthropologists suggest that the "native" ratio of n-3 to n-6 fatty acids in the human diet is roughly from 1:1 to 1:4; the corresponding ratio in the typical modern American diet is about 1:10 (56). Consumption of a diet with a high n-3 to n-6 ratio has been associated with decreased risk of breast cancer (57) and diabetes (58); however, a recent Cochrane review noted an association between increased n-3 fatty acid intake and prostate cancer (59). Previously, it was thought that n-3 fatty acids were always "good" and antiinflammatory, and n-6 fatty acids were "bad" and pro-inflammatory. However, recent research now points to cardiovascular health benefits from both n-3 and n-6 PUFAs, with growing consensus that the total amount of n-6 and n-3 fatty acids in the diet is more important than the ratio (60–62). Further, the ratio can be misleading because it does not provide quantitative information about the amounts of each fatty acid present, nor is information provided about the specific fatty acids that make up the ratio. A ratio of 5 to 1 could provide either very low or very high amounts of n-6 fatty acids along with corresponding high or low amounts, respectively, of n-3 fatty acids. Moreover, qualitatively, the ratio does not provide information about the specific fatty acids that make up the ratio (63).

As of the 2005 *Dietary Reference Intakes* (64), the recommended dietary allowance (RDA) had not been established for either n-6 or n-3 EFAs. RDAs require scientific evidence indicating the level of nutrient intake required to meet the needs of nearly all individuals in a given age and gender group. When this standard cannot be met, the Acceptable Macronutrient Distribution Range (AMDR) may be provided instead. At present, the AMDR for linoleic acid intake (or other n-6 fatty acids) is 5% to 10% of total daily calories, where the lower boundary of the range meets the adequate intake (AI) for linoleic acid and the upper boundary corresponds to the highest linoleic acid intake from foods consumed by individuals in the United States and Canada. The recommended AMDR for ALA (or other n-3 fatty acids) is 0.6% to 1.2% of total daily calories. The AI for linoleic acid (n-6) is 14 to 17 g/day for men and 11 to 12 g/day for women. The AI for ALA (n-3) is 1.6 g/day for men and 1.1 g/day for women (Table 2.2). The evidence used in determining the *Dietary Reference Intakes* is detailed online at https://doi.org/10.17226/10490. The 2015–2020 *Dietary Guidelines for Americans* recommends 250 mg/day of EPA plus DHA (65).

TABLE 2.2

Dietary Reference Intakes for Alpha-Linolenic Acid and Linoleic Acid

Nutrient	Gender	Age Group (years)	AI	AMDR
Alpha-linolenic Acid (n-3)	Male	9–13	1.2	0.6–1.2
		14–18	1.6	
		19–30	1.6	
		31–50	1.6	
		50–70	1.6	
		>70	1.6	
Alpha-linolenic Acid (n-3)	Female	9–13	1.0	0.6–1.2
		14–18	1.1	

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		19–30	1.1	
		31–50	1.1	
		50–70	1.1	
		>70	1.1	
Linoleic acid (n-6)	Male	9–13	12	5–10
		14–18	16	
		19–30	17	
		31–50	17	
		50–70	14	
		>70	14	
Linoleic acid (n-6)	Female	9–13	10	5–10

AI = Adequate Intake, AMDR = Acceptable Macronutrient Distribution Range.

CURRENT INTAKE PATTERNS AND RECOMMENDATIONS

Dietary fat constitutes as little as 10% or less of energy in some Asian countries, as much as 45% in some European countries, and between 30% and 40% in the United States. The National Health and Nutrition Examination Surveys suggest that fat ingestion as a proportion of total calories is declining in the United States, from more than 40% to a current level of approximately 33% (66,67). However, total fat intake (gram amount) has remained relatively constant, because of an increase in total energy consumption (68).

The proportion of fat contributed by vegetable oils has increased in recent years because of consumption of fast foods cooked with such oils, as well as dressings, spreads, condiments, and processed foods that incorporate vegetable fat. In the U.S. diet, major food sources of unsaturated fat include grain-based desserts, chicken dishes, nuts, seeds, salad dressing, and pizza (69).

The health effects of dietary fat in the United States are predominantly those of excess rather than those of deficiency, although the contributions of relative n-3 fatty acid deficiency to chronic disease may be considerable. Saturated fat in the diet is the principal exogenous determinant of serum cholesterol levels, which in turn influences risk of cardiovascular events (see Chapter 7). Dietary cholesterol may contribute as well to serum cholesterol, but the effect is less than that of saturated fat. Despite the minimal contribution of dietary cholesterol to serum levels, high dietary cholesterol intake (often in the form of eggs) is associated with a higher risk of cardiovascular disease and all-cause mortality in a dose-dependent manner (70) (see Chapter 7).

Contemporary dietary recommendations advise consumption of an eating pattern that provides 20% to 35% of calories from fat and less than 10% of calories from SFA. Of the 20% to 35% of calories from fat, the optimal distribution of dietary fat consists of less than 10% from SFA, 5% to 10% from PUFA, and the remainder from MUFA (64) (see Chapters 7 and 45).

Saturated fats derived from both animal and plant sources constitute approximately 11% of calories in the U.S. diet. Americans derive the majority of their SFA from burgers, sandwiches, snacks, sweets, protein foods, and dairy products. Most naturally occurring oils and fats contain a variety of fatty acids. Butter fat, beef fat, and coconut oil are all highly saturated, although the fatty acid profile is considerably variable. Butter fat is high in C16 and C18 along with shorter chain fatty acids. Beef fat is high in palmitic acid, and coconut oil is high in lauric acid. Tropical oils—coconut oil, palm oil, and palm kernel oil—are among the few predominantly saturated oils of plant origin (71). These oils were used to replace

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animal fat (e.g., lard and tallow) in the U.S. food supply several decades ago and were in turn substantially replaced by partially hydrogenated oils (trans fat), which have since been banned in the United States.

Pressure on the food industry to eliminate trans fats existed for nearly a decade before the ban was enacted. On December 2006, New York City's Board of Health voted to ban trans fats in restaurants, making this the first major city to strictly limit trans fats. Then in July 2008, California became the first to pass a statewide ban on trans fats in restaurants. These efforts culminated in 2015, when the FDA designated industrialized TFAs as no longer "Generally Recognized as Safe," or GRAS. In early 2020, this ban fully went into effect, virtually eliminating TFA from the U.S. diet. Since the implementation of these restrictions, the food industry has begun to explore several TFA alternatives, including novel hydrogenation procedures using metal catalysts that reduce the formation of trans stereoisomers (72); selective plant breeding and genetic engineering to create edible seed oils with modified fatty acid composition; interesterification, a process that involves hydrolysis and reformation of the ester bond between fatty acid and glycerol to produce fats with a wide range of melting points; and a return to the use of tropical oils, including palm oil and coconut oil.

A potential hazard of efforts to significantly reduce total fat intake is that healthy oils may be eliminated, with the consequent adverse health effect. Specifically, replacement of SFA with high-quality carbohydrates, such as fiber-rich whole grains, decreases heart disease risk, but if dietary fats are replaced with refined carbohydrates and added sugars, the reverse effects are seen—with associated decreased HDL, increased triglycerides, and no cardiovascular benefit (73). Oils (and some spreads) are typically the main sources of EFAs, whereas the fat added during food processing is predominantly either saturated or monounsaturated and thus, the former is most apt to exert an adverse influence on health, and the latter, although considered a healthy alternative to SFA, will decrease EFAs in the diet. It is recommended that saturated fat in the diet be replaced by unsaturated fat by substituting animal protein sources with PUFAs such as seafood, seeds, legumes, and nuts. This substitution aids in lowering total and LDL cholesterol, and, in turn, reducing risk of CVD morbidity and mortality.

A number of recent studies have shed some doubt on the impact of SFA on health (74–76), though it has long been generally accepted that SFAs are harmful and should be limited in the diet. This recommendation had been based on classical research in the 1970s that populations with high SFA intake also had high rates of cardiovascular disease (77). This together with evidence that restricting dietary fat lowered LDL-cholesterol levels, thus preventing atherosclerosis (78), and eventually became the diet-heart hypothesis. This theory emphasized the potential health benefits of reducing SFA intake to prevent heart disease and has guided the U.S. dietary guidelines for decades. Today, the direct link between SFA and cardiovascular disease is subject to ongoing evaluation. However, authoritative bodies such as the American Heart Association, the American College of Cardiology, and the 2020 Dietary Guidelines Advisory Committee have rated the strength of the recommendation to reduce saturated fat and replace it with unsaturated fat as "strong to moderate" (79, 80).

Of note, there is increasing appreciation for variability in the health effects of SFAs. Whereas myristic acid (14 carbons) and palmitic acid (16 carbons) are both classified as atherogenic, stearic acid (18 carbons) does not seem to increase the risk of atherosclerosis. This is generally thought to have limited implications for dietary guidance at present because of the correlation between stearic acid and atherogenic fats in many foods (81). Whether stearic acid might prove useful in the formulation of oils with favorable properties for both health and commerce remains to be seen. The relevance of stearic acid to the health effects associated with consumption of dark chocolate (i.e., a source of stearic acid) is addressed in Chapter 39. Lauric acid, a shorter-chain (12-carbon) saturated fat, constitutes about half of

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the fatty acid content in coconut oil and palm kernel oil. Consumption of lauric acid, similar to that of many other saturated fats, has been shown to increase total cholesterol and LDL cholesterol (82). Concomitantly, the lauric acid in coconut oil raises HDL. Modern advertisements have equated this increased HDL to cardiovascular benefit; however, it should be noted that taken in total, coconut oil is not healthful and should not be used as a regular cooking oil (83). Coconut oil simultaneously results in higher LDL-cholesterol than nontropical vegetable oils; thus, no clear cardiovascular health benefit of coconut oil exists over other alternative cooking oils (84).

Linoleic acid is found in a variety of commonly used vegetable oils, including corn, soybean, sunflower, and safflower. Evening primrose oil provides gamma-linolenic acid, a form that bypasses an intermediate metabolic step. Plant sources particularly rich in linolenic acid (n-3) include flaxseed, soy, rapeseed (canola), and walnuts. Long-chain n-3 fatty acids are abundant in salmon, mackerel, tuna, sardines, and oysters. Farm-raised fish typically provide the same amount of n-3 fatty acid compared to wild fish, although farm-raised fish are typically higher in n-6 PUFA. The fatty acid profile of fish is a function of the diet they consume.

EFAs are derived from either vegetable sources or the flesh of herbivorous animals consuming plant matter that contains these nutrients. During processing of vegetables for the production of vegetable oils, much of the sterols and phospholipids are removed. Sterols interfere with cholesterol absorption; for this reason, cholesterol absorption may increase as a result of consumption of processed vegetable oil (with sterols removed). The plant sterol beta-sitosterol has been used to lower serum cholesterol modestly by interfering with cholesterol absorption. Phosphatidylcholine, a phospholipid, also interferes with cholesterol absorption. Plant stanols and sterols have been incorporated into “functional” foods that are often recommended for lipid lowering. Reductions in serum LDL cholesterol between 10% and 15% have been observed with intake of 2 to 3 g of phytosterols/stanols per day.

It is also important to discuss the increasingly popular ketogenic diet. This diet places an emphasis on high levels of fat, with moderate protein consumption and virtually no carbohydrates. Typically, greater than 70% of calories consumed are from fats, which causes the body to produce ketones as stored fats are burned. This diet has long been used in the treatment of epilepsy in children; however, it has been more recently discussed in the context of obesity and type 2 diabetes. While interesting to consider, this high-fat and very low-carbohydrate diet is not superior to other weight loss methods and neglects healthy, unrefined carbohydrates—legumes, whole grains, fruits—that enhance a healthful and balanced diet (85). The benefit of the keto diet for patients with type 2 diabetes also necessitates further exploration. Patients desiring to start a ketogenic diet should discuss the risks and benefits with their clinician and be seen by a registered dietician for nutrition counseling. The evidence for the ketogenic diet’s efficacy in treating these conditions is limited and requires further study of long-term efficacy and safety (86).

SUMMARY

Fat is an important nutrient in the diet and provides both energy and essential nutrients. Fatty acids and triglycerides are a highly concentrated source of energy, while cholesterol is important for cell membrane, myelin, and hormone synthesis. Excess energy consumed in the diet is principally stored as triglycerides in adipose tissue, providing a depot of fuel for fasting states and when energy intake does not meet needs. Current dietary recommendations support a diet with 20% to 35% of calories from fat, with less than 10% from SFA, 5% to 10% from PUFA, and the rest from MUFA. Also, 250 mg/day of EPA + DHA is recommended. Largely, a healthful diet should be low in SFA, replacing this fat with unsaturated fat or high-quality carbohydrates. These recommendations provide sufficient quantities of

EFAs—linoleic acid and linolenic acid—while also promoting a diet that lowers serum LDL cholesterol and benefits cardiovascular health.

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Clinically Relevant Protein Metabolism

Christopher Gardner

INTRODUCTION

Protein represents one of three principal classes of macronutrients; the two other classes are carbohydrate and fat. All three are composed of carbon, hydrogen, and oxygen. Protein is unique among the macronutrient classes because it contains nitrogen, part of the amine group of amino acids. Dietary protein is required as a source of amino acids, both essential and nonessential. Amino acids are essential if they cannot be synthesized endogenously. There are nine essential amino acids in humans: histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, and valine. Two other amino acids, cysteine and tyrosine, become essential if intake of their precursors, methionine and phenylalanine, respectively, is limited. The nonessential amino acids include arginine, alanine, aspartic acid, asparagine, glutamic acid, glutamine, glycine, proline, and serine (see Table 3.1).

TABLE 3.1

Amino Acids of Importance in Human Metabolism, Categorized as Essential, Conditionally Essential, or Nonessential

Amino Acid Classification	Structural Category[a]
Essential	
Histidine	Aromatic
Isoleucine	Neutral (branched chain)
Leucine	Neutral (branched chain)
Lysine	Basic
Methionine	Sulfur containing
Phenylalanine	Aromatic
Threonine	Neutral
Tryptophan	Aromatic
Valine	Neutral (branched chain)
Conditionally Essential[b]	
Cysteine	Sulfur containing
Tyrosine	Aromatic
Nonessential	
Alanine	Neutral
Arginine	Basic

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Aspartic acid	Acidic
Asparagine	Acidic
Glutamic acid	Acidic
Glutamine	Acidic
Glycine	Neutral
Proline	Cyclic
Serine	Neutral

[a]*Amino acids are categorized based on their molecular structure as neutral, sulfur containing, cyclic, aromatic, basic, and acidic (amino acids and amides). Leucine, isoleucine, and valine are also referred to as branched-chain amino acids.*

[b]*Required in diet if precursor from column 1 is consumed in inadequate quantity.*

Ingested amino acids serve a broader range of purposes than carbohydrates or fat. The most essential of these purposes is the synthesis of structural proteins (e.g., hair, fingernails, collagen, myosin) and functional proteins (e.g., enzymes, hormones). The amount of amino acids needed is driven by the constant turnover of body tissues, the demands of growth and development, anabolism induced by muscle use, and tissue repair.

DIGESTION AND ABSORPTION

Ingested proteins are broken down by pepsin in the stomach and further by pancreatic enzymes activated on release into the duodenum. Pancreatic enzyme release is stimulated by the presence of protein in the stomach and inhibited when the level of trypsin, a protein-directed pancreatic enzyme, exceeds the available protein to which it can bind. Unbound trypsin inhibits the release of trypsinogen, a precursor to trypsin. Trypsin and other pancreatic proteases—enzymes that break down protein—are specific to peptide bonds adjacent to particular amino acids or amino acid classes (see Table 3.1). Intestinal cells also have proteases, such that it is primarily single amino acids that are absorbed through the mucosa of the small intestine and then enter the hepatic portal vein to be delivered to the liver. The amount of protein absorbed daily is derived from that ingested, as well as the protein from gastrointestinal secretions and the sloughing of gastrointestinal cells into the intestinal lumen. Digestion and absorption efficiency is usually >90% on average, with animal proteins being digested and absorbed with modestly greater efficiency (1).

DIETARY PROTEIN REQUIREMENTS

Protein requirements have been estimated on the basis of replacing obligate nitrogen losses (i.e., those losses that persist on a protein-free diet) and on the basis of maintaining healthy adults in nitrogen balance. For children, estimates have been based on the maintenance of optimal growth. Requirements during pregnancy and lactation have been estimated on the basis of optimal fetal and neonatal growth.

Obligate nitrogen losses on a protein-free diet have been estimated at approximately 54 mg/kg. To replace this amount of nitrogen, 340 mg of protein is required. (Nitrogen is multiplied by 6.25 to give an average relative protein mass.). Therefore, 0.34 g/kg/day of protein is required to replenish obligate losses of sedentary adults. The World Health Organization increases that value to 0.45 g/kg/day to account

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for individual variation. Replacement studies have further demonstrated that as protein is replenished, the efficiency of its utilization declines as intake approaches requirements. This inefficiency adds 30% to required intake, increasing the estimate for adults to 0.57 g/kg/day. Where energy intake is not clearly in excess of need, this estimate is further raised to 0.8 g/kg/day (1).

In the United States, the average daily requirement for total protein has been estimated at 0.66 g/kg/day, given the availability of both abundant nutrient energy for most of the population and of protein of high biologic quality (see Table 3.2). This figure was increased by two standard deviations to 0.75 g/kg/day and then rounded up to 0.8 g/kg/day to establish the recommended dietary allowance (RDA) for adult men and women in the United States, age 19 years and older. Pregnancy adds approximately 10 g to daily protein needs, and lactation adds nearly 15 g/day for the first 6 months, then in the range of 12 g/day thereafter. Rapid growth in early childhood results in substantially higher needs for protein per kilogram body weight. The RDA for infants up to 6 months of age is 2.2 g/kg/day; between 6 months and 1 year, it is 1.2 g/kg/day; between 1 and 3 years, it is 1.05 g/kg/day; between 4 and 13 years, it is 0.95 g/kg/day; between 14 and 18 years, it is 0.85 g/kg/day 7 (2). It has been proposed that the RDA for older adults be increased to 1.0 g/kg/day or higher due to observed lower rates of protein synthesis in this age category, particularly when engaging in resistance training (3) (see Chapter 32).

TABLE 3.2

Recommended Dietary Allowance of Protein Based on Age and Sex, Pregnancy, and Lactation

Population Group	RDA for Protein in g/kg/day
Infants, 0–6 months	1.52*a*
Infants, 7–12 months	1.2
Children, 1–3 years	1.05
Children, 4–8 years	0.95
Children, 9–13 years	0.95
Children, 14–18 years	0.85*b*
Adults, 19 to >70 years	0.80*b*
Pregnant women	1.1
Lactating women	1.3

[a]The AI, or adequate intake, rather than the RDA; an RDA value is not available.

[b]Whereas the recommended protein intake per kilogram body weight is the same for males and females in these age groups, the absolute protein intake recommended differs due to prevailing differences in body mass.

Adapted from Panel on Macronutrients, Food and Nutrition Board, Institute of Medicine of the National Academies of Science. Protein and amino acids. In: Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids. Washington, DC: National Academy Press; 2005:589–768.

Estimates are available of the required daily intake of each of the essential amino acids for both

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children and adults (see Appendix E). The proportion of daily protein intake that must be made up of essential amino acids declines from over 40% in infancy to approximately 35% in children and further to 20% in adults. When protein losses attributable to acute illness or injury are being made up during the convalescent period, protein with 35% to 40% essential amino acids is generally favored. Protein restriction is required during acutely decompensated hepatic insufficiency (see Chapter 17) and to delay progression of chronic kidney disease (see Chapter 16).

While nutrition texts at one time asserted the need for all essential amino acids to be ingested concomitantly for anabolism to occur, this is now known to be false. Such metabolic fastidiousness would certainly have posed a survival threat to our nutritionally challenged forebears. The liver maintains a modest pool of amino acids ready for use for up to several hours. We now know that as long as the full panoply of essential amino acids is consumed over a reasonable span of time, certainly up to 24 hours, anabolism proceeds apace (2,4–7).

Protein Needs for Athletes and for Increasing Muscle Mass

The Dietary Reference Intake (DRI) recommendation for adults of 0.8 g protein/kg body weight is intended to be adequate for meeting or exceeding the needs of 97.5% of the healthy population for maintaining muscle mass (2). Higher amounts have been suggested for athletes and for those trying to increase muscle mass, in the range of 1.2 to 1.7 g/kg body weight (8,9). While this is in the range of doubling the recommendation of the standard RDA and may appear daunting, it is important to put this into the perspective of typical protein intake levels. In the United States, according to self-reported data over the period 2001 to 2014 from the National Health and Examination Survey (NHANES), adults 19 to 70 years of age consume an average amount of protein in the range of 1.1 to 1.5 g/kg (10). The NHANES data also indicate that the average daily energy intake reported is in the range of 1,800 kcal/day for women and 2,500 kcal/day for men—a level that likely involves underreporting (39). Adjusting NHANES protein intake upward to account for underreporting would bring the level of 1.1 to 1.5 g/kg/day well within the range of or higher than the suggested range of 1.2 to 1.7 g/kg/day for athletes. To this, add an additional adjustment upward to account for athletes consuming substantially higher daily energy levels than the average adult—in the range of 3,000 to 5,000 total kcal/day. Together, this suggests that simply meeting daily energy needs should meet and exceed protein requirements for maintaining and building muscle mass. A 2017 systematic review and meta-analysis concluded that for men 40 years and older, protein intakes >1.6 g/kg/day do not contribute meaningfully to gains in muscle mass or strength induced by resistance exercise training (11). Despite widespread promotion of protein and amino acid supplements, a diet with adequate energy intake and reasonable variety of healthy food sources should provide adequate protein for the needs of athletes (12) and those training to increase muscle mass. And while the timing of protein intake before and after exercise is also a topic of interest in the physical activity community (13,14), a 2013 meta-analysis concluded that simply consuming adequate protein over the course of the day, in combination with resistance exercise, is likely the key factor for maximizing protein accretion, more so than the timing of protein intake (15) (see Chapter 32).

CONVERSION OF PROTEIN TO CARBOHYDRATE AND FAT WHEN CONSUMED IN EXCESS OF REQUIREMENTS

Obtaining adequate daily dietary protein is not difficult for individuals with access to a diet of reasonably diverse foods and adequate energy intake, including vegetarians and vegans. Protein deficiency is extremely rare, particularly in economically developed countries. The flip side of the relative absence of

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deficiency is widespread presence of daily protein intake that exceeds requirement for almost all individuals on almost all days. Unlike carbohydrates and fats, there is no designated location in the body that serves primarily as a storage depot for protein. Whereas the body has an almost limitless ability to store excess fat in adipose tissue, and a modest ability to store glucose as glycogen in the liver and muscle, no such storage depot exists for protein. Thus, on a daily basis, the protein consumed in excess of requirement is metabolized to carbohydrate and fat. In this conversion, the removal of nitrogen is necessary before the carbon skeleton of the amino acids can be metabolized to carbohydrates or fats.

Amino acid degradation in the liver results in the formation of urea, most of which is secreted in urine. In the gut, about 20% of urea is converted to ammonia, which in turn is cleared by the liver via the enterohepatic circulation. Nitrogenous intermediates, such as ammonia, are toxic, and are accumulated when hepatic (see Chapter 17) or renal (see Chapter 16) function is impaired. For this reason, protein restriction is often warranted in states of hepatic and/or renal insufficiency.

When protein intake exceeds requirement, the destiny of excess amino acids that are subsequently metabolized can involve several alternatives. The first priority would be glucose if immediate carbohydrate needs are not being met. If the immediate need for glucose is already being met, the next priority would be repletion of glycogen stores. If glycogen stores are replete, the carbon skeletons of the amino acids consumed in excess of requirements would be metabolized to fatty acids for storage in adipose tissue. This interconversion of macronutrients—protein to carbohydrate or protein to fat—is both efficient and common on a daily basis.

Carbohydrate ingestion stimulates insulin release, and insulin facilitates the entry of amino acids into muscle. Because insulin is involved in protein metabolism, ingestion of a mixed meal containing protein and carbohydrate typically induces a more brisk insulin response than does ingestion of carbohydrate alone, a point obscured in recent years by proponents of low-carbohydrate diets (see Chapters 5 and 6).

Given that the primary functions of carbohydrates and fats are to fuel the body, and that some protein is converted on a daily basis to carbohydrates and fats, protein has been assigned a caloric value when utilized in this manner as fuel. In its function as a source of fuel, protein is the least energy dense of the macronutrient classes, providing an energy density that closely approximates—but is a bit lower than—that of carbohydrate, close enough that protein is typically assigned the same caloric value of 4 kcal/g as carbohydrate.

PROTEIN QUALITY

Historically, the concept of protein quality has focused on two factors—amino acid proportions and digestibility. Regarding specific amino acid proportions needed for protein synthesis, the proportional requirements vary tremendously; the highest proportional requirements are for glutamate/glutamine and aspartate/asparagine (these two pairs are combined in some databases because they are so interchangeable—nonessential amino acids with side chains that differ simply by an amine group), while the lowest proportional requirements are for methionine, cysteine, and tryptophan. As an example, for an individual with a protein requirement of 40 g of protein/day, this would not translate to 2 g each for each of the 20 amino acids. Rather, the need for glutamate/glutamine and aspartate/asparagine is several fold higher than the three amino acids needed in lowest proportions—methionine, cysteine, and tryptophan.

For the 20 amino acids needed in protein synthesis for humans, the proportions in animal foods (meat and dairy) are well matched to those in humans. Regarding the amino acid proportions in plant foods, there are pervasive misunderstandings. It is commonly stated that plant foods are “missing” some of the essential amino acids. This is not true. All plant foods contain all 20 amino acids, including all 9 of the

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essential amino acids. It is commonly stated that the amino acids in animal foods are “complete”, while the amino acids in plant foods are “incomplete”. This, again, is misleading. The amino acid proportions of plant foods are strikingly similar to animal foods, and to human physiological needs, overall, as represented in **Figure 3.1**. The primary difference between amino acid proportions in animal versus plant foods is more specific and modest than is commonly presented and involves a concept referred to as the *limiting amino acid*. Rather than being the amino acid with the lowest concentration, the *limiting amino acid* is that specific amino acid that is lowest in concentration relative to its proportional human requirement. Lysine is one of the amino acids with the highest proportional requirement in protein synthesis, and while it is not “missing” in grains, as in “not absent,” it is the amino acid found in grains in the lowest proportion relative to its need in humans. Similarly, the sulfur-containing amino acid, cysteine, is the limiting amino acid of beans.

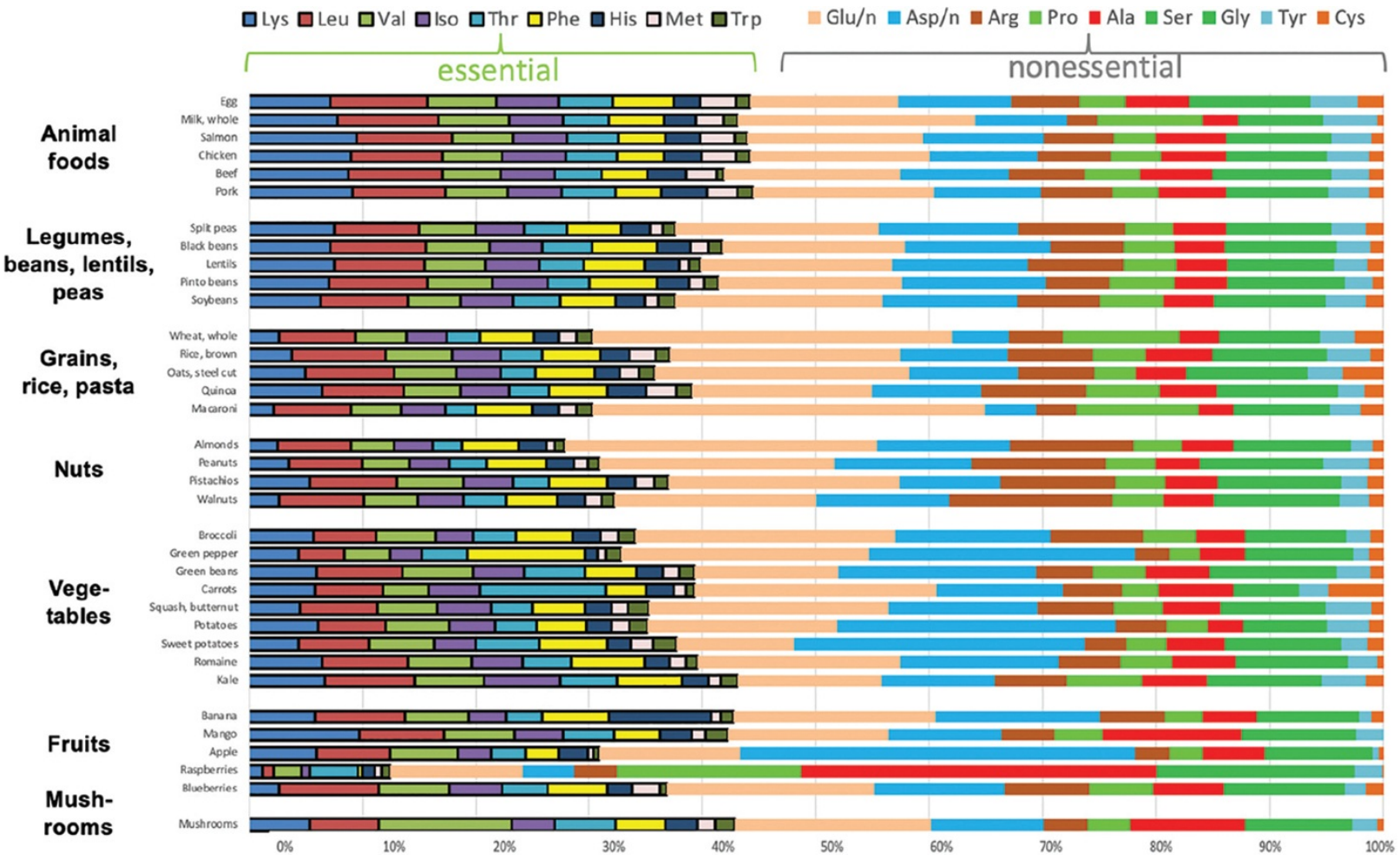

FIGURE 3.1 Proportions of amino acids in selected foods across food groups. Grouped by essential and nonessential, in descending order of prevalence within groups.(Data from Nutrition Database System for Research, University of Minnesota; http://www.ncc.umn.edu/ndsr-database-page/. Reprinted from Gardner CD, Hartle JC, Garrett RD, Offringa LC, Wasserman AS. Maximizing the intersection of human health and the health of the environment with regard to the amount and type of protein produced and consumed in the United States. *Nutr Rev*. 2019 April 1;77[4]:197–215.)

The impact of the limiting amino acid in plant foods is more of a theoretical issue than a practical one. If, for example, an individual requiring 40 g of protein/day were to eat only grains all day, such that their

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only source of protein were grains, even if they were able to get 40 g of protein from those grains, it would not meet their requirement because it would be lower than required in lysine. Similarly, if the same individual requiring 40 g of protein/day were to only eat beans all day, such that their only source of protein were beans, and they were able to get 40 g of protein from those beans, it would not meet their requirement because it would be lower than required in cysteine. However, it would be unusual for someone to eat only grains or only beans for the entire day.

Not only would it be unusual for an individual to eat only grains or only beans, it would also be unusual for an individual to consume only 40 g of protein/day. As described earlier, most people with access to a reasonably varied diet and adequate energy intake consume 80 to 100 g of protein/day (16). This is substantially higher than the RDA (45–55 g/day for the reference woman or man), and the RDA already includes a safety buffer so that achieving the RDA is intended to exceed the individual requirement of 97.5% of the population. Vegetarians, particularly the typical ovo-lacto group (who include eggs and dairy), should not find it difficult to meet their protein requirement (17). Vegans, who avoid all animal products, including eggs and dairy, can also easily meet their individual protein requirement, provided they have access to and consume a reasonable variety of foods and adequate energy (18–20).

Another factor in determining protein quality is digestibility. This is a simpler issue than amino acid proportions. Animal proteins tend to be more easily digested, and therefore more readily absorbed, than plant proteins. The difference is approximately 90% digestibility for animal proteins and 80% digestibility for plant proteins, although this will vary depending on the food matrix of the specific food and the other foods consumed with that food.

Taken together—amino acid proportions and digestibility—animal proteins are superior to plant proteins in both categories. One measure of protein quality, the Protein Digestibility Corrected Amino Acid Score (PDCAAS, 1989), ranks almost all animal proteins with a perfect score of 100 relative to other foods. By comparison, scores for plant protein sources are 91 for soy, 67 for pea, 57 for oat, and 45 for wheat (21). A related score is the Digestible Indispensable Amino Acid Score (DIAAS), proposed in 2011 (1). For many foods, the data on PDCAAS and DIAAS are not available from human studies and rely on studies done in pigs or rats. For both metrics, animal foods like meat score higher than plant foods like grains and beans.

Given that most people with access to adequate energy intake and a reasonable diversity of foods tend to eat amounts of protein substantially in excess of their requirement and the RDA, it is likely important to consider alternate criteria for “quality” beyond the PDCAAS and DIAAS. Two of those considerations would be overall nutrient content of foods and agricultural impact on environmental sustainability. Red and processed meats are among the major animal sources of protein in the diet, and these are also major sources of saturated fat and devoid of fiber. In contrast to meeting and exceeding protein recommendations, the average individual consuming a Western diet gets only half the recommended daily fiber intake. Beyond fiber, many national and international dietary guidelines suggest limiting red and processed meat and increasing plant foods such as legumes, whole intact grains, vegetables, nuts and seeds, and fruits for the purpose of increasing nutrient density. From an environmental perspective, red meat in particular has been identified as the greatest contributor to greenhouse gas (GHG) emissions among food groups (22). It has been proposed that the definition of protein quality should be modernized to include overall nutrient density and environmental impact, in addition to the criteria of digestibility and amino acid patterns (23). This would flip the scoring of protein quality of many plant foods, to be higher than or comparable to—not lower than—animal-based foods.

Historical discussions of shifting from animal to plant proteins have often involved discussing the

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importance of "complementary" plant proteins (e.g., consuming grains and beans together). However, as described previously, it is now recognized that it is not difficult to meet protein needs from plant-based sources, and the concept of *complementary proteins* is now considered outdated. Rather, greater emphasis is now placed on recognizing that consuming a diet containing protein primarily derived from plant sources as opposed to animal sources may also help reduce the risk of coronary artery disease and stroke (24,25).

PROTEIN DEFICIENCY

In the event that protein intake is lower than daily structural and functional demand, the body will catabolize existing structural protein to recycle amino acids and provide them for higher priority structural or functional uses (e.g., cardiac muscle or insulin). However, catabolizing structural proteins leads to impairment (e.g., muscle wasting) and should be avoided.

Malnutrition develops when protein and energy needs are not met. In the developing world, a protein energy deficiency results in conditions known as kwashiorkor or marasmus (26). Infants and children with kwashiorkor are edematous whereas those with marasmus are non-edematous. In kwashiorkor, a lack of adequate protein can result in a defect in hepatic fat secretion (i.e., impaired construction and secretion of very low-density lipoproteins), resulting in fatty liver. Such children's rotund bellies tend to misrepresent their severe malnourishment (27). Conversely, there is no mistaking a condition of wasting and emaciation known as marasmus.

In the United States during the 1970s, the use of very-low-calorie liquid diets that did not provide adequate protein was associated with sudden cardiac death due to the leaching of amino acids from viscera, including the heart. Susceptibility to this effect may be greater during such diets than during complete starvation because of other metabolic effects of total starvation (see Chapter 26). During starvation, approximately 25% of structural proteins can be turned over before life is threatened—often enough to sustain a fast for as long as 30 to 50 days. Very-low-calorie liquid diets now provide protein, to allow for a so-called protein-sparing modified fast (see Chapter 5), considerably mitigating the risks involved.

Interaction/Interconversion of Macronutrients Related to Deficiency

Protein metabolism is linked to carbohydrate and fat metabolism. In the fasted state, insulin levels are low and glucagon levels are elevated. Lipases in adipose tissue release fatty acids and glycerol. Glycogen stores in the liver are consumed to meet energy needs for the first 12 to 18 hours of fasting. With more protracted fasting, energy needs are met by the release of protein from muscle and intestine, serving as a substrate for gluconeogenesis in the liver. The gluconeogenic amino acids are alanine, glutamine, glycine, serine, and threonine. Free fatty acids are used in the liver to produce ketone bodies. Muscle uses free fatty acids, and subsequently ketone bodies, as an alternative fuel to glucose. Lysine and leucine are ketogenic, whereas isoleucine, phenylalanine, threonine, tryptophan, and tyrosine are potentially both ketogenic and gluconeogenic. With feeding, insulin levels rise and glucagon levels subside. Glucose is carried into the liver and muscle, both to reconstitute glycogen and to be used as fuel. Insulin suppresses the action of lipases in adipose tissue and inhibits the release of fatty acids.

PROTEIN AND SATIETY

In the context of the seemingly intractable global obesity epidemic, the potential role of dietary satiety is

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frequently raised as a factor that could contribute to reducing energy intake. Weight loss requires achieving and maintaining a caloric deficit. Lowering energy consumption for extended periods of time typically leads to hunger sensations; most individuals find it difficult to allow these hunger sensations to persist when food for consumption is available. A plausible strategy is to manipulate food choices so as to allow for adequate satiety while consuming fewer calories. In this context, the conventional position about the relative satiety of the three main macronutrients has been protein > carbohydrate > fat (28,29). However, upon closer examination, the hierarchy of satiety is less clear and more complex.

Protein, carbohydrate, and fat are nutrients, and virtually all foods contain combinations of these macronutrients. Under tightly controlled and reductionist conditions, these nutrients can be studied in isolation. But in several studies involving more generalizable conditions, a higher satiety of foods rich in protein relative to foods rich in carbohydrate or fat intake has not been supported (30–32). One of these studies involved lunch and dinner entrées that had been covertly manipulated to look identical but to differ dramatically across five levels of protein—10%, 15%, 20%, 25%, and 30% (e.g., casserole). Study participants reported no differences in hunger, fullness, taste, or appearance across the five conditions, leading the investigators to conclude, "Varying the protein content of several entrées consumed ad libitum did not differentially influence daily energy intake or affect ratings of satiety" (32).

Two additional factors that have been consistently reported to contribute to satiety are fiber and water (33,34). The foods containing the highest amounts of fiber and water are vegetables and fruits—both high carbohydrate foods. Other factors that contribute to satiety include taste, palatability, and energy density, as well as sensory characteristics and cognitive appraisal (35–37). Taking all of this into account, although protein content is one of the factors contributing to satiety, there are many other contributing factors that can make the satiety of one specific food or meal relative to another variable from one individual to the next. In terms of weight control, the available evidence generally indicates that simply adjusting the levels of various macronutrients in the diet is unlikely to exert a significant influence on total calories consumed over time (30,36,38,39).

SPECIFIC AMINO ACIDS AND METABOLITES

Several specific amino acids and proteins have unique and/or important roles in health or metabolism that are of clinical interest and/or importance. A selected set of these is briefly described in the following sections.

Branched-Chain Amino Acids

The liver is the principal site of catabolism for all the essential amino acids, except those with branched chains. The branched-chain amino acids (BCAAs; leucine, isoleucine, and valine) are principally taken up in the muscle and kidney, which provides a rationale for their use in selected cases of advanced liver disease (see Chapter 17).

Leucine, in particular, among the BCAAs, has been determined to have an important role in muscle synthesis due to its demonstrated impact on mammalian target of rapamycin (mTOR) signaling (40). This may be especially relevant in older populations in the context of sarcopenia and minimizing muscle loss. However, a 2015 critical review on this topic concluded that supplemental leucine as a stand-alone nutritional intervention was not effective in older populations (41). A similar finding was reported in young males in a resistance training intervention where it was reported that leucine supplementation to a diet that was already adequate in protein did not provide additional benefits (12). In a review by van Vliet et al. on the topic of plant versus animal protein regarding anabolism in skeletal muscle, the

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theoretical possibility was raised that plant proteins might need to be supplemented with additional amino acids, such as leucine, to support optimal muscle building (21). However, the main conclusion of the review was that more studies are needed to effectively address this question (21). As illustrated in **Figure 3.1**, a direct comparison of the amino acid distribution in plant versus animal foods shows that leucine is present in plant foods in proportions very similar to those in animal foods.

Circulating levels of BCAAs, in particular, fall after a carbohydrate-rich meal, with attendant insulin release. BCAAs compete with tryptophan for uptake by brain cells. Thus, a carbohydrate-rich meal inducing a brisk insulin response will result in preferential uptake of tryptophan by the brain by reducing plasma levels of competitive amino acids.

Tryptophan

Tryptophan is used in the production of serotonin, which is thought to be both soporific and mood enhancing. Selective serotonin reuptake inhibitor (SSRI) antidepressants work by raising serotonin levels in the brain (42). Tryptophan is rate limiting in the synthesis of serotonin, and thus serotonin levels depend largely on hepatic regulation of protein degradation and the release of tryptophan and its uptake by the brain. Tryptophan is also a precursor for vitamin B_3, niacin; on a daily basis, a substantial proportion of the body's requirement for niacin (RDA = 14 mg/day for women, 16 mg/day for men; daily intake of tryptophan is likely to be 1–2 g/day [1,000–2,000 mg]) can be met by conversion of tryptophan.

Albumin, Prealbumin, Retinal Binding Protein

The most readily accessible, and therefore measurable, pool of proteins is that circulating in plasma. Plasma proteins are predominantly glycoproteins and albumin. The levels of plasma proteins fall and rise with nutritional status. Albumin levels decline with significant malnutrition, but they are relatively insensitive to minor or short-term aberrations in dietary intake. Prealbumin and retinol-binding protein are better indicators of short-term deficits of dietary protein or energy (see Chapter 26).

Creatine and Creatinine

Arginine and glycine are metabolized in the kidney and liver to produce creatine. Creatine is transported to muscle, where it is stored as creatine and creatine phosphate. A dehydration reaction in muscle converts creatine and creatine phosphate to creatinine, which is released from muscle into the pool of total body water. Slightly <2% of creatine in the body is converted to creatinine each day. The quantity of urinary creatinine is a product of muscle mass, the concentration of creatine in muscle, and dietary intake of creatine in meat. Creatinine rises in kidney disease, whereas serum creatinine concentrations are often decreased in older men and women who have little muscle mass.

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Chapter 4

Overview of Clinically Relevant Micronutrient Metabolism

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INTRODUCTION

Needs for nutrient energy are met by the macronutrient classes discussed in Chapters 1 through 3. Macronutrients—protein, carbohydrate, and fat—are consumed in quantities measured in grams and are plainly visible to the naked eye. In contrast, specific metabolic needs are met by various classes of micronutrients that are typically consumed in milligram or microgram amounts.

Micronutrients include vitamins and vitamin-like substances, minerals, and specific subclasses of macronutrients essential for survival. This chapter provides an overview of clinically relevant micronutrients and micronutrient classes. More detailed information for specific nutrients of interest can be found in the nutrient reference tables in Appendix E.

VITAMINS

By definition, vitamins are organic compounds the body requires in small amounts for metabolic processes but cannot produce endogenously. In some instances, some endogenous production does occur but either is inadequate for metabolic demand or requires ingestion of a precursor. The consumption of provitamin A carotenoids is an example of the latter; vitamin D production in the skin can be an example of the former.

Vitamins are divided into water-soluble and fat-soluble groups. In addition, there are vitamin-like compounds—essential nutrients that meet some but not all of the defining criteria for vitamins. Historically, their reclassification as a vitamin would be predicated upon identifying a deficiency syndrome. The letter designations of vitamins are something of an anachronism, reflecting the sequence in which essential dietary "factors" were discovered in the early part of the 20th century. The essential functions of vitamin B, for example, came over time to be attributed to a variety of nutrients that then took on numeric designations as well. In some instances, the numeric designations came into wide use (e.g., vitamins B_6 and B_{12}), whereas in other instances, the chemical name supplanted the alphanumeric (e.g., thiamine). Further subdivisions have been identified over time, so that each of certain vitamins (e.g., vitamins A, D, and B_6) comprises a group of related compounds. Therefore, although the chemical name is preferred in most instances, the alphanumeric designation retains value in reference to a group of compounds with a shared biologic function.

Water-Soluble Vitamins

Water-soluble vitamins are generally readily available in the food supply, are well absorbed via the intestine, and are stored to a very limited extent in the body (1). The water-soluble vitamins include the B

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complex—thiamine (B_1), riboflavin (B_2), niacin (B_3), pantothenic acid (B_5), pyridoxine (B_6), folate, biotin, cyanocobalamin (B_{12})—and ascorbic acid, or vitamin C. Vitamins included in the B complex are not chemically related to one another, but rather represent discrete nutrients initially thought to be a single water-soluble vitamin.

Thiamine (B_1)

Thiamine is an essential component of metabolic activity at the cellular level. It is a cofactor for multiple enzymes involved in glucose metabolism and is needed to generate reducing power in cells to protect them from oxidative stress (1,2). Current RDA (recommended dietary allowance) of thiamine is 0.5 mg/1,000 kcal, or 1.2 mg/day for men, 1.1 mg/day for women, and 1.4 mg/day during pregnancy and lactation. Thiamine is innocuous in high doses and therefore does not have an upper limit of intake (3). Paleolithic intake is estimated to have been nearly 4 mg/day in adults. Thiamine is widely found in foods but is abundant in relatively few, including pork, and grains and seeds with intact bran. Of note, heat during food preparation may affect thiamine function.

With increasing access to a varied diet and dietary supplements in developed societies, thiamine deficiency is now uncommon. Cases today are most commonly associated with alcoholism due to poor nutrition and reduced absorption and storage of thiamine, but may also be secondary to food insecurity or monotonous diets, malabsorption following bariatric surgery, hypermetabolic states such as sepsis, or due to long-term use of medications such as furosemide (3). Overt deficiency manifests as beriberi and occurs at an intake below 0.12 mg/1,000 kcal in adults. Beriberi manifests in adults in two forms, dry or wet beriberi. Wet beriberi presents as neuropathy with cardiac involvement. Dry beriberi presents with symmetrical peripheral sensory and motor neuropathies and includes the spectrum of Wernicke–Korsakoff syndrome (WKS). Wernicke's encephalopathy is characterized by confusion, ataxia, and ophthalmoplegia, and can progress to permanent deficits in memory and confabulation, known as Korsakoff syndrome. WKS is not exclusive to chronic alcoholism, though is most often recognized in this scenario. Patients with alcoholism should receive thiamine supplementation (100 mg daily) to prevent WKS. In the acute setting, the administration of dextrose to thiamine-deficient patients can further deplete thiamine and induce an acute encephalopathic state; therefore, patients with alcohol dependence seen for acute care should receive thiamine before dextrose.

Several studies have shown potential therapeutic applications for high-dose thiamine in treating diabetic retinopathy and nephropathy (4–6).

Riboflavin (B_2)

Riboflavin is a precursor to coenzymes essential for energy production in the mitochondria. The metabolic functions of vitamin B_6 and niacin require adequate riboflavin. The RDA for riboflavin is 0.6 mg/1,000 kcal, or 1.3 mg/day for men, 1.1 mg/day for women, 1.4 mg/day during pregnancy, and 1.6 mg/day during lactation. Paleolithic intake is estimated to have been upward of 6 mg/day. Riboflavin is naturally abundant in meat, eggs, dairy, and fortified grain products. It is largely inactivated when exposed to light, which is why milk is generally not stored in clear containers (7).

Deficiency of riboflavin is very rare in the United States; it most often accompanies multiple other nutrient deficiencies due to malnutrition but can also result from endocrine disorders or use of certain medications (8). Riboflavin deficiency manifests as pathology of the skin and mucous membranes, particularly glossitis and stomatitis, though this presentation can be related to multiple concurrent nutrient deficiencies. Supplementation is well tolerated. At doses of 50 to 400 mg/day, evidence supports its use

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for migraine prophylaxis (9). Emerging evidence also suggests a role for high-dose riboflavin supplementation in neurodegenerative disorders (10) and cataract prevention (11), though more rigorous evaluation is needed.

Niacin (B_3)

Niacin refers to a group of precursors to nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP), critical coenzymes in cellular redox reactions for energy production. They are also involved in non-metabolic functions, such as DNA repair and gene expression (12). Niacin can also be synthesized from the amino acid tryptophan; therefore, niacin ingestion is not essential when tryptophan is available in sufficient amount. However, conditions requiring increased demand for tryptophan, including carcinoid syndrome, isoniazid therapy, and Hartnup disease, can present with niacin deficiency. Estrogen enhances conversion of tryptophan to niacin. Approximately 60 mg of tryptophan produces 1 mg of niacin; therefore, either is considered one niacin equivalent (NE). The RDA for niacin is 16 mg NE for adult males and 14 mg NE for adult females, with increased needs for females during pregnancy and lactation (18 and 17 mg NE, respectively). A paleolithic intake estimate is not available. Niacin is widely distributed in nature and is especially abundant in meat, dairy products, eggs, legumes, nuts, seeds, and fortified grain products.

Overt deficiency of niacin manifests as pellagra, a syndrome characterized by three D's: photosensitivity dermatitis, diarrhea (with abdominal pain and vomiting), and, when advanced, dementia. Pellagra can be associated with alcoholism, anorexia nervosa, HIV infection, and malabsorptive disease. High-dose niacin (1.5–3 g/day) can be used as pharmacotherapy for hyperlipidemia, though it is often poorly tolerated due to prostaglandin-induced vasodilation and flushing. Niacin also appears to play a role in neuronal health; its use in neurodegenerative disorders is under investigation (12). Other potential uses include osteoarthritis, schizophrenia, and prevention of nonmelanoma skin cancers (13). Long-term therapy may induce insulin resistance, and high doses are potentially hepatotoxic; special attention should therefore be given to patients with diabetes and the monitoring of liver enzymes during niacin treatment.

Pantothenic Acid (B_5)

Pantothenic acid is a precursor to coenzyme A and the acyl carrier protein of fatty acid synthetase, which is integrated with the Krebs cycle and biotin-dependent processes. As such, the vitamin is vital to the metabolism of, and energy release from, carbohydrate, protein, and fat. It plays a role in the synthesis of acetylcholine, functions in cholesterol and steroid hormone biosynthesis, and is required for protoporphyrin production. An adequate intake (AI) for pantothenic acid has been set at 5 mg/day for adults, 6 mg/day during pregnancy, and 7 mg/day during lactation; this is based on data about usual intakes for U.S. adults, as insufficient information is available for setting a true RDA. High doses of pantothenic acid are apparently safe, though one small prospective study suggested a correlation between higher dietary intake of pantothenic acid and cerebral amyloid burden in patients with cognitive impairment (14). An estimate of paleolithic intake is not available. Pantothenic acid is found in fish and poultry, organ meats, eggs, tomato products, broccoli, legumes, and whole grains; it can also be produced by colonic bacteria.

Deficiency induced under experimental conditions leads to a wide range of manifestations, but a naturally occurring deficiency syndrome is not known to exist. Malnourished prisoners of war have been known to develop paresthesias of the feet (burning foot syndrome) relieved by administration of pantothenic acid. Topical application for wound healing has also been suggested (15).

Pyridoxine (B_6)

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Vitamin B_6 refers to pyridoxine, pyridoxal, and pyridoxamine, which function in transamination reactions. Vitamin B_6 is therefore of fundamental importance to amino acid metabolism, and B_6 requirements rise as protein intake rises. It also functions as a coenzyme in pathways of gluconeogenesis, heme, sphingolipid, and neurotransmitter biosynthesis. The RDA for vitamin B_6 is 0.016 mg/1 g of protein, resulting in a recommendation of 1.3 mg/day for most adults between 19 and 50 years old. The RDA is 1.5 mg/day for females 51 years and older and 1.7 mg/day for males. During pregnancy, the RDA is 1.9 mg/day and during lactation, 2 mg/day. High doses well above the RDA, generally used for treating neuropathies, are relatively safe but may induce a transient dependency and may be neurotoxic (16). An estimate of paleolithic intake is not available. Fish, poultry, potatoes, and fortified cereals are good sources of B6, and other common sources in the U.S. food supply include avocados, bananas, spinach, and nuts.

Overt deficiency manifests as dermatitis, anemia, depression, and seizures. Numerous drugs, including oral contraceptives, antituberculosis drugs, L-dopa, and theophylline, alter vitamin B_6 metabolism such that supplementation may be advised to prevent deficiency. Genetic syndromes, including homocystinuria, cystathioninuria, and xanthurenic aciduria, can mimic vitamin B_6 deficiency; pyridoxine is used to treat homocystinuria. Pyridoxine in combination with doxylamine, an antihistamine, has been recommended as a first-line pharmacologic treatment for nausea and vomiting of pregnancy (17), though evidence on efficacy is mixed (18).

Folic Acid

Folic acid, or folate, is essential in methylation reactions needed for metabolism of many amino acids and the biosynthesis of nucleic acids. All rapidly dividing tissues are dependent on folate for viability. The RDA for folate has been set at 400 mcg/day for all adults. Due to its role in prevention of neural tube defects when taken at the time of conception, the United States has mandated fortification of grain products since 1998. Current recommendations advise supplementation of 400 to 800 mcg/day for women during the critical period beginning at least one month before conception and continued through the first trimester; given that many pregnancies are unplanned, all women capable of becoming pregnant are advised to take folate supplementation daily (19). Women with epilepsy may need higher folate supplementation since antiepileptic drugs have been known to alter folate metabolism and increase the risk of neural tube defects. The upper limit of intake from supplements or fortified foods is 1000 mcg. There is no upper limit for naturally occurring folate in foods (20). The principal risk of high-dose intake of folate is thought to be the masking of B12 deficiency, which can lead to irreversible damage. Estimated paleolithic intake is 380 to 420 mcg/day. Folate is abundant in fruits and vegetables, particularly green leafy vegetables, beans, peas, and in fortified grains.

Folate deficiency is the most common nutrient deficiency in the United States. While it is generally associated with poor nutrition, it is also associated with smoking, chronic alcohol use, malabsorption, and certain drug use, including trimethoprim, methotrexate, and phenytoin (21). Patients with the methylenetetrahydrofolate reductase (MTHFR) gene polymorphism are also at risk for folate deficiency due to reduced ability to convert folate to its active form (22). Manifestations of deficiency include macrocytic anemia, gastrointestinal disturbances, and glossitis.

Folate supplementation can lower levels of blood homocysteine, and therefore has been hypothesized to decrease risk of cardiovascular disease (CVD) and dementia. However, evidence to support efficacy of folate supplementation for these purposes is still lacking (23,24). Supplementation may also play a role

in prevention of colorectal cancer in patients with inflammatory bowel disease (25).

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Biotin

Biotin functions as a component of several enzymes involved in the transfer of carboxyl units. These enzymes participate in fatty acid synthesis, gluconeogenesis, and the citric acid cycle. The RDA for biotin is not established, but the National Research Council has recommended intake in the range from 30 to 100 mcg/day in adults. High doses are not associated with any known toxicity. Paleolithic intake has not been estimated. Good sources of biotin include yeast, soybeans, egg yolks, peanut butter, and mushrooms.

Biotin deficiency is unusual but can be induced by the ingestion of sufficient raw egg albumin, which contains avidin, a biotin antagonist. Deficiency is characterized by alopecia, seborrheic dermatitis, nausea and vomiting, depression, glossitis, and lethargy. Biotin is utilized for treating multiple carboxylase deficiency, a rare in-born error of biotin metabolism. Preliminary studies also suggest a potential role for biotin supplementation in the treatment of progressive multiple sclerosis (26). Though biotin has gained recent popularity as a supplement for hair quality and quantity, it has no supporting evidence to date (27).

Vitamin B_{12}

Vitamin B_{12} refers to a group of cobalamin-containing compounds; the commercially available form is cyanocobalamin. Vitamin B_{12} is required to produce the active form of folate and participates in most aspects of folate metabolism. In addition, vitamin B_{12} is necessary for the conversion of methylmalonyl CoA to succinyl CoA. Methylmalonyl CoA accumulates when B_{12} is deficient; this deficiency impairs myelin formation and results in neuropathy. Methylmalonic acid is used as a screening marker to distinguish B_{12} deficiency from folate deficiency. The RDA for adults is 2.4 mcg/day, 2.6 mcg/day during pregnancy, and 2.8 mcg/day during lactation. There is no known toxicity associated with high doses. Paleolithic intake of B12 has not been estimated. Vitamin B12 is found in meats, dairy products, shellfish, and eggs; it is naturally absent in all plant foods but is contained in fortified breakfast cereals.

Unlike other water-soluble vitamins, which are replenished frequently from diverse dietary sources, B_{12} is stored in the liver in reserves that can last up to 30 years. Therefore, deficiency results when either dietary intake is deficient for protracted periods or absorption is impaired. Dietary insufficiency is rare but can be associated with a strictly vegan diet (no consumption of animal products). Impaired absorption is more common, arising from atrophic gastritis, gastric bypass surgery, *Helicobacter pylori* infection, chronic proton pump inhibitor use, or pernicious anemia, an autoimmune gastritis causing lack of a protein required for B_{12} absorption called intrinsic factor (see Chapter 43). Deficiency can manifest with hematologic abnormalities, such as macrocytic anemia, and neurologic abnormalities, such as peripheral neuropathy, cognitive deficits, or a myelopathic syndrome known as subacute combined degeneration. Sufficient folate intake can overcome the effects of B_{12} deficiency on the bone marrow but not the nervous system. Like folate, vitamin B_{12} lowers serum homocysteine levels, and therefore, several studies have evaluated its role in reducing risk of CVD. However, evidence does not support vitamin B12 supplementation for CVD (28).

Vitamin C (Ascorbic Acid)

Vitamin C, or ascorbic acid, is both an antioxidant and a cofactor in redox reactions that are important in gene expression and the production of collagen, carnitine, and cathecholamines (29). The RDA,

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previously set at 60 mg/day for adults, has been revised upward to 90 mg/day as the importance of antioxidants to health has become increasingly clear. Currently, the RDA is 90 mg/day for men, 75 mg/day for women, 85 mg/day during pregnancy, and 120 mg/day during lactation. Patients who smoke are recommended to add an additional 35 mg/day. High doses of vitamin C are relatively innocuous, but toxic effects, particularly gastrointestinal discomfort, at doses in excess of 500 mg/day have been reported. The serum level of vitamin C peaks at an intake in the range of 150 mg/day. Paleolithic intake of vitamin C is estimated to have been slightly above 600 mg/day. Vitamin C is abundant in fruits, especially citrus fruits, and a variety of vegetables.

Overt deficiency manifests as scurvy—characterized by fatigue, gingivitis, and poor wound healing—and occurs at an intake level of approximately 10 mg/day in adults. This can occur with malnutrition or monotonous diets, or with severe malabsorption. Smokers and those exposed to cigarette smoke also have lower serum levels of vitamin C (30).

Given its function as a potent antioxidant, studies have investigated its role in treatment of diseases related to oxidative stress, such as cancer and CVD; however, compelling evidence is still lacking (31).

Fat-Soluble Vitamins

In general, fat-soluble vitamins are stored in the body in sufficient reserves so that daily intake (DI) is not required. The fat-soluble vitamins include A, D, E, and K. Deficiencies in fat-soluble vitamins are associated with fat malabsorption which is present in several diseases, including cystic fibrosis, celiac disease, cholestatic liver disease, small bowel Crohn's disease, and pancreatic disease. Additionally, bariatric surgery can predispose patients to fat malabsorption and, therefore, patients will likely need postsurgical supplementation of fat-soluble vitamins (32).

Vitamin A

Vitamin A refers to a group of compounds known as retinoids with varying degrees of vitamin A activity; the predominant compound is retinol. Active vitamin A can be synthesized endogenously from carotenoid precursors. More than 500 carotenoids are known, but only approximately 10% have provitamin A activity. Among that 10% are beta-carotene, alpha-carotene, and cryptoxanthin. Vitamin A is incorporated into the rod and cone cells of the retina; in the rods, it is a structural constituent of rhodopsin and functions in night vision, whereas in the cones, it is utilized to produce iodopsin, a pigment used for color and higher-acuity vision. Vitamin A also functions in the generation of epithelial cells, in the growth of bones and teeth, in reproduction, and in immune function, and is now known to play an important role in gene expression (33).

The RDA for vitamin A is measured in retinol activity equivalents (RAE), so called because of the various nutrients that can be used to produce active vitamin A. One RAE is equal to 1 mcg of all-trans retinol, 12 mcg of food-based all-trans-beta-carotene, or 24 mcg of other all-trans provitamin A carotenoids. An intake of 900 RAE is recommended daily for adult males and 700 RAE for adult females, 770 RAE during pregnancy, and 1,300 RAE during lactation (34 National Institute of Health [NIH]). The upper limit has been set at 3,000 RAE vitamin A/day for adults. Paleolithic intake is estimated to have been three to four times the RDA and approximately twice the current intake among adults in the United States. Preformed vitamin A is found in organ meats, especially liver, and in fish, egg yolks, and fortified milk. Carotenoids are abundant in brightly colored fruits and vegetables.

Deficiency of vitamin A, due to malnutrition or fat malabsorption, results in night blindness and, in more extreme cases, more severe eye injury and visual impairment resulting from drying of the eye, or xerophthalmia. Deficiency is also associated with increased susceptibility to infectious disease and

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increased mortality in children. It remains a widespread problem in resource-poor countries, and therefore, universal supplementation in young children susceptible to deficiency has been recommended (35).

Vitamin A is potentially teratogenic in high doses, and thus prenatal vitamins generally provide lower levels than do standard supplements (see Chapter 27). Toxicity does not result from the ingestion of provitamin A carotenoids; rather, it can result from preformed vitamin A, which is efficiently absorbed in the small intestine. Symptoms of vitamin A toxicity include headache, vomiting, visual disturbances, elevated cerebrospinal fluid pressure, desquamation, and liver damage. Symptoms may result from single doses greater than 100,000 RAE in adults or 60,000 RAE in children.

Retinoids have therapeutic uses in certain diseases including measles (36), acne vulgaris (37), and acute promyelocytic leukemia (38).

Vitamin D

Vitamin D refers to calciferol and related chemical compounds. Unique among vitamins, vitamin D is essential in the diet only when the skin is not exposed to sufficient ultraviolet light, which acts to produce vitamin D from a precursor stored in skin. Melanin in skin impedes vitamin D synthesis, so that those with darker skin in temperate climates are particularly subject to deficiency without adequate dietary intake. The development of pale skin is now thought to be the result of a single, discrete genetic mutation that favored survival among peoples migrating northward out of Africa as a result of enhanced vitamin D production (39). After synthesis or ingestion, vitamin D undergoes two hydroxylation reactions, one each in the liver and the kidney, to the metabolically active 1,25-dihydroxycholecalciferol, or calcitriol. Calcitriol functions as a hormone that regulates the metabolism of calcium and phosphorus. Fundamentally, vitamin D promotes the intestinal absorption of calcium and therefore is critical in bone mineral homeostasis. Its function is not limited to bone health, however; the vitamin D receptor is widely distributed throughout the body, including the heart, gut, nervous system, and immune system (40). Vitamin D is closely regulated by parathyroid hormone, as well as estrogen, placental growth hormone, and prolactin, which play a role in meeting increased demands during pregnancy and lactation.

When sun exposure is abundant, there is no requirement for dietary vitamin D; therefore, the recommended intake is predicated on the inconsistency of population exposure to sunlight. The AI developed for vitamin D is 15 mcg (600 IU) daily from childhood through adulthood, including during pregnancy and lactation; AI increases to 20 mcg daily for adults ages 70 and older. The new recommendations were established while assuming minimal sunlight exposure. Vitamin D supplementation is required in infants who are exclusively breast-fed due to low content of vitamin D in human milk. Patients receiving steroids will require increased vitamin D supplementation due to the steroid's inhibitory effect on vitamin D absorption in the gut. Sun exposure cannot result in vitamin D toxicity, but high-dose supplements can. The recommended safe upper limit is no more than 4,000 IU/day; intake greater than this may cause vitamin D intoxication, characterized by soft tissue calcification, kidney stones, and hypercalcemia. An estimate of paleolithic intake is unavailable. Vitamin D is found in fatty fish, but the principal source in the United States is milk, which is generally fortified with 100 IU/cup.

Deficiency occurs with inadequate dietary intake and inadequate sun exposure, manifesting as rickets in children and osteomalacia in adults. Supplementation is recommended in adults with osteoporosis and those with serum 25-hydroxyvitamin D levels lower than 30 nanomolar/L.

Given wide distribution of the vitamin D receptor throughout multiple organ systems, vitamin D deficiency and supplementation has been studied in a wide variety of medical conditions. One study demonstrated that vitamin D deficiency was associated with increased mortality from all causes, CVD,

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cancer, and respiratory diseases (41). Despite the association between vitamin D deficiency with numerous conditions—pancreatic beta-cell dysfunction, insulin resistance, atherosclerosis, coronary artery disease, malignancies, and immune dysfunction (42)—the current literature does not support a causative role of deficiency. Vitamin D deficiency is common, for example, in patients with cognitive impairment and dementia, though research has failed to show that supplementation improves functioning (43). Adequate evidence is also lacking to support improvement in depression with supplementation (44).

Vitamin E

Vitamin E refers to a group of compounds collectively known as tocopherols and tocotrienols. The most abundant and biologically active is alpha-tocopherol. Vitamin E functions as a lipid antioxidant, protecting and preserving the integrity of cellular and subcellular membranes.

The RDA is expressed in alpha-tocopherol equivalents (TE) and is 15 mg (equivalent to 22.5 IU)/day for adults, including pregnancy, and 19 mg/day during lactation. Higher intakes are required when the diet is rich in polyunsaturated fatty acids (PUFAs) that are subject to rancidification. Vitamin E is found in vegetable oils, so intake tends to rise with intake of PUFAs. The recommended upper limit for vitamin E is 1,500 IU from natural sources and 1,100 IU of synthetic vitamin E for adults without fat malabsorption. Paleolithic intake is estimated to have been approximately 33 mg/day, approximately twice the current RDA. Vitamin E is found in vegetable oils, nuts, and seeds. Due to its distribution in fat, high dietary intake is unusual and not recommended.

Overt deficiency is rare because of the distribution of vitamin E in the food supply. Deficiency is thought to manifest as muscle weakness, hemolysis, ataxia, and impaired vision. A variety of health benefits have been claimed for supplementation with doses between 200 and 800 IU daily; however, supplementation has been associated with increased mortality and is therefore not routinely recommended (45). In one study, an addition 400 IU of vitamin E/day significantly increased risk of prostate cancer (46). Vitamin E interferes somewhat with vitamin K metabolism and therefore increases bleeding risk for patients on anticoagulants or platelet-inhibiting drugs. Supplementation is currently recommended for some patients with non-alcoholic fatty liver disease (47) and in combination with zinc for treatment of age-related macular degeneration (48). Its potential role in treatment of cancer, type 2 diabetes, and Alzheimer’s disease is also being investigated (49). No clear benefit has been established for its use in CVD.

Vitamin K

Vitamin K refers to a group of compounds including phylloquinone and menaquinones that are essential in the production of prothrombin; clotting factors VII, IX, and X; and proteins C and S. Vitamin K appears to have other functions as well, particularly related to bone and kidney metabolism. Limited amounts of vitamin K are stored in the body, but it can be recycled via the vitamin K-epoxide cycle (49). Of interest, high doses of vitamins A and E may decrease vitamin K absorption and activity. The AI for an adult male is 120 mcg/day and for an adult female is 90 mcg/day. An estimate of paleolithic intake is not available. There is no particular toxicity associated with high-dose vitamin K. The vitamin is abundant in green leafy vegetables, cruciferous vegetables, and parsley; additionally, production of menaquinone by intestinal bacteria is another important source (50).

Deficiency of vitamin K, such as that induced by oral anticoagulant treatment, results in coagulopathy. Warfarin blocks an enzyme used to recycle vitamin K, thereby depleting the body’s stores. Warfarin-induced coagulopathies can often be reversed by vitamin K supplementation. Newborns, who are particularly susceptible to deficiency due to a lack of intestinal flora, receive a prophylactic parenteral

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dose soon after birth. Vitamin K is a cofactor for some proteins involved in bone mineralization, thus prompting interest in its potential role in osteoporosis treatment; however, studies show conflicting results (51,52).

VITAMIN-LIKE SUBSTANCES

Certain organic nutrients have vitamin-like properties, but do not meet full criteria for classification as vitamins (due to endogenous production in the body or no known deficiency syndrome, for instance). Nonetheless, the nutrients listed here play essential roles.

Choline

Choline is a water-soluble amine that functions as a precursor to key components of the cell membrane as well as the neurotransmitter acetylcholine and other cell signaling molecules. It also is vital to lipid transport and metabolism, homocysteine metabolism, and methylation reactions for gene expression (53). Although humans can synthesize choline endogenously in the presence of adequate supplies of serine, methionine, vitamin B_{12}, and folate, the Institute of Medicine Food and Nutrition Board (FNB) established a recommended AI of 550 mg/day for adult males, 425 mg/day for adult females, 450 mg/day during pregnancy, and 550 mg/day during lactation. Increased demand during pregnancy and lactation is due to its critical role in brain development; low maternal choline intake was associated with higher risk of neural tube defects (54). The upper limit of intake is 3.5 g/day due to a hypotensive effect seen with higher doses (53). Choline is widely distributed in the food supply though is most concentrated in animal products, including liver, eggs, and beef. Choline deficiency is known to cause nonalcoholic fatty liver disease and muscle damage (55). Potential utility of supplementation in treatment of CVD and Alzheimer's disease is being investigated; a large prospective trial showed higher dietary consumption of choline was associated with an increased risk of all-cause and CVD-associated mortality (56).

Taurine

Taurine, an amino acid, functions in a variety of metabolic activities, including neuromodulation, stabilization of cell membranes, and osmotic regulation. Its influence on osmotic regulation, which occurs primarily in the brain and kidneys, can be beneficial in epilepsy, congestive heart failure, hypertension, and diabetes (57). It is required for the production of certain bile salts. Taurine is not considered an essential nutrient because it can be synthesized from cysteine or methionine. However, because dietary taurine is thought to be essential during infant development, taurine is currently added to all infant formulas. Taurine is relatively abundant in meat and seafood. There is no clear evidence of a deficiency syndrome or evidence of toxicity associated with high doses; nevertheless, it should be used with caution in patients with a history of hemostatic disorders. Animal studies have suggested a link between low dietary taurine intake with obesity (58), and other studies are investigating its potential in treating complications of diabetes (59) and CVD (60).

l-Carnitine

L-Carnitine is a nitrogenous compound synthesized from lysine and methionine in the liver and kidney (its enantiomer, d-carnitine, is toxic and is not naturally occurring in humans). It functions in transesterification reactions and in the transport of long-chain fatty acids into mitochondria; due to this important role in energy production, it is highly concentrated in skeletal and cardiac muscle (61). Endogenous synthesis is adequate in children and adults—thus there is no RDA—though may be low in

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infants, particularly those born prematurely. Supplementation therefore becomes important for premature infants. Certain drugs, including valproic acid, and stress states associated with sepsis, trauma, and organ failure can require increased demand for carnitine as demonstrated in humans and animals (62–64). L-Carnitine is abundant in meats, especially red meat, and dairy products.

Deficiency in humans has been established, generally resulting from inborn errors of metabolism or end-stage renal disease. Deficiency is predominantly manifest as muscle weakness, cardiomyopathy, and hypoglycemia. Supplementation is inconsistently beneficial in deficiency syndromes, including in patients on hemodialysis (65). Due to its predominance in skeletal muscle, research has examined the effects of L-carnitine supplementation on athletic performance; however, no consistent benefit has been shown (66).

Inositol

Inositol is an alcohol, structurally similar to glucose. It functions as a constituent of phospholipids in biologic membranes and has been found to be essential for the replication of many human cell lines. It also functions as an insulin sensitizer. To date, human deficiency has not been established. Inositol is found in cereal grains and can be synthesized from glucose. Research so far suggests a potential role in treatment of depression (67), insulin resistance in polycystic ovarian syndrome (PCOS) (68), and cancer (69).

Bioflavonoids

Bioflavonoids are water soluble polyphenol compounds responsible for the bright colors of fruits and vegetables, as well as beverages such as tea and wine. Important in various aspects of plant physiology, they are believed to have a wide variety of therapeutic uses in humans as well due to antioxidant, anti-inflammatory, and anti-angiogenic properties (70). Of particular interest is their potential to protect against CVD and dementia, due to anti-atherosclerotic properties identified in in vivo studies (71). Thousands of bioflavonoids have been discovered, and are divided into four main groups: flavones, found in green vegetables, onions, and berries; flavanones, found in citrus fruit and peels; catechins, found in red wine and tea; and anthocyanins, found in dark red or blue fruits such as berries and grapes (71). A deficiency has not been defined in humans. Evidence of health benefit from this class of antioxidants is accumulating (see Chapters 7, 39, and 45).

Alpha-Lipoic Acid

Alpha-lipoic acid (not to be confused with alpha-linolenic acid, the omega-3 fatty acid) is an endogenously produced compound that functions as a coenzyme in energy metabolism. It is known for its antioxidant and insulin-mimetic properties and therefore, has generated interest in treatment of complications of diabetes (72). Specifically, alpha-lipoic acid was found to improve symptoms of diabetic neuropathy (73,74). Studies examining anti-hyperglycemic effects are also promising (75). Lipoic acid is also being investigated for its potential to treat multiple sclerosis (76). It is present in low levels in a variety of fruits vegetables, as well as red meat. A deficiency state is only known in rare, inherited mutations of its biosynthetic pathway (77).

Coenzyme Q (Ubiquinone)

Coenzyme Q refers to a group of lipid-like compounds, structurally related to vitamin E. Coenzyme Q_{10}, the group member of greatest interest to date, is the variety native to human mitochondria and functions in the electron transport chain. It also functions as an antioxidant in cellular membranes. The highest cellular

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concentration of ubiquinone is in the inner membrane of the mitochondrion. Due to its role in energy metabolism, the highest tissue concentrations of ubiquinone reside in the heart, liver, and kidneys. Coenzyme Q10 is endogenously synthesized but is also widely distributed in the food supply. Rare genetic mutations preventing adequate endogenous production can lead to deficiency; tissue concentrations are observed to decrease with age, though clinical relevance of this is uncertain (78). Interest in the potential benefits of higher doses than are generally provided by diet is considerable (see Appendix E). Of particular interest is its therapeutic potential related to atherosclerosis and CVD. A randomized, double-blind trial found long-term supplementation in heart failure patients to reduce symptoms and decrease all-cause mortality and cardiovascular events (79). The role of coenzyme Q10 in counteracting statin-associated muscle symptoms has also been evaluated. Statin drugs and some beta-blockers, including propranolol, can reduce endogenous production of ubiquinone by as much as 40% (36). There are limited studies demonstrating the efficacy of coenzyme Q10 supplementation with statin use; the American Heart Association does not currently recommend its use for statin-associated muscle symptoms (80). Studies are also examining the role of coenzyme Q10 supplementation in migraine treatment, type 2 diabetes prevention, and perioperatively during coronary angioplasty (78).

ANTIOXIDANTS

Multiple epidemiologic studies have demonstrated that diets with high amounts of fruit, vegetables, and nuts reduced the risk of developing multiple chronic conditions, including cancer, CVD, and chronic obstructive pulmonary disease (COPD). Specifically, antioxidant nutrients within these food sources, including vitamin C, vitamin E, carotenoids, flavonoids, and selenium, impede atherogenesis and carcinogenesis by preventing oxidative damage of DNA, lipids, and proteins. Several observational studies have shown that patients with high occurrence of CVD, cancer, and COPD usually have decreased plasma levels of several antioxidants. However, multiple prospective studies have not clearly demonstrated a decreased risk of CVD, cancer, or COPD, with supplementation of either a single or combination of antioxidant nutrients (81,82). Of note, the Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group in 1994 showed that vitamin E supplementation was associated with an increase in hemorrhagic stroke mortality, and beta-carotene was associated with increased incidence of cerebral hemorrhage (83). A meta-analysis conducted in 2007 actually showed that treatment with high dose beta-carotene, vitamin A, and vitamin E may increase mortality (84). While intake of antioxidants from a diet with ample fruits and vegetables is encouraged, additional antioxidant supplementation is not recommended for prevention of chronic disease in the general public.

MINERALS AND TRACE ELEMENTS

Although the term *mineral* is often applied to essential dietary inorganic elements, some of this group are not minerals, and elements is the proper designation. Nonetheless, those elements found most abundantly in human tissue are minerals and, given their abundance, are referred to as dietary macrominerals. They include calcium, phosphorus, magnesium, potassium, sodium, chloride, and sulfur. These substances are present in the body in amounts above 100 mg, up to as much as hundreds of grams. In contrast, trace elements are present in the body in milligram or even microgram quantities. Trace elements essential to human health include iron, copper, zinc, cobalt, molybdenum, selenium, manganese, iodine, chromium, fluoride, silicon, nickel, boron, arsenic, tin, and vanadium.

Macrominerals

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Calcium

Healthy adults store more than 1 kg of calcium in the body, predominantly in bones and teeth. Calcium, a vital structural component of the skeleton, is essential for muscular contraction and participates in a variety of other biologic processes, including coagulation. Adequate calcium intake has many health benefits including lower cholesterol values, improved blood pressure, reduced risk of hypertension disorders in pregnancy, prevention of osteoporosis and colorectal adenomas (85). Calcium deficiency results in osteopenia, with the skeletal depot serving to maintain serum levels under most circumstances. The RDA for calcium varies throughout the life cycle, with peak requirements in adolescents and the elderly; 1,200 mg/day is adequate for most adults. During pregnancy and lactation, the RDA for calcium is 1,300 mg/day for 14- to 18-year-old women, and 1,000 mg/day for 19- to 50-year-old women (86). The U.S. Preventive Task Force (USPSTF) reports that current evidence is insufficient to estimate the balance of benefits and harms in recommending supplementation with doses greater than 1000 mg of calcium in community dwelling postmenopausal women for prevention of fractures (87). Paleolithic intake is estimated to have been nearly 2 g/day, more than twice the typical intake in the United States. Excessive intake accompanied by vitamin D supplementation may lead to dyspepsia, constipation, soft tissue calcification, and hypercalcemia, although these outcomes are not associated with high intake from whole-food sources. Associations between calcium supplementation and increased cardiovascular risk have been suggested, however current evidence is inconclusive (88). Supplementation of greater than 500 mg/day should be divided due to a plateau in calcium absorption. Further, high protein intake can cause hypercalciuria due to decreased renal calcium reabsorption, and will require increased calcium intake (89). Dairy products, including milk, cheese, and yogurt, are the best dietary source of readily bioavailable calcium, providing approximately 300 mg/serving. Other sources of calcium include dark green vegetables, nuts, breads, and cereals.

Phosphorus

Phosphorus is an essential mineral and primarily incorporated along with calcium into the hydroxyapatite of bones and teeth. Phosphorus also functions in the synthesis of nucleic acids and phospholipids and in the formation of high-energy phosphate bonds in Adenosine triphosphate (ATP). Like calcium, the RDA for phosphorus varies throughout the life cycle, with a peak requirement of 1,250 mg/day in adolescence, pregnancy and lactation and 700 mg/day for most adults (90). Phosphorus deficiency is rare but can occur in patients with chronic alcoholism or those recovering from diabetic ketoacedosis. Symptoms of deficiency include muscle weakness, paresthesias, ataxia, confusion, seizures, hemolytic anemia, and impaired white blood cell function. Paleolithic intake has not been estimated but likely corresponds with the higher calcium intake. Excess dietary phosphorus, exceeding the calcium intake by more than twofold, can lead to hypocalcemia, secondary hyperparathyroidism and is a serious complication in patients with chronic kidney disease. Hidden phosphate additives in processed foods and carbonated beverages are estimated to contribute 10% to 50% of phosphorus intakes in Western countries and should be considered in patients needing to eat a low phosphate diet (91). Food sources of phosphorus include dairy products, meats and poultry, fish, eggs, nuts, legumes, vegetables, and grains.

Magnesium

Magnesium is an essential mineral which plays an important role in over 600 enzymatic reactions. The 20 to 30 g of magnesium stored in an adult body are principally in bone and muscle. Magnesium has an

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important physiological role, particularly in the brain, heart, and skeletal muscles. It is involved in hormone receptor binding, calcium channel gating, cellular membrane function, neuronal activity, muscular contraction and excitability (92–94). Magnesium is used therapeutically as an antiseizure and an antihypertensive agent during eclampsia and preeclampsia, and a tocolytic during labor. It has been shown to be beneficial for treating acute myocardial infarctions by providing protection against ischemia, reperfusion injury, and arrhythmias, while also improving contractility in stunned myocytes. A typical DI of 3.6 mg/kg is necessary to maintain magnesium balance in the human body. The average dietary intake (ADI) for adults is between 320 to 420 mg/day. It is estimated that 60% of adults do not achieve the ADI and 45% of Americans are magnesium deficient. Magnesium deficiency has been attributed to diet, medications (diuretics, proton-pump inhibitors), and farming techniques. The estimated mineral content of vegetables has declined approximately 80% to 90% over the last 100 years (95). Magnesium deficiency can cause a systemic stress response through neuroendocrinological pathways as well is linked to inflammation resulting in pro-atherogenic changes in the metabolism of lipoproteins, endothelial dysfunction, and high blood pressure. Severe deficiency, generally the result of malabsorption, diabetes, or alcoholism, is manifest as anorexia, irritability, psychosis, and seizures. Accumulating evidence suggests that chronic mild magnesium deficiency may contribute to the development of diabetes, asthma, preeclampsia, rheumatoid arthritis, metabolic syndrome, atherosclerosis, coronary artery disease, cardiac arrhythmias, and sudden cardiac death (96,97). Adults with higher risk of deficiency due to diet or medical conditions may benefit from magnesium supplementation. In people with normal kidney function, supplements are generally tolerated in doses below the upper tolerable limit of 350 mg/day. Higher doses can cause gastrointestinal upset which acts as a limiting factor in the amount that can be consumed and prevents reaching toxicity levels. Changes in the serum magnesium concentration occur within weeks of initiation of supplementation (98). Excess intake of magnesium appears to be dangerous only in individuals with impaired renal function; toxicity is manifest as nausea, vomiting, and hypotension. Severe hypermagnesemia is life threatening. Higher serum magnesium levels can cause neuromuscular dysfunction, including drowsiness or even respiratory dysfunction. Severe hypermagnesemia may also lead to bradycardia, complete heart block, atrial fibrillation, and asystole (94). There are no reported cases of hypermagnesemia from food alone (98). Paleolithic intake has not been estimated. Dietary sources of magnesium include green vegetables, grains, beans, and seafood.

Potassium

Potassium is the principal cation of the intracellular space. It functions in osmotic regulation, acid–base balance, and muscle cell depolarization. The cardiac muscle is particularly sensitive to potassium concentrations. Dietary deficiency of potassium is uncommon, but conditions producing fluid shifts, such as surgery, or metabolic imbalances such as diabetic ketoacidosis, can produce life-threatening derangements of the serum potassium. Potassium deficiency manifests with constipation, muscular weakness, paralysis, and confusion. Deficiency is usually associated with increased gastrointestinal or urinary losses, most commonly due to vomiting diarrhea, laxative abuse, or diuretics. High potassium intake has been shown to reduce blood pressure, decrease the risk of developing CVD, and mitigate the adverse effects of salt on blood pressure (99). High dietary potassium intake is not associated with toxicity when renal function is normal. Currently there is insufficient data to derive an RDA for potassium. The recommended intake of 2.6 to 3.4 gm/day for adults is based on an Adequate Intake (AI), a level which is assumed to ensure nutritional adequacy based on the highest median potassium intakes in healthy children and adults (100).

Paleolithic intake is estimated to have been more than 10 g/day, exceeding current intake levels by a

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factor of four. Potassium is abundant in grains, legumes, vegetables, and fruits. Apricots, prunes, raisins, lentils and acorn squash are particularly good sources.

Sodium

Sodium is the major extracellular cation. The body of an adult stores approximately 100 g of sodium; more than half is in the extracellular space, and much of the remainder is in bone. Sodium functions to regulate the distribution of water in the body, regulate acid–base balance, and maintain transmembrane potential. Sodium deficiency, which results in hyponatremia, causes weakness, fatigue, anorexia, and confusion; if severe, hyponatremia can cause seizures and be life threatening.

There is no RDA for sodium. A minimum average requirement of 115 mg for adults is thought to be essential, but due to wide variation of physical activity patterns and climatic exposure, a minimum intake of 500 mg/day is advised (101). Intake should be limited to not more than 2,300 mg/day; typical DI in the United States is nearly 3,400 mg (102). High dietary salt adversely affects vasculature, heart, kidneys, skin, brain, and bone through heightened inflammation and oxidative stress (103). Reduced dietary sodium decreases the risk of CVD events and mortality (104). Paleolithic intake of sodium is estimated to have been less than 1,000 mg/day. Of note, the sodium intake was approximately 7 times lower the potassium in the prehistoric diet of humans whereas the sodium intake in the modern diet is about 3 times higher than the DI of potassium (105). Sodium is abundant in foods of animal origin, but it is present in the food supply principally as a seasoning or preservative added to processed foods.

Chloride

Chloride is distributed with sodium in the extracellular fluid, where it functions to maintain fluid and acid–base balance. Chloride plays an essential part in digestion as a constituent of hydrochloric acid in the stomach. Chloride deficiency does not generally occur under normal circumstances, but it can accompany sodium deficiency in the context of volume depletion or result from metabolic derangements. Chloride deficiency results in alkalosis and impaired cognition. The RDA for chloride has not been established; dietary deficiency is not considered a health threat. Chloride toxicity has not been reported. Paleolithic intake has not been estimated to date, but it likely corresponds to the lower sodium intake. Dietary chloride is derived largely from table salt or sea salt as sodium chloride. Food sources include seaweed, rye, tomatoes, lettuce, celery, olives, and other vegetables (106).

Sulfur

Sulfur is present in all cells, principally as a component of the amino acids cystine, cysteine, methionine, and taurine. Cysteine is the rate-limiting substrate in glutathione synthesis, which is an antioxidant and involved in drug metabolism. Sulfur functions in collagen synthesis and in energy transfer. A deficiency syndrome has not been described. Sulfur is derived in the diet from the amino acids in which it is incorporated; therefore, intake corresponds with the quality and quantity of protein intake.

Trace Elements

Iron

Iron is a vital mineral for humans. Most of the 3 to 4 g in the body is stored in red blood cells. The primary function of iron is to transport oxygen as a component of hemoglobin. Iron is also incorporated in myoglobin and plays a crucial role in oxidative metabolism, cellular proliferation, and many catalytic reactions. The amount of iron in the human body needs to be maintained within the ideal range to be

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beneficial and therefore the amount of iron absorbed by the intestine is tightly controlled to balance the daily losses (107).

Iron deficiency manifests in sequence as depleted ferritin, impaired erythropoiesis, and then microcytic hypochromic anemia, and it develops over time because of blood losses or inadequate intake. Iron deficiency is associated with impaired immunity, impaired cognition and learning difficulties in children, and is the most common nutritional deficiency worldwide. Behavioral symptoms of iron deficiency include apathy, lethargy, and pica. Toxicity from dietary iron in healthy individuals is virtually unknown, although a role in oxidative injury to cells has been proposed. Iron supplements can be lethal at a doses of 36 to 443 mg in children and 60 mg/kg in adults. In individuals with hemochromatosis, a genetic disease resulting in enhanced iron absorption, iron accumulates to toxic levels, producing multiorgan system failure.

The RDA for iron is 8 mg/day for adult males and 18 mg/day for adult females, with variations over the life cycle. During pregnancy the RDA for iron is 27 mg/day, and during lactation is 9 mg/day (108). Paleolithic intake is estimated to have been nearly 90 mg/day, which is sixfold to ninefold higher than the RDA. Iron is absorbed in the upper small intestine. Absorption is enhanced by ascorbic acid and impaired by fiber, phytates, and oxalates in plant foods. Heme iron in meat, poultry and seafood is more readily absorbed than nonheme iron in plants which is why the RDAs for vegetarians are 1.8 times higher than for people who eat meat. Good sources of heme iron include beef, lamb, liver, poultry and seafood. Beans, peas, broccoli, nuts and seeds, and green leafy vegetables are good sources of nonheme iron.

Copper

The store of copper—approximately 50 to 120 mg—in an adult body functions in at least 15 enzyme systems. Copper is a cofactor for enzymes (known as “cuproenzymes”) involved in oxidation and energy production. Copper also participates in enzymes influencing immune cell function, collagen and elastin synthesis, iron metabolism and neurotransmitter generation. Dietary intake of copper generally readily exceeds requirements, and deficiency is rare. However, deficiency may occur in premature infants, and patients with malabsorption from celiac disease, cystic fibrosis, or Crohn’s disease. Copper deficiency may also occur in patients with nephrotic syndrome, prior gastric bypass surgery (109). Manifestations of copper deficiency include abnormal hair, skin depigmentation, myeloneuropathy, microcytic hypochromic anemia, neutropenia, and bone demineralization.

Excess zinc intake of approximately 60 mg/day or higher, which may occur with supplementation for treatment of the common cold and other conditions, can chelate ingested copper, prevent its absorption, and consequently cause deficiency (109–111). The RDA for copper is 900 mcg/day for adults. An estimate of paleolithic intake is not available.

Copper toxicity from whole-food ingestion is unknown. However, copper toxicity has been reported in people who consume water containing high levels of copper as a result of stagnant water in copper-containing pipes and fixtures and from copper alloys in water distribution systems and household plumbing. The tolerable upper intake level is 10 mg for adults (112). Copper toxicity symptoms include vomiting, diarrhea, and liver damage. Severe neurocognitive effects of copper toxicity are seen in Wilson’s disease, a recessive genetic defect in copper metabolism. Good sources of copper include shellfish, chocolate, shiitake mushrooms, legumes, nuts, seeds, and liver.

Zinc

Zinc is an essential micronutrient for human beings. The amount of zinc stored in the adult human body, approximately 2 to 2.5 g, resides primarily in bone, but it is distributed to all body tissues. Zinc functions

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in nearly 100 enzyme systems, plays prominent roles in CO2 transport and digestion, antioxidant processes and maintaining protein structure and nuclear stability. Zinc also influences DNA and RNA synthesis, immune function, collagen synthesis, olfaction, and taste. Zinc deficiency can manifest as anorexia, impaired growth and sexual maturation, impaired immune function and wound healing, skin lesions, impotence, hypogonadism, oligospermia, alopecia, night blindness, and ageusia. Dermatologic changes associated with zinc deficiency primarily manifest in the extremities or around body orifices.

Although overt deficiency is rare in the absence of malnutrition, mild deficiency may be prevalent in the United States, particularly among the elderly. Zinc absorption can be impaired in alcoholism, gastrointestinal diseases such as ulcerative colitis and Crohn's, as well as chronic liver and renal disease, sickle cell disease, diabetes and malignancy. Vegetarians, and pregnant and lactating women are also at risk for deficiency. Dietary phytate, a natural chelator of zinc ions that is present in corn, rice and cereals, can result in deficiency (113). Prior paragraph includes symptoms of deficiency, this is redundant. The RDA for zinc is 11 mg/day for adult males and 8 mg/day for adult females (114). Paleolithic intake is estimated to have been three to four times the RDA. High-dose zinc supplementation can result in vomiting; over time, zinc supplementation can interfere with copper metabolism. Therefore, the established tolerable upper intake level is 40 mg/day but higher doses may be used for medical treatment with physician supervision. Zinc supplements, including intranasal zinc, have been associated with anosmia (115). Zinc is found in meat, shellfish (especially oysters), legumes, nuts, and, to a lesser extent, grains.

Cobalt

Cobalt is an integral component of vitamin B12, and a normal adult body contains approximately 1 mg of the element. Toxicity, manifesting as cardiomyopathy, has been observed in heavy drinkers of beer to which cobalt was added to improve foaming. There is no RDA for cobalt. Seafood represents the best dietary source.

Molybdenum

Molybdenum is an essential trace mineral stored in the liver, kidneys, adrenal glands, and bones in the form of molybdopterin. It is a component of several enzyme systems that function in uric acid formation and in fluoride, iron, copper, and sulfur metabolism. Deficiency under natural conditions is unknown, but it has been observed in individuals with inborn errors of metabolism and following long-term total parenteral nutrition lacking the element. Manifestations of deficiency are principally neurocognitive, including irritability and eventually coma. The recommended DI for adults is 45 mcg (116). An estimate of paleolithic intake is not available. Toxicity occurs at intakes in the range from 10 to 15 mg/day and has been associated with aching joints, gout-like symptoms, hyperuricosuria, and elevated blood molybdenum (117). High intake of molybdenum interferes with copper metabolism and possibly copper absorption and has been used clinically to treat Wilson disease. Molybdenum is found in legumes, liver, dairy products, leafy vegetables, cereal, and grains; concentration in food varies with concentration in soil.

Selenium

Selenium is a trace mineral stored in the thyroid gland and muscle tissue. It is a constituent of glutathione peroxidase, an important antioxidant, and enzyme systems involved in reproduction, thyroid hormone and DNA synthesis. Severe selenium deficiency is associated with two diseases endemic to areas of China with low soil selenium content: Keshan disease is a type of cardiomyopathy, and Kashin–Beck syndrome is a form of osteoarthritis. Selenium deficiency in the United States is rare. Low selenium intake,

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however, is suspected to increase the risk of certain cancers, neurogenerative diseases, cardiovascular disorders and infectious disease. There is clinical evidence that selenium supplementation can delay CD4 decline in HIV-infected patients, thus prolonging the onset of AIDS (118). The RDA is 55 mcg/day for adults and 20 to 40 mcg/day for children (119). Estimates of paleolithic intake of selenium have not been reported.

Toxicity can occur at high doses (well above 200 mcg/day) and manifests as nausea, diarrhea, fatigue, neuropathy, loss of hair and nails, respiratory distress, tremors, kidney or cardiac failure, and, in rare cases, death. Selenium is widely distributed in the food supply, with concentrations varying with soil content. In the United States, selenium content in the soil is lowest in the Northwest, Northeast, Southeast, and areas of the Midwest abutting the Great Lakes (120). Dietary sources of selenium include Brazil nuts, young barley seedlings, green vegetables, shiitake mushrooms, fish, seafood, beef and poultry that consume selenium containing plant-based foods in areas with adequate selenium in the soil.

Manganese

Approximately 12 to 20 mg of manganese is stored in the body of an adult, with most found in bone, liver, and the pituitary gland. Manganese is concentrated in mitochondria. It functions as a cofactor for numerous enzyme systems involved in amino acid, cholesterol, glucose, and carbohydrate metabolism as well as reactive oxygen species scavenging, bone formation, reproduction, and immune response. In conjunction with vitamin K, manganese also plays a role in blood clotting and hemostasis. Manganese deficiency has not been observed in humans under natural conditions and signs and symptoms of deficiency have not been clearly defined. The RDA has not been established, but 1.8 to 2.3 mg/day is recommended as AI for adults (121). Estimates of paleolithic intake have not been reported. Toxicity due to ingestion is rare; dementia and psychosis have been seen in manganese miners with heavy inhalation exposure. Manganese absorption is increased in iron deficiency, formula feeding, biliary obstruction, and long-term total parenteral nutrition. Dietary sources of manganese include legumes, nuts, grains, shellfish, coffee and tea.

Iodine

The adult body contains approximately 20 to 50 mg of iodine, virtually all of which is incorporated into thyroid hormones (thyroxine and triiodothyronine). Iodine deficiency, common in regions with low soil iodine and lack of food supply fortification, results in endemic goiter. Maternal iodine deficiency during pregnancy and deficiency in infancy are associated an increased risk of pregnancy loss and infant mortality, neonatal hypothyroidism, cretinism, and neuropsychomotor retardation (122). Dietary pattern can influence susceptibility to goiter. Iodine metabolism is impeded in people with iodine deficiency by goitrogens contained in soy, cassava, and cruciferous vegetables such as broccoli, cauliflower and cabbage.

The RDA is 150 mcg/day for adults, 220 mcg/day during pregnancy, and 290 mcg/day during lactation. In the United States, this level is met through fortification of salt. Paleolithic intake of iodine has not been reported. Dietary iodine intake in excess of the RDA is rarely toxic. Prolonged supplementation exceeding 1100 mcg/day can cause a paradoxical effect with symptoms similar to iodine deficiency including goiter, elevated thyroid stimulating hormone (TSH) levels, hypothyroidism, thyroiditis, and thyroid papillary cancer (123). Acute toxicity can cause burning of the mouth, throat, eye irritation, acneiform skin lesions, cough, gastric upset, diarrhea, and depression (124). Seaweed, fish, and shellfish are good sources of iodine, although fortified salt is the most reliable dietary source.

Chromium

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The adult body contains 6 to 10 mg of chromium that is widely distributed throughout the body. The principal function of chromium is as a component of glucose tolerance factor, a complex that apparently facilitates binding of insulin to its receptors. Chromium supplementation may be of therapeutic benefit in insulin resistance (see Chapter 6). Chromium also functions in macronutrient oxidation and lipoprotein metabolism. Deficiency is associated with glucose intolerance, peripheral neuropathy, and, if severe, encephalopathy. Absorption in the small intestine is decreased with higher levels of zinc and iron. In contrast, vitamin C has been shown to increase chromium uptake. The RDA for chromium has not been established, but the FNB has advised an intake of 25 to 35 mcg/day for adults. Estimates of paleolithic intake of chromium have not been reported. Toxicity from dietary sources is unknown primarily because of poor oral bioavailability. Food sources include brewer's yeast, eggs, beef, cheese, grains, and fresh vegetables and fruits.

Fluoride

An adult body contains less than 1 g of fluoride, virtually all of which is in the bones and teeth. Definitive evidence that fluoride is an essential nutrient is lacking, but a role for fluoride in preventing dental caries and strengthening bone is well established. Fluoride deficiency is associated with increased susceptibility to dental caries and osteoporosis. The RDA has not been established, but a daily AI range from 3 to 4 mg/day for adults is recommended (125). The recommended intake for infants and children ranges from 0.01 to 3 mg/day, depending on age and weight. These recommendations are also based on the level of fluoridation of the drinking water. Children should not receive additional fluoride supplementation if the fluoride level in the drinking water is greater than 0.7 mg/L (126). In developed countries, fluoride intake and urinary excretion is no longer dependent on the level of drinking water fluoridation as fluoride toothpaste comprises a significant proportion of ingested fluoride (127). Estimates of paleolithic intake have not been reported.

Fluoride intake in the range of 2 to 8 mg/kg/day in childhood can produce mottling of the teeth known as fluorosis. Intake of 40 to 65 mg/day in adults can cause lower extremity pain and stress fractures. Prolonged high intake of 10 mg/day for 10 or more years can cause skeletal fluorosis which presents as joint stiffness and pain, followed by osteosclerosis, muscle wasting, and neurological defects (128). Acute fluoride toxicity can cause gastrointestinal disturbances like pain, nausea, vomiting, and diarrhea. Severe cases may progress to renal and cardiac dysfunction, which can ultimately lead to death. Fluoride is ubiquitous in the food supply, but in very small amounts, varying with the concentration in soil and ground water. The principal source in the Unites States is supplemented water supplies.

Silicon

Silicon is present in all tissues in trace amounts, functioning in calcification, cell growth, and mucopolysaccharide formation. Deficiency in humans has not been established. There is no RDA, and optimal intake is unknown. Good dietary sources include barley and oats.

Nickel

Approximately 10 mg of nickel is widely distributed in the adult body. Nickel appears to play a role in nucleic acid metabolism. A deficiency state in humans has not been elucidated, although deficiency is well established in animal models. An RDA for nickel has not been established. The tolerable upper intake level for adults is 1 mg/day. Adverse effects include nausea, vomiting, abdominal pain, and diarrhea. Larger quantities of nickel might increase the risk of lung, nose, larynx, and prostate cancers as

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well as variable degrees of kidney, liver, and cardiovascular system toxicity (129). Nickel is found in chocolate, nuts, seeds, beans, fruits, vegetables, seafood, eggs, and milk.

Boron

Boron is a trace mineral that has not been classified as an essential nutrient because research has not yet clearly identified the biological functions in humans. Boron is thought to influence calcium and estrogen metabolism, vitamin D inactivation, and, consequently, to play a role in bone mineralization. Boron may also function in cell membrane formation and brain function. An overt deficiency state has not been defined, but low levels are associated with osteoporosis and impaired brain function (130). An RDA has not been established, but the World Health Organization (WHO) estimates an acceptable safe range intake of 1 to 13 mg/day for adults (131). The tolerable Upper Intake Level (UL) is 20 mg/day for adults. Symptoms of acute toxicity include nausea, vomiting, diarrhea, dermatitis, and cognitive impairment (132). Boron is found in beans, nuts, vegetables, beer, and wine.

Arsenic

The adult body is thought to contain approximately 20 mg of arsenic, widely distributed in all tissues and concentrated in skin, hair, and nails. Several animal studies have demonstrated that arsenic may be essential for amino acid metabolism and regulation of gene expression; however, clear evidence for its importance in human nutrition is lacking (133,134). No RDA exists, but an intake of 12 to 25 mcg/day is thought to be appropriate for adults. Toxicity from food sources is unknown; arsenic toxicity results from ingestion of concentrated arsenic or industrial exposure and has become a known problem in Bangladesh and West Bengal, India, where long-term ingestion of inorganic arsenic from drinking wells led to arsenicosis in hundreds of thousands. Manifestations of toxicity include a burning sensation in the mouth, abdominal pain, nausea, vomiting, and diarrhea, hypotension, shock, pulmonary edema, and heart failure. Hepatotoxicity and encephalopathy can occur with higher doses, and chronic arsenic exposure can cause multiple health consequences, including increased risk for developing multiple forms of cancer, diabetes, skin disease, and can interfere with the body’s endocrine system (135). Neurotoxicity from exposure in utero and in young children is associated with impaired intellectual development (136). There have been several reports demonstrating greater than expected amounts of arsenic in common food sources. Seafood is the richest source of dietary arsenic. Recent consumer reports have shown elevated arsenic levels in multiple food groups including various rice, cereal and fruit juice products. An analysis of 3,633 study participants found that on average, people who ate one rice food item had 44% greater total urinary arsenic levels and people who consumed two or more rice products had levels 70% higher levels compared to no rice consumed (137). There are also concerns that organic brown rice syrup, a common alternative sweetener to high-fructose corn syrup, may add significant amounts of arsenic into the diet. For instance, milk formula containing brown rice syrup was determined to contain arsenic concentrations greater than six times the safe drinking water limit (138). Another review examined the total arsenic in young chicken from data obtained by the Food Safety and Inspection Service from 1994 to 2000, and found arsenic levels in chicken that were three to four times greater than other meat sources. Therefore, average levels of arsenic intake may have been underestimated in people consuming mostly chicken (139).

Tin

Approximately 14 mg of tin is widely distributed in the tissues of adult humans, although none is found in brain tissue. Tin is thought to function in oxidation-reduction reactions, but its exact role is unknown. Tin

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is considered to be an ultratrace mineral, meaning the estimated dietary requirement is typically less than 1 mg/day (140). Tin deficiency in humans has not been elucidated. The RDA has not been established, and the range of optimal intake is unknown. Tin is thought to be minimally toxic, as it is poorly absorbed. Intake of food contaminated with large amounts of tin may cause gastrointestinal effects, including diarrhea, stomach pain, nausea, and anemia. Tin is widely distributed in the food supply, but in very small amounts. Dietary intake rises as much as 30-fold when food stored in tin cans is eaten frequently.

Vanadium

Approximately 100 to 200 mcg of vanadium is widely distributed in the tissues of adult humans. The element is concentrated in serum, kidney, liver, spleen, bones and adipose tissue. Vanadium appears to influence several important enzyme systems, including that of ATPase and enzymes associated with blood glucose regulation. Vanadium stimulates glycolysis via glucokinase and phosphofructokinase and may decrease gluconeogenesis by decreasing the activity of glucose-6-phosphatase. Due to its contributions to glucose regulation, vanadium is purported to have beneficial effects in patients with diabetes (141). Additionally, vanadium regulates lipid metabolism, including lowering triglycerides and total cholesterol and increasing high-density lipoprotein (HDL) (142). Deficiency in humans has not been established. There is no RDA, and optimal intake levels are unknown. The average diet provides 10 to 160 mcg of vanadium/day. Toxicity is low due to poor absorption, but inhalation of vanadium dust in industrial settings may lead to abdominal cramps, diarrhea, hemolysis, hypertension, and fatigue. Shellfish, mushrooms, grains, spinach and several spices, including pepper and dill, are relatively rich sources of vanadium.

Other

Restrictions of dietary cadmium, lead, and lithium have produced abnormalities in laboratory animals, but there is as yet no evidence of human requirements.

ESSENTIAL AMINO ACIDS

Dietary proteins are composed predominantly of a group of 20 amino acids. Of these, humans can readily synthesize 11. The remaining nine—histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, and valine—must be ingested to meet metabolic demand and therefore are referred to as essential (see Chapter 3). An absolute dependence on dietary histidine in adults is uncertain. Infants may also require dietary arginine. Cysteine and tyrosine are synthesized endogenously from methionine and phenylalanine, respectively, and therefore are semi-essential. The need for dietary intake varies inversely with the ingestion of their precursors.

The RDA for protein in adults has been established at or near 0.8 g/kg/day. Paleolithic intake is thought to have been much higher, in the range from 2.5 to 3.5 g/kg/day. Essential amino acid needs are met when protein of high biologic value is consumed. The four least abundant essential amino acids—lysine, methionine/cysteine, threonine, and tryptophan—are used to gauge the quality of dietary protein. Sources of high-quality protein include egg white, milk, meat, soybeans, beans, and lentils. These issues are addressed in more detail in Chapter 3.

ESSENTIAL FATTY ACIDS

The PUFAs required for normal metabolism that cannot be synthesized endogenously are essential dietary

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nutrients. Two such fatty acids, linoleic acid (C18, omega-6) and alpha-linolenic acid (C18, omega-3), are unconditionally essential, whereas arachidonic acid (C20, omega-6), which can be synthesized from linoleic acid, is essential when supplies of its precursor are deficient. Essential fatty acids participate in a wide variety of metabolic functions, including eicosanoid synthesis and biomembrane development.

Overt deficiency of essential fatty acids has not been observed in free-living adults, but its manifestations, including hair loss, desquamative dermatitis, and impaired wound healing, are known from cases of deficient parenteral nutrition. The RDA has not been established for essential fatty acids, but 1100 to 1600 mg/d is recommended as AI for adults (142). Of note, the omega-6:omega-3 ratio in the typical U.S. diet is more than 10:1, whereas the ratio estimated for the paleolithic diet is between 4:1 and 1:1. A high dietary omega- omega-6: omega-3 ratio is associated with an increased risk of CVD, cancer, inflammatory and autoimmune diseases, whereas a low omega-6:omega-3 ratio suppresses low grade inflammation and may benefit numerous chronic diseases (143,144).

Dietary sources of linoleic acid include most vegetable oils; evening primrose oil is a particularly rich source. Sources of alpha-linolenic acid include linseeds and flaxseeds and their oils, and marine foods, especially salmon, mackerel, sardines, scallops, and oysters. The omega-3 content of fish is derived from phytoplankton and algae, so farmed fish are generally lower in omega-3 than their free-living counterparts. For further details, see Chapter 2 and Appendix E.

MULTIVITAMINS

Multivitamin supplementation consists of taking a combination of vitamins and minerals at amounts greater than the level of recommended DI. U.S. nutrient intake is typically lower than recommended, and both caloric and nutritional intake decreases with age, and therefore, providing a strong rationale for recommending multivitamin supplementation. However, there has not been clear evidence for recommending multivitamin supplementation as a preventative measure. A randomized, double-blind, placebo controlled trial (“Physicians” Health Study II) showed daily multivitamin supplementation modestly but significantly reduced the risk of total cancer in men 50 years and older (145). However, a recent analysis of findings from 277 clinical trials using 24 different interventions concluded that multivitamins had no significant effect on mortality or CVD (146). Importantly, there have been studies suggesting that supplementation is not completely benign. The risks of high-dose antioxidant supplementation was discussed earlier, and another study demonstrated an increased in total mortality risk in older woman using dietary multivitamin supplements (147). Although specific nutrient supplementation may be indicated to prevent certain diseases, including osteoporosis in the elderly, multivitamin supplementation is primarily recommended for treating nutritional deficiency and not for specific disease prevention.

WHOLE-FOOD-BASED SUPPLEMENTS

Whole-food supplements are extracts from food sources that maintain the original context of nutrients found in food. These substances are more complex than vitamin supplements but can still be delivered in pill form. The extracts used to construct these supplements, consisting of variety of nutrients, enzymes, coenzymes, antioxidants, trace elements, and other factors, are expected to work synergistically as they do in their original food source toward providing the desired health benefits. For example, regular consumption of fruits and vegetables are beneficial for a several reasons including their antioxidant properties. However, vitamin C alone only accounts for 0.4% of the total antioxidant activity in an apple,

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and additional phytochemicals found in fruits may therefore be essential for providing the desired health benefits (148). There may even be harms to using single extracts rather than whole foods supplements. The SELECT trial showed significant increase in the risk of prostate cancer following long-term intake of vitamin E supplements (46). The CARET intervention was stopped 21 months early due to findings of excess lung cancer incidence and mortality amount participants receiving beta-carotene and vitamin A supplements (149). Newer studies are beginning to examine whole-food rather than single nutrient interventions for addressing etiologies and possible therapies for certain diseases. A whole-food intervention demonstrated that tomato sauce constituents significantly decreased leukocyte oxidative damage in patients with prostate cancer (150). Lycopene is considered the primary antioxidant constituent in tomato extracts and has shown to have antitumor effects; however, a study in rats demonstrated that whole tomato and broccoli interventions were superior in reducing tumor weight than lycopene alone (151). Whole-food-based supplementation may prove superior to conventional approaches to nutrient supplementation by preserving the native context of nutrients; research in this area is ongoing.

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Chapter 5

Diet, Weight Regulation, and Obesity

Scott Kahan

INTRODUCTION

When earlier editions of this text were written, the United States was the epicenter of a global obesity pandemic. Unfortunately, this is no longer the case, as much of the developed world has caught up, resulting in a widespread international pandemic with no clear epicenter (1,2). Driven in part by advances in food production that have made palatable, economical calories in excess of need readily available to almost the entire population almost all the time and by comparable advances in labor-saving technologies, obesity and overweight now engulf over two thirds of adults in the United States and one third of children and adolescents (3–6). With rates rising to unprecedented levels with each passing year, obesity is rightly referred to as an epidemic and is among the most poorly controlled and worrisome health threats facing the United States. Obesity is the major modifiable risk factor for type 2 diabetes (itself now epidemic) and a major contributor to most predominant causes of premature death and disability. Obesity has been linked to more than 200 diseases (7), including but not limited to diabetes, cardiovascular disease, numerous cancers, stroke, obstructive pulmonary disease, and degenerative arthritis. Secular trends are similar in most other developed countries. Cultural transitions in developing countries are associated with a rapid rise in the rate of obesity as well, even while historical public health scourges such as microbial diseases persist. Obesity thus constitutes a global health crisis. At the International Congress on Obesity in Sydney, Australia, in September 2006, it was announced that for the first time in history, the planetwide population of overweight (over 1 billion) outnumbered the "undernourished" (roughly 600–700 million) (8).

The investigation of obesity rightly subsumes metabolism, genetics, endocrinology, psychology, and even newly emerging disciplines such as nutrigenomics, but it must be conceded that human physiology is much the same as it ever was and thus cannot house the explanation for suddenly skyrocketing obesity rates. That answer likely resides in an environment that is not the same as it was before, rendering human adaptations to a world of caloric scarcity and a high demand for physical exertions largely obsolete. In short, our patients (and we) are gaining weight in record numbers for the simple reason that they (and we) can do so—for the first time in history. It is scarcely an exaggeration to say that human intelligence, since it first evolved, has been dedicated to making obesity possible by establishing a reliable supply of palatable food and by inventing technologies to reduce the physical ardors required for survival. We have become victims of our own resourcefulness and success.

But while accounting for the obesity epidemic may be straightforward, reversing it will be anything but easy, requiring a comprehensive holistic approach involving policy, population health, and clinical medicine. Recognizing the complexity of the disease should not be a barrier that paralyzes meaningful actions. The role of clinicians in contending with this challenge is itself a subject of debate. The US Preventive Services Task Force (USPSTF) recommends that although behavioral counseling has small-to-moderate benefits in improving diet, such counseling should be done in selected patients rather than

routinely (9).
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Being less bound by the constraints of applied evidence, if no less respectful of them, the potential fallacy allowing the complexity of obesity to create hopelessness and cripple action can be pointed out. An analogy best serves.

Imagine that a landslide traps a hiker behind a mound of boulders. Then imagine that rescue workers each try, one at a time, to move the boulders. Because no one of them can do so, the conclusion is reached that efforts to move boulders are probably futile and best abandoned. Or, minimally, the evidence may be insufficient to recommend for or against attempts to move boulders. This tack abandons the hiker to their fate as well, of course.

The fallacy here is that while no one person can move a boulder, several people working together perhaps can. We are accustomed in medical research to some degree of reductionism, the study of active ingredients. Thus, when obesity interventions are studied, they are generally examined discretely, independently of societal trends. When such interventions fail to make appreciable differences in the outcome(s) of interest—generally some measure of weight—we conclude that they are ineffective. Or, at best, we fail to conclude that they are effective.

But the "mass" against which we are working is daunting. The world is powerfully, and ever more, "obesigenic." Even singular interventions that apply an effective counterforce may fail to move this massive and ever-accumulating resistance. The implications are that for there to be any hope of curtailing the obesity epidemic, we must apply a range of reasonable countermeasures concurrently, forcefully, and sustainably. In fact, a 2012 report issued by the Institute of Medicine (IOM) acknowledges that there is no one panacea for the obesity epidemic and that a broad, integrated approach is needed to curtail the epidemic (10). Numerous national and international consensus reports have since concurred with and furthered the IOM stance (11).

Clinical counseling is among these countermeasures, and it is a potentially vital element. Schools, families, industry, media, policy makers, and public health practitioners have roles to play, too, and we may accomplish little until such efforts align (12,13). But in pursuit of that alignment, who better than we to lead? Certainly, it would be shameful to merely follow, and it would be disgraceful to get out of the way.

Sufficient research evidence is available to inform rational and promising approaches to weight control counseling in clinical settings (see Chapters 46 and 47). When such efforts are adopted, evaluated, refined, and combined with the mobilization of other weight management programs, policies, and resources, we may at last come to find that we can move boulders, and even mountains, after all.

OVERVIEW

Definitions of Overweight and Obesity and Measures of Anthropometry

The predominant measure used to characterize weight at the population level is body mass index (BMI), generally expressed as weight (mass), in kilograms, divided by the height, in meters squared (kg/m^2). This measure of weight adjusted for height offers the benefits of simplicity and convenience for assessing weight in large populations and for monitoring trends over time. BMI, however, is a notoriously crude measure of adiposity (body fat stores) and anthropometry (the distribution of those fat stores)—let alone weight-related health outcomes. BMI is limited in that it does not distinguish between fat and muscle mass, nor between peripherally versus centrally distributed fat mass.

Despite its limitations when applied to an individual, BMI performs well at the population level for

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several reasons. BMI trends reflect trends in adiposity, not muscularity. There is nothing to suggest that increasing legions of the muscular and fit are responsible for consistent increases in BMI in the United States and other countries; there is much to suggest that rising BMI is indicative of increasing adiposity. The distinction between excess body fat and muscularity can often be made at the individual level, and thus the use of the BMI is unlikely to generate clinically relevant confusion (14–16). Finally, such crude measures as the BMI, and even casual inspection, correlate fairly well with costly and sophisticated measures of adiposity (17–20).

Overweight in adults is defined as BMI at or above 25 kg/m^2 (21). Adult obesity is defined in grades. Grade 1 obesity is a BMI of 30 to 34.9; grade 2 obesity is a BMI of 35 to 39.9; and grade 3 obesity is a BMI of 40 or higher (see Table 5.1). A BMI of 25 to 29.9 is "overweight." Class III obesity was formerly known as "morbid obesity" and now more readily labeled as "severe" or "extreme" obesity (3). The name change is appropriate and important for three reasons. First, although a BMI of 40 is quite high, it is not invariably associated with morbidity. Second, and of greater importance epidemiologically, morbidity is often induced by obesity at a BMI well below 40. The risks of complications of excess adiposity may, in general, be considered low, moderate, and high as BMI rises through overweight to class III obesity, but the actual risk in an individual will vary (22–25). The correspondence between BMI and common measures of height and weight is shown in Table 5.2, and a BMI calculator is displayed in Table 5.3. Third, this terminology is widely felt to be pejorative and stigmatizing (26). Children are classified with obesity if they are at or above the 95th percentile for age- and sex-adjusted BMI (based on a historical reference population from 1971) and as overweight if they are at or above the 85th percentile (27). To more accurately classify severe obesity in children with a BMI >99th percentile, new growth charts have been adopted that indicate change in relation to the percentage of the 95th percentile. Children in the Class I Obesity category have a BMI ≥95th percentile to <120% of the 95th percentile. Children in the Class II Obesity category have a BMI ≥120% to <140% of the 95th percentile, or BMI ≥35 to ≤39 (select lowest indicator); lastly, children in the Class III obesity category have a BMI ≥140% of the 95th percentile or BMI ≥40 (selecting lowest indicator (28).

TABLE 5.1

Current Definitions of Overweight and Obesity in Adults

BMI	Category
<18	Underweight
18 to <25	Healthy weight
25 to <30	Overweight
30 to <35	Stage I obesity
35 to <40	Stage II obesity
≥40	Stage III obesity (formerly "morbid" obesity)

TABLE 5.2

Weights that Correspond to Overweight and the Three Stages of Obesity for Men and Women of Average Height and Frame

Gender	Average Height	Weight Corresponding	Weight Corresponding to	Weight Corresponding to	Weight Corresponding to

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		to BMI of 25 (Overweight) (lb)	BMI of 30 (Stage I Obesity) (lb)	BMI of 35 (Stage II Obesity) (lb)	BMI of 40 (Stage III Obesity) (lb)
Female	5′4″	145	174	203	233
Male	5′9″	169	203	237	270

TABLE 5.3

BMI Based on Measures of Height and Weight

		Height in Feet and Inches								
		4′10″	5′	5′2″	5′4″	5′6″	5′8″	5′10″	6′	6′2″	6′4″
		2	20	18	<18	<18	<18	<18	<18	<18	<18
	110	23	21.5	20	19	<18	<18	<18	<18	<18	<18
	120	**25**	23.5	22	21	19	18	<18	<18	<18	<18
	130	27	**25**	24	22	21	20	19	<18	<18	<18
	140	29	27	**26**	24	23	21	20	19	18	<18
	150	**31**	29	27.5	**26**	24	23	22	20	19	18
	160	33.5	**31**	29	27.5	**26**	24	23	22	20.5	19.5
	170	**36**	33	**31**	29	27.5	**26**	24	23	22	21
	180	38	**35**	33	**31**	29	27	**26**	24.5	23	22
	190	**40**	37	**35**	33	**31**	29	27	**26**	24.5	23
Weight in Pound	200	>40	39	37	34	32	**30**	29	27	**26**	24
	210	>40	**41**	38	**36**	34	32	**30**	28.5	27	**26**
	220	>40	>40	**40**	38	**35**	33	32	**30**	28	27
	230	>40	>40	>40	**40**	**36**	**35**	33	31	**30**	28
	240	>40	>40	>40	>40	37	37	34.5	33	31	29
	250	>40	>40	>40	>40	39	38	**36**	34	32	**30.5**
	260	>40	>40	>40	>40	**40**	**40**	37	**35**	33	32
	270	>40	>40	>40	>40	>40	>40	39	37	**35**	33
	280	>40	>40	>40	>40	>40	>40	**40**	38	36	34
	290	>40	>40	>40	>40	>40	>40	>40	39	37	**35**
	300	>40	>40	>40	>40	>40	>40	>40	**41**	39	37

[a]*Height in feet and inches is shown across the top, and weight in pounds is shown in the left-hand column. Each entry in the table represents the BMI for a particular combination of height and weight. BMIs that represent the transition points from lean to overweight, from overweight to obese, and from one stage of obesity to the next are shown in bold. BMI values are close approximations due to rounding. BMI values in the recommended, or "healthiest," range are shaded in gray. Note that if a patient is very slight, or very muscular, that person's BMI might fall above or below the shaded area and still be consistent with excellent health. An online BMI calculator is available at* http://www.nhlbisupport.com/bmi/bmicalc.htm.

Alternatives to BMI for classifying obesity vary in complexity and suitability for the clinical setting.

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Perhaps of most potential value is the waist circumference, which has supplanted the waist-to-hip ratio (WHR) over recent years. This measure requires looping a tape measure about the waist at the narrowest point, generally corresponding to the level of the umbilicus and the posterior superior iliac crests. In general, a waist circumference above 40 inches (approximately 102 cm) is of concern in an adult man, and above 34 inches (88 cm) is elevated for a woman (29). An elevated waist circumference is a hallmark of central adiposity, and in particular it is a risk factor for insulin resistance (see Chapter 7).

Men are generally more subject to central or abdominal obesity (therefore also known as android obesity) than women; this anthropometric pattern has been referred to descriptively as the "apple" pattern of obesity. An elevated BMI with a normal waist circumference is consistent with peripheral obesity, also referred to as gynoid obesity, or the "pear" pattern. Although in general men are more subject to abdominal obesity and women to peripheral obesity, the patterns are not gender specific. Following menopause in particular, women are increasingly subject to abdominal obesity (30,31).

Abdominal obesity is distinct from peripheral obesity with regard to its physiology and complications. Central obesity correlates with the accumulation of visceral adipose tissue. This body habitus is linked to insulin-resistance syndrome and diabetes risk (see Chapter 6). As a result, there is a strong association between central obesity and cardiovascular disease risk (32) (see Chapters 6 and 7); this association is much less apparent for peripheral obesity. One mediating mechanism of cardiovascular risk in central obesity appears to be an association with high sympathetic tone (33–38). This, in turn, may be related to the density of adrenergic receptors in centrally distributed and visceral adipose tissue. Although associated with metabolic complications of obesity, central fat tissue tends to be more readily mobilized than peripheral fat, in part because adrenergic receptors facilitate fat oxidation during catabolism. Thus, the frequently reported complaint of women that men lose weight more readily is often valid.

Of note, not even all centrally distributed fat is of comparable metabolic importance. Work by Després et al. (39) suggested that some individuals accumulate central fat predominantly in the subcutaneous layer, whereas others have a particular predilection for accumulating visceral fat. Visceral fat, and specifically fat accumulation in the liver, is the particular arbiter of cardiometabolic implications of excess adipose tissue. Visceral fat in even relatively modest excess appears to induce metabolic perturbations, notably insulin resistance (see Chapters 6 and 7). There is apparent ethnic as well as inter-individual variation in the propensity to deposit fat in the liver; Asian populations consistently show evidence of insulin resistance at lower weights, even levels considered normal in Caucasian groups. It has been recommended that weight ranges for Asians and Asian Americans include BMI of 23 to 26.9 kg/m^2 (overweight) and BMI >27 kg/m^2 (obesity), compared with the traditional cutoffs of 25 to 30 kg/m^2 and >30 kg/m^2, respectively (40,41).

Other anthropometric measures, such as skinfold thickness, bioelectrical impedance, dual-energy x-ray absorptiometry (DEXA), and hydrostatic weighing are unlikely to be of use in the clinical practice setting. Each of these techniques can be used to calculate or directly measure lean body mass and adipose tissue mass, with varying degrees of time, trouble, cost, and accuracy. Body density can also be measured by the administration of "heavy" (tritiated) water, with evaluation of adiposity based on the volume of distribution (42). Underwater weighing permits assessment of body density as well. Bioelectrical impedance also is used to calculate fat mass. DEXA or dual-photon absorptiometry may be the best available method for measuring total body fat. Computed tomography and magnetic resonance imaging may be used to quantify body fat, with particular utility for visualizing and quantifying visceral fat (43,44).

Along with fat tissue distribution, adipocyte size versus number has implications for the health effects

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of obesity (23). An excess of adipose tissue can result from enlargement of existing adipocytes, the generation of additional adipocytes, or some combination of these. Weight gain attributable to enlargement of existing adipocytes is termed “hypertrophic” obesity, and it is the predominant mechanism for the storage of excess fat weight gained in adulthood. Extreme weight gain in adults will induce the generation of new adipocytes. When excess fat weight is gained in early childhood and near puberty, there is a particular predisposition to generate new adipocytes; weight gain in this pattern is termed “hyperplastic” obesity.

As is true of virtually all cell types, adipocytes have a characteristic size range. Adipocytes exert an influence on the central nervous system, via chemical messengers such as leptin (see appetite, in the following section, and Chapter 38), to remain within their normal size range. Once an excess number of adipocytes have been generated, losing weight through decreasing the quantity of cells becomes increasingly difficult. There is apparently less resistance to attempts at reducing overly enlarged adipocytes to a smaller size within the standard range.

The implications of these patterns and their effects on weight regulation are that predominantly hyperplastic obesity is uniquely resistant to weight loss and control efforts relative to predominantly hypertrophic obesity. This suggests that weight gain early in life will compound the difficulty involved in achieving weight control. In light of this physiologic mechanism, the dangers of ever-earlier-onset obesity and the rising prevalence of childhood obesity are clear. Sustainable weight loss is notoriously difficult even when overweight first occurs in adulthood; it may be exceedingly more difficult for those subject to obesity from early childhood—highlighting the imperative of obesity prevention (45).

Weight Trends and the Epidemiology of Obesity

In the United States, obesity is not only epidemic but also one of the gravest and most poorly controlled public health threat of our time (46–48). Over two thirds of the adults in the United States are overweight or have obesity. Data available suggest that the prevalence of obesity may have plateaued over the past few years (3,4). While this may offer a glimmer of hope, there are less sanguine interpretations of the data. A plateau in any trend is inevitable as the limits of its range are approximated. Further, the prevalence of overweight and obesity does not adequately reflect the distribution of actual weights in the population.

More extreme degrees of obesity are increasing in prevalence particularly rapidly (49,50). This suggests that the minority in the population that has resisted the tendency toward excessive weight gain thus far may remain resistant to significant weight gain. Those, however, who have already succumbed to obesity trends may remain vulnerable to increasing weight gain over time, thus transitioning through overweight to progressively severe degrees of obesity. This implies that even if the cumulative prevalence of overweight and obesity were to stabilize at current levels, the health effects of obesity may well continue to worsen.

Trends in Children

The rate of childhood obesity has more than tripled in the past three decades (6,51). Over 30% of children in the US population are classified in the range of overweight or obesity. In some ethnic minority groups, this figure rises to 40% (4).

Moreover, obesity is occurring at ever-younger ages. A marked rise in the prevalence of overweight among infants and toddlers has been documented both in the United States and globally (52–55). As in adults, BMI is a crude indicator of adiposity and fat distribution in children. Although there is a lack of good reference ranges, data does indicate that waist circumference has been rising in tandem with BMI in

children, which is of concern since abdominal adiposity has worse health implications (56).

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Global Trends

The increasingly global economy has rendered obesity an increasingly global problem (57–59). Worldwide, more than 1.4 billion adults carry excess weight; more than 600 million adults and more than 100 million children have obesity (2,60). Rates of obesity are already high and rising in most developed countries, and they are rapidly growing in countries undergoing cultural transitions (61). In China, India, and Russia, the constellation of enormous population, inadequate control of historical public health threats such as infectious disease, and the advent of epidemic obesity and attendant chronic disease represent an unprecedented challenge (62–64). In countries undergoing a time of even more rapid cultural transition and development, the effects on obesity and chronic disease are astonishing. For example, in Qatar, the rates of obesity and diabetes are even higher than those in the United States, with 70% of adults overweight or having obesity and 17% of adults with type 2 diabetes (65,66). Obesity control is among the current priorities of the World Health Organization. Universal dietary preferences (see Chapter 44) evidently predominate over cultural patterns as nutrient-dilute, energy-dense foods become available (67,68). At the 10th International Congress on Obesity held in Sydney, Australia, in September 2006, World Health Organization data were reported, indicating that for the first time in history, there are more overweight than “undernourished” people on the planet.

The fundamental health implications of obesity appear to be universal. Appropriate threshold values for the definition of overweight and obesity, however, vary with ethnicity, anthropometry, and other factors. As noted, Asian populations appear to have a predilection for central and visceral fat deposition and thus a vulnerability to insulin resistance at lower BMI ranges—even at levels deemed normal and innocuous for most occidental populations. There are noteworthy variations in BMI, waist circumference, and lean body mass among diverse ethnic groups (40,41). As addressed in Chapter 44, genetic variability in the susceptibility to obesity and its metabolic sequelae is quite pronounced.

Obesity and Morbidity

The health consequences of obesity are in general well characterized, as is the economic toll (69–77). The toll of the epidemic is most starkly conveyed by the impact on children. In the past two decades, due to childhood obesity, type 2 diabetes has been transformed from a condition occurring almost exclusively at or after middle age into a pediatric epidemic affecting progressively younger children (78,79). Less than a generation ago, type 2 diabetes was routinely referred to as “adult onset” diabetes.

The National Cholesterol Education Program (NCEP) Adult Treatment Panel issues guidance for the identification and management of cardiovascular risk factors in adults. The guidance for management of hyperlipidemia with lifestyle or pharmacotherapy varies on the basis of other risk factors. The potent influence of diabetes on cardiovascular risk is indicated by the fact that recommendations for the management of hyperlipidemia in patients with diabetes are the same as for patients with established coronary disease (80). Clinically, diabetes is considered an equivalent of coronary artery disease.

There is no reason to think the implications of diabetes for vascular disease should differ between adult and pediatric populations. There is also little reason to think that chronic diseases are tethered to chronological age, from which biological age can differ markedly. That type 2 diabetes has migrated down the age curve to become an increasingly common diagnosis among the ranks of young children is a potentially ominous portent for the evolution of other obesity-related chronic diseases. To some extent, obesity early in life may be seen as accelerating the aging process itself.

On our current trajectory, the prevalence of type 2 diabetes will quadruple by 2050, with the rate of

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growth outpacing that of type 1 diabetes (81). While the actual percentage of children subject to type 2 diabetes is still low (82,83) (see Chapter 6), even that may change as obesity develops at ever earlier ages. When type 2 diabetes occurs in 7- and 8-year-olds, we may expect to begin seeing cardiovascular events in 17- and 18-year-olds who by that age will have had diabetes for a decade. Personal communication suggests that such cases, though thankfully still rare, do already occur. The rate of overweight is rising among even infants and toddlers, and a rise in waist circumference in children seems to bode ill for future trends in insulin resistance (84) (see Chapter 7). The Centers for Disease Control and Prevention (CDC) currently projects that nearly one in three individuals born in the United States in the year 2000 or later will develop diabetes in their lifetime, and for African Americans, the figure is one in two (85).

Data from the National Center for Health Statistics (86) indicate that children growing up in the United States today will ultimately suffer more chronic disease and premature death due to poor dietary habits and lack of physical activity than from exposure to tobacco, drugs, and alcohol combined. These data also suggest that current trends in the United States could translate into shorter life expectancy for children than for their parents, although such projections are complicated by a host of countervailing influences, including advances in medical technologies (87).

Obesity is an often-important step along the causal pathway to most prevalent chronic diseases in developed countries. The link between obesity and diabetes is especially strong, with rising obesity rates directly responsible for epidemic type 2 diabetes in adults and children alike. Obesity, at least when distributed centrally, engenders a plethora of cardiac risk factors and is thus an important contributor to cardiovascular disease (see Chapter 7). Obesity is now known to be a clear risk factor for more than a dozen forms of cancer (88,89). Obesity is associated with asthma, sleep apnea, osteoarthritis, and gastrointestinal disorders as well. More detailed discussion of these associations is provided in Chapters 6 to 8, 12, 15, and 18.

Obesity in children has been linked to increased risk of developing hypertension (90–93), hypercholesterolemia (94,95), hyperinsulinemia (94), insulin resistance (96,97), hyperandrogenemia (96,97), gallstones (98,99), hepatitis and fatty liver (100–103), sleep apnea (104–108), orthopedic abnormalities (e.g., slipped capital epiphyses) (109–113), and increased intracranial hypertension (114–119). Obesity during adolescence increases rates of cardiovascular disease (121–125) and diabetes (121,125) in adulthood, in both men and women. In women, adolescent obesity is associated with completion of fewer years of education, higher rates of poverty, and lower rates of marriage and household income (121). In men, obesity in adolescence is associated with increased all-cause mortality and mortality from cardiovascular disease and colon cancer (121,126). Adults who had obesity as children have increased mortality and morbidity, independent of adult weight (121,127–130). Childhood obesity appears to be accelerating the onset of puberty in girls and may delay puberty in boys (131).

Reports that weight cycling may be associated with morbidity or mortality, independently of obesity, are of uncertain significance (129,132–134). There is evidence that when other risk factors are adequately controlled in the analysis, weight cycling does not predict mortality independently of obesity (135–137). There is also evidence that cardiovascular risk factors are dependent on the degree of obesity and fat accumulation over time rather than weight regain following loss (138,139). The benefits of weight loss are thought to override any potential hazards of weight regain (140); therefore, efforts at weight loss generally should be encouraged even in individuals with obesity who have a prior history of weight cycling (141). However, repeated cycles of weight loss and regain may render subsequent weight loss more difficult by affecting body composition and metabolic rate, although this is an area of some controversy. For this reason, among others, weight-loss efforts should be predicated on sustainable

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adjustments to diet and lifestyle, whenever possible, rather than extreme modifications over the short term.

Psychological Sequelae of Obesity and Weight Bias

Often overlooked but of clear relevance to office-based dietary counseling is the relationship between obesity and mental health. Body image, adversely affected and even distorted by obesity, is important to self-esteem (142,143). Thus, poor self-esteem is a common consequence of obesity (the converse often also being true, with poor self-esteem adversely affecting diet; see Chapter 34) (144). This has important implications for dietary modification efforts (see Chapters 46 and 47). Repeated cycles of weight loss and regain may have particularly adverse effects on psychological well-being, although research in this area is limited (132,145,146).

Evidence consistently and clearly indicates that obesity engenders antipathy, resulting in stigma, social bias, and discrimination (142,147,148). Children with obesity suffer from poor self-esteem (144,149,150) and are subjected to teasing, discrimination, and victimization (127,151,152). Bullying and weight status can develop into a vicious cycle in which the stress of being teased may make the child more likely to seek out comfort food as a coping mechanism, thus further hindering healthful dietary intake and weight management. The topic of weight bias is of ever-increasing concern as the worsening epidemic of obesity directs increasing societal attention to the topic.

The pervasiveness and severity of prejudice against people with obesity is startling (153). Studies among youth consistently indicate a strong and nearly universal distaste for obesity as compared to other noticeable variations (154).

In addition to its implications for health and well-being, weight bias has implications for public policy. There is some evidence to suggest that the routine measurement of student BMI by schools, with reports home to parents, may enhance awareness of, and responses to, childhood obesity. This intervention has been implemented successfully in several school districts and, utilized appropriately, may be valuable for obesity prevention and health promotion (155,156). Nonetheless, there is considerable opposition to this strategy, due largely to its potential for stigmatizing children and vilifying their parents (157). The solution to weight bias, however, cannot be to deny the problem of obesity. Rather, obesity and prejudice must both be confronted. And when the problem of obesity is addressed, it must be consistently and abundantly clear that the attack is against the condition and its causes, *not* its victims. All clinicians share in the responsibility for highlighting this distinction.

As is true of the metabolic effects of obesity, psychosocial sequelae of the condition tend to vary with its severity (158).

Economic Toll of Obesity

Overweight and obesity are thought to add an estimated $147 billion (159) to national health-related expenditures in the United States each year—nearly 10% of the nation's medical bill (160). Obesity has been a major driver of increased Medicare expenditures (161). Compared to medical spending on healthy weight adults, medical spending on adults with obesity may be as much as 100% higher (71). Additionally, if the current childhood obesity epidemic is not halted, researchers forecast that from 2030 to 2050, there will be an additional $254 billion of obesity-related costs from both direct medical costs and loss of productivity (162).

There is also evidence to suggest that obesity results in personal financial disadvantage; poverty is predictive of obesity, and obesity is also predictive of less upward financial mobility (163–165). Thorpe et al. (161) have attributed to obesity alone 12% of the increase in healthcare spending in the United

States over recent years (166–168). Obesity-related expenditures by private insurers purportedly increased tenfold between 1987 and 2002.

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A report in the *American Journal of Health Promotion* (169) indicates that obesity increases healthcare- and absenteeism-related costs by $460 to $2,500 per worker per year. Roughly one third of this cost is induced by higher rates of absenteeism, and two thirds are induced by healthcare expenditures. Annual US productivity costs of obesity-related absenteeism is estimated at $3.4 to 6.4 billion (170).

But some may actually profit from obesity, notably those in businesses responsible for selling the excess calories that make weight gain possible. In a provocative piece in the *Washington Post*, Michael Rosenwald (171) suggested that obesity is an integral aspect of the American economy, influencing industries as diverse as food, fitness, and healthcare. The trade-off between obesity-related profits and losses has been considered elsewhere (172). Costs and benefits are often a matter of perspective, and what is good finance for the seller may be bad for the buyer. Close and Schoeller (173) have pointed out that bargain pricing on oversized fast-food meals and related products actually increases net cost to the consumer, largely as a consequence of weight gain. The higher costs over time relate to adverse health effects of obesity as well as increased food intake by larger persons. (Note the paradox here: In order to sustain the market for the excess calories that contribute to obesity, obesity is necessary, as it drives up the calories required just to maintain weight; obesity depends on an excess of calories, and the effective peddling of that excess of calories depends on obesity.) Another cost of obesity is reduced fuel efficiency when driving and carrying more weight. Stated bluntly, the “all-you-can-eat” buffet is not much of a bargain both because excess calories resulting in excess weight lead to increased costs of living and because most beneficiaries of discounted dietary indulgences wind up willing to spend a fortune to lose weight they gained at no extra charge. There may be some utility in pointing this out to patients.

Obesity and Mortality

One of the most contentious and controversial aspects of the obesity epidemic has been a reliable accounting of the mortality toll. Debates on this issue have been particularly intense. (174,175).

In 1993, McGinnis and Foege (176) identified the combination of dietary pattern and sedentary lifestyle as the second leading cause of preventable, premature death in the United States, accounting for some 350,000 deaths per year. Obesity contributes to the majority of these deaths and was considered to be directly or indirectly responsible for approximately 300,000 annual deaths (177). Calle et al. (178) reported a linear relationship between BMI and mortality risk, based on an observational cohort of more than 1 million subjects followed for 14 years. In this cohort, high BMI was less predictive of mortality risk in Blacks than in Whites. Manson et al. (179) found a linear relationship between BMI and mortality risk in women from the Nurses’ Health Study; the lowest risk of all-cause mortality occurred in women with a BMI 15% below average with stable weight over time. Including women with a smoking history in the analysis yielded a J-shaped mortality curve, with a higher mortality rate among the leanest women. In a study of over 2 million men and women, Engeland et al. (180) also found a J- or U-shaped mortality curve with the lowest rate of death at a BMI between 22.5 and 25. In a study of over half a million adults by Adams et al. (181), after controlling for smoking status and initial health, both overweight and obesity was associated with an increased risk of death. Most recently, a highly publicized meta-analysis by Flegal et al. (182) found that while obesity was associated with a higher all-cause mortality relative to normal weight, overweight was associated with a significantly *lower* all-cause mortality rate.

Data supporting the relationship between obesity and mortality risk come from a variety of sources and generally are consistent (183,184). There is evidence that obesity in adolescence, at least in males, is predictive of increased all-cause mortality (126). Data from the Iowa Women’s Health Study suggested

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that WHR (now supplanted by waist circumference) might be a superior predictor of mortality risk to BMI in women. Whereas BMI produced a J-shaped curve, WHR and mortality were linearly related (185). This issue remains important but is often neglected in the obesity/mortality debate: Not all obesity is created equal in terms of cardiometabolic risk. Although earlier studies often demonstrated a J-shaped relationship between BMI and mortality, in the largest cohort studies, the relationship is linear (186). It is unsurprising that people thin due to serious illness have a high rate of mortality. Studies that assessed participants for chronic illness and excluded them in various ways yielded a straightening of the BMI/mortality curve over virtually its entire length, as noted previously (181,186).

Partly on the basis of this new evidence, a National Institutes of Health (NIH) consensus conference was held in 1998 to revisit the definition of overweight then in common use. It was at that time that the now prevailing definitions (see Table 5.1) of overweight and obesity were established. Because the prior threshold for overweight had been higher (BMI 27.2 in women, 27.8 in men), the sardonic observation was made that more than 10 million people who had gone to bed lean 1 day woke up overweight the next.

The revised definitions of obesity, revised mortality curves, and increasing prevalence of obesity all contributed to a heightened concern for the mortality toll of overweight. The data published in 1993 by McGinnis and Foege that had established tobacco as the leading, modifiable root cause of premature death in the United States, were perceived to have contributed to societal efforts to curtail the harms of smoking. It was in this context that Mokdad et al. (174) made extrapolations from population data to suggest in 2004 that some 400,000 premature deaths each year in the United States were attributable to obesity and that obesity would soon overtake tobacco as the leading cause of premature death.

The most ardent rebuttal to this claim was made by Flegal et al. (175), who used data from the National Health and Nutrition Examination Surveys (NHANES) to extrapolate the mortality toll of obesity. Contending that Mokdad et al. had failed to adjust appropriately for age distribution, Flegal et al. reported a much weaker association between BMI and mortality, with as few as 100,000 to 150,000 premature deaths ensuing. Most provocatively, Flegal et al. (182) reported both in this study and a subsequent meta-analysis that overweight in middle-aged adults, a BMI between 25 and 30, was actually associated with a lower mortality rate than so-called ideal weight.

A related controversy is the likely impact of obesity on life expectancy in the future. The claim has been made that due to epidemic obesity, we are now raising the first generation of children with a shorter projected life expectancy than that of their parents (87,187). This view, too, has been refuted, with claims that life expectancy will continue to rise into the future.

There is now a rich litany of arguments on both sides of the obesity/mortality divide, with arguments for and against a high mortality toll now (188–191) and in the future (see **Figure 5.1**). The CDC has officially addressed the controversy on more than one occasion, with much of the debate spilling over into the popular press (174,175,177,192–218).

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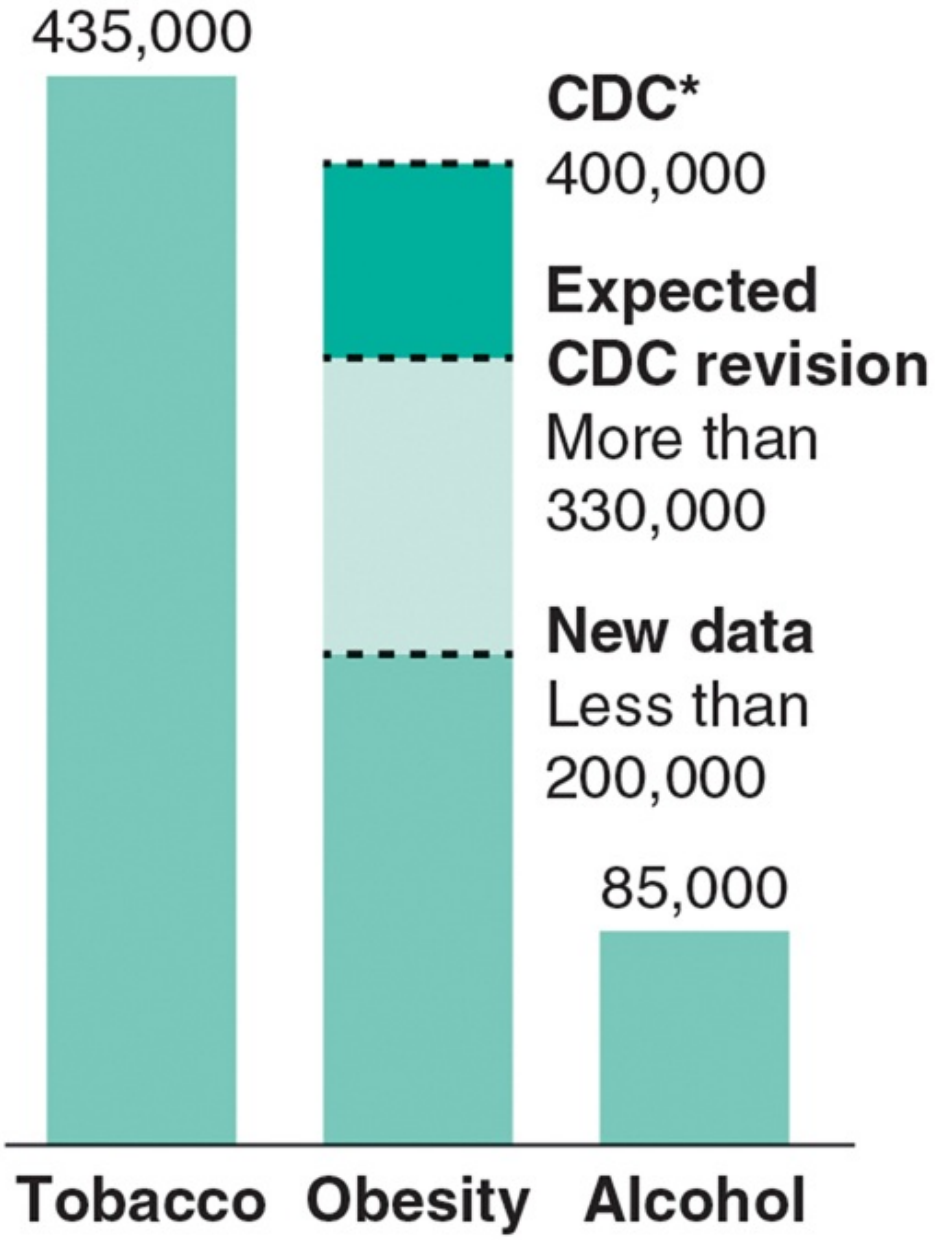
Losing Weight

Scientists debate new estimates for obesity-related deaths in 2000.



*Published in JAMA in March

Sources: JAMA: WSJ research

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FIGURE 5.1 How many Americans die each year from obesity? *(From* Mckay B. *Wall Street Journal*. *December 3,* 2004:A15.)

Fortunately, there is no need to reach absolute consensus on the death toll of obesity to appreciate the threat it represents. It may be that obesity is killing fewer people than projected because of advances in tertiary care. Certainly, the means of compensating for chronic diseases in advanced states improve with each passing year. But compensation for chronic disease by such means as endovascular procedures, polypharmacy, and/or surgery is not nearly as good as, and is vastly more expensive than, preserving good health. That obesity accounts for an enormous burden of chronic disease is beyond dispute; it lies on the well-established causal pathways toward virtually all of the leading causes of premature death and disability in industrialized countries, including diabetes, cardiovascular disease, cancer, degenerative arthritis, stroke, and, to a lesser extent, obstructive pulmonary disease. Thus, while the number of years obesity may be taking out of life is debatable, there is no argument that it is taking life out of years.

Of note, the Flegal meta-analysis (182) focused on mortality and did not examine the impact of obesity on morbidity. Moreover, when people become ill, they generally lose weight; however, the study did not exclude those who were thin due to illness. Additionally, the study did not exclude individuals who were thin for other reasons, for example, anorexia nervosa, severe depression, cocaine use, all of which may cause increased mortality in healthy weight individuals as compared to overweight individuals.

While the arguments about the impact of obesity on mortality are based on statistical subtleties and projections from relatively small samples, the American Cancer Society data are based on an observational cohort study involving nearly 1 million people now followed for nearly 20 years. This robust sample, cited in neither the Mokdad nor Flegal papers, demonstrates a linear association between BMI and mortality. This association is clear and unencumbered by contentious statistics (219,220).

There is, finally, a simple logic about the association between obesity and mortality. Obesity contributes mightily to the prevalence of diabetes, cancer, heart disease, and, to a lesser extent, stroke. These, in turn, are the leading proximal causes of death in the United States. It would seem far-fetched that a condition contributing to all the leading causes of death is entirely unimplicated itself in the causation of death.

Less far-fetched is the lack of a direct association. Death certificates rarely cite obesity as cause of death because it is generally a distal, or “upstream,” factor. Obesity contributes to chronic diseases, which in turn contribute to acute events that contribute directly to death. Standard data-gathering mechanisms may simply be blind, or nearly so, to the contributions of obesity to mortality. This is especially probable in light of the relative neglect of obesity in the standard medical history. A prototypical causal pathway is shown in **Figure 5.2**, with indications of the causes of death certain, likely, and unlikely to appear on a death certificate.

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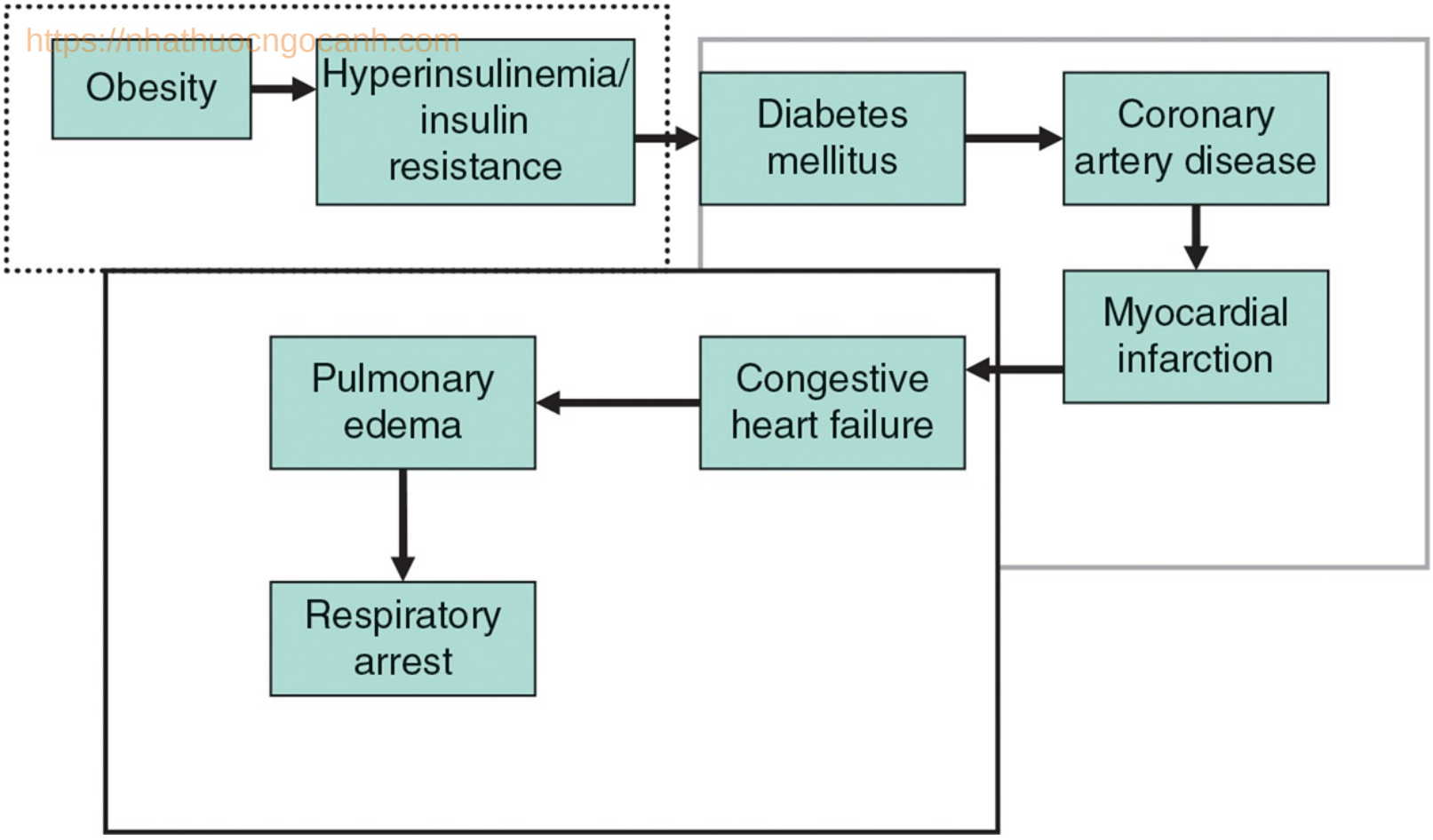

FIGURE 5.2 Obesity is a distal, "upstream," factor in premature death from multiple causes.Because of its distance from the actual precipitating events at the time of death, obesity is unlikely to be identified on a death certificate. The solid black bars enclose what is certain to be listed on a typical death certificate as cause of death, the solid gray bars enclose what is likely to be listed as the underlying cause of death, and the dashed bars enclose information that is unlikely to appear on the death certificate at all.

Another important consideration is that BMI, as noted previously, is a relatively poor index of health at the level of any given individual. A low or normal BMI attributable to a healthful diet and regular physical activity is obviously quite distinct from a normal or low BMI attributable to depression, isolation, chronic illness, or an eating disorder. Similarly, an elevated BMI due to fitness and muscularity has health implications opposite those of excess adiposity. Finally, even excess adiposity differs in its effects on health on the basis of fat distribution, as discussed previously. In each case, these factors would bias assessment of the obesity/mortality association toward the null. The waist circumference appears to be a far better predictor of morbidity and mortality than the BMI (221–224), in much the same way that low-density lipoprotein (LDL) and the LDL:HDL (high-density lipoprotein) ratio (the ratio between LDL and HDL) discriminate cardiovascular risk far more reliably than does total cholesterol.

The implications of this line of reasoning are that obesity is a major contributor to premature mortality, but that generating an accurate and precise body count attributable to obesity per se will long remain elusive. The attribution of significant morbidity to obesity is far less challenging and is a sufficient basis in its own right to treat epidemic obesity as a bona fide clinical and public health imperative.

Energy Balance and the Pathogenesis of Obesity

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The relentlessly increasing global prevalence of obesity (see Global Trends) has engendered understandable frustration among policy makers, public health practitioners, and healthcare providers alike. People who gain excess weight over time are in a state of positive energy balance. The longer that state persists, and the greater the imbalance, the more weight is gained.

The balance referred to in "energy balance" is between energy units (typically, but not necessarily, measured in kilocalories or kilojoules) taken into the body and energy units expended by the body. Because the relationship between energy and matter is governed by fundamental laws of physics, the implications of energy balance are substantially self-evident. When more energy is taken into the body than is consumed by all energy-expending processes, the surplus is converted into matter. When energy expenditure exceeds energy intake, matter must be converted into energy to make up the deficit. Thus, positive energy balance increases a body's matter, and negative energy balance decreases it. When energy intake and output are matched, matter—body mass in this case—remains stable.

Several details of clinical interest complicate this otherwise simple construct. The first is that while energy intake is limited to a single activity, eating, energy output is expressed in several ways, including thermogenesis, physical activity, basal metabolism, and growth. The second is that while excess energy intake is convertible into matter, the nature of that matter can vary. Namely, and in simple terms, excess calories can build lean body tissue, fat, or a combination of the two.

The calorie is a measure of food energy and represents the heat required to raise the temperature of 1 g, or cm^3, of water by 1°C at sea level. A kilocalorie, the measure applied to foods, is the heat required to raise the temperature of 1 kg or L, of water by the same extent, under the same conditions (225). The joule is an alternative measure of energy used preferentially in most applications other than food. The joule, and the corresponding kilojoule, is 4.184 times smaller than the calorie and kilocalorie, respectively.

There has long been controversy asking the question "is a calorie, a calorie?" (226). However, as already stated, a calorie is simply a unit of energy, and as such, 1 cal will always equal 1 cal (just as 1 m will always equal 1 m). Where the difference truly lies is that some foods are better for us than others, and one of the many virtues of better-for-us foods is that they tend to help us feel full on fewer calories and thus can tip the balance in the energy balance equation (227).

Calories consumed ("energy in") is at least conceptually relatively simple: food. As noted, calories expended ("energy out") is the more complicated combination of resting energy expenditure (REE), basal metabolic rate (BMR), physical activity, and thermogenesis. The formula includes energy dedicated to linear growth in children, which contributes to basal requirements. There is a limited literature to suggest an association between relatively greater protein intake and relatively higher REE at a given body mass than that associated with other macronutrient classes (see discussion of macronutrient classes, page 673). Thermogenesis is primarily influenced by sympathetic tone and leptin, which in turn may be influenced by insulin (see Chapter 6) and, therefore, to some degree, by macronutrient distribution. A comparable number of calories from different macronutrient sources almost certainly will not be comparably satiating (see Chapter 42), so macronutrient distribution may influence satiety and, thereby, subsequent energy intake.

If an individual is genetically predisposed to insulin resistance, high levels of postprandial insulin may contribute to weight gain, all else being equal (see Chapter 6). If that individual restricts calories sufficiently, however, weight gain will not occur. But given the difficulty people with access to abundant and tasty food have restricting calories, the likelihood is that the individual will not do so effectively. High insulin levels may result in more efficient conversion of food energy to body fat, given adequate energy intake for fat deposition to occur. Body fat deposition will lead, in predisposed individuals, to the accumulation of visceral fat and thereby to more insulin resistance, raised insulin levels, and potentially

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more fat deposition. Thus, while the predominant dietary determinant of weight regulation is total energy intake, macronutrient distribution, endocrine factors, and diverse genetic predispositions may contribute important mitigating influences at any given level of calorie consumption.

In essence, then, the pathogenesis of obesity involves the complex details of an otherwise straightforward energy balance formula: when calories consumed exceed energy expended, weight rises, and vice versa. Specifically, in the short term, when caloric intake exceeds caloric expenditure by roughly 3,500 to 4,000 kcal, a pound of body fat will be generated. (Theoretically, a pound of fat stores 4,086 kcal [9 kcal/g of fat, multiplied by the 454 g in a pound]). However, a pound of living tissue is not actually just fat but must also contain the various structures and fluids required for the viability of that fat, such as blood, blood vessels, neurons, etc. By convention, an excess of 3,500 kcal is used to approximate the energy requirement for a pound of weight gain. By the same convention, a deficit of 3,500 kcal relative to expenditure will translate into a pound of body fat lost. For this reason, a daily caloric deficit of roughly 500 kcal is generally advised to achieve weight loss at the modest and sustainable pace of 1 lb/week. However, because caloric intake and expenditure are not independent quantities, this rule of thumb breaks down after a few weeks of sustained energy deficit (228,229). Due to counter-regulatory mechanisms (such as the reduction in leptin levels during weight loss) involved in weight regulation—and, indeed, survival—a sustained reduction of caloric intake will lead to lesser weight gain over time, such that the 3500-cal-per-pound rule of thumb is only applicable over a relatively short period of time.

The complexity underlying the energy balance formula is reflected in a wide range of genetic, physiologic, psychological, and sociologic factors implicated in weight gain. Efforts to control weight, prevent gain, or facilitate loss must address energy balance to be successful. Control of body weight relies on achieving a stable balance between energy input and energy consumption at a desired level of energy storage.

Working against this goal is the natural tendency of the body to accumulate fat. The storage of energy in the form of adipose tissue is adaptive in all species with variable and unpredictable access to food. In humans, only about 1,200 kcal of energy is stored as glycogen in the prototypical 70-kg adult, enough to support a fast of approximately 12 to 18 hours. A human's ability to survive a more protracted fast depends on energy reserves in body fat, which average 120,000 kcal in a 70-kg adult. The natural tendency to store available energy as body fat persists, although the constant availability of nutrient energy has rendered this tendency maladaptive, whereas it once was, and occasionally still is, vital for survival.

The development of obesity appears to be related to an increase in both the size and number of adipocytes. Excess energy intake in early childhood and adolescence is thought to lead more readily to increases in fat cell number. In adults, excess energy consumption leads initially to increases in adipocyte size and only with more extreme imbalance to increased number (see Definitions of Overweight and Obesity and Measures of Anthropometry, page 65). Childhood obesity does not lead invariably to adult obesity, as the total number of adipocytes in a lean adult generally exceeds the number in an overweight child. Thus, correction for early energy imbalance can restore the number of adipocytes to the normal range. However, childhood obesity is a strong predictor of obesity, and its complications, in adulthood (230).

In general, lesser degrees of obesity are more likely to be due to increased fat cell size (hypertrophic), whereas more severe obesity often suggests increased fat cell number (hyperplastic) as well. Weight loss may be more difficult to maintain in hyperplastic as compared to hypertrophic obesity because it requires reducing an abnormally high number of total adipocytes down to an abnormally low size. Adipocytes may actively regulate their size so that it is maintained within the normal range. Such signaling involves

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various chemical messengers released from adipose tissue, including angiotensinogen, tissue necrosis factor, and others, along with leptin. Adipocytes also produce lipoprotein lipase, which acts on circulating lipoprotein particles, especially very LDL, to extract free fatty acids, which then are stored in the adipocyte as triglyceride.

The imbalance between energy consumption and expenditure that leads to excess weight gain can be mediated by either and generally is mediated by both. Relative inactivity and abundantly available calories both contribute. As noted previously, energy expenditure is composed of BMR, the thermic effect of food, and physical activity (Table 5.1). On average, BMR accounts for up to 70% of total energy expenditure, thermogenesis approximately 15%, and physical activity approximately 15%. The contribution of physical activity to energy expenditure is, of course, quite variable. REE can be measured by various methods, with the doubly labeled water method representing the prevailing standard in research settings (225,231).

In clinical settings, basal energy requirements for weight maintenance can be estimated in many ways, most notably via the Harris–Benedict Equation (see Appendix A). A rough estimate of calories needed to maintain weight at an average level of activity is derived by multiplying the ideal weight of a woman (in pounds) by 12 to 14 and that of a man by 14 to 16. BMR is lower in women than in men when matched for height and weight due to the higher body fat content in women; muscle imposes a higher metabolic demand than fat at equal mass. A strong genetic component to the BMR results in familial clustering as well as clustering within ethnic groups predisposed to obesity (232–236) (see Chapter 44). BMR is largely explained by lean body mass, but among subjects matched for lean body mass, age, and sex, a variation of as much as 30% may be seen. This explains, in part, why comparable energy intake will produce obesity in some individuals but not in others. There is a clear implication in this for clinicians: What patients contend about predisposition to weight gain may very well be true (see Chapter 47).

Total body weight generally correlates inversely with BMR at the population level but correlates positively with BMR in an individual, as weight loss reduces BMR, and weight gain increases it (237). Larger people require more calories at rest than smaller people to maintain their weight.

BMR may fall by as much as 30% with dieting and muscle efficiency improves with weight loss, which explains why the maintenance of weight loss becomes increasingly difficult over time—particularly in cases of extreme weight loss (238). The phenomenon of the “weight-loss plateau” is, in part, attributable to the equilibration of lower caloric intake with lower energy requirements resulting from reduced body mass. The counterregulatory forces leading to diminished BMR also contribute to increased appetite, further frustrating long-term maintenance of lost weight (239). While both predictable and understandable, this phenomenon is often intensely frustrating for patients. Weight-management counseling should anticipate and address this tendency.

Reductions in BMR may contribute as well to increasing difficulty in losing weight after successive attempts (240), although this concept is debated (241–243). A plausible mechanism is that both fat mass and lean body mass are reduced when calories are restricted, whereas weight regain due to caloric excess will result in an increase in fat mass preferentially. Thus, cycles of weight loss and regain have the potential to increase the percentage of body fat and thereby lower calorie requirements for maintenance at any given weight.

Exercise may forestall these changes in body composition and metabolic rate. While resistance training, in particular, may minimize the fall in BMR that occurs with weight loss, all forms of physical activity, whether aerobic exercise or strength training, can have this benefit. As muscle is more metabolically active than fat, the conversion of body mass from fat to muscle at a stable weight will increase BMR. This pattern may frustrate patients who rely on a scale to gauge weight loss success, but in

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fact a reduction in fat mass and an increase in lean body mass clearly are a weight management success and should be regarded as such, despite the unmoving dial on a bathroom scale. There is consensus among authorities that in those experiencing cardiometabolic complications of obesity, a weight reduction of 5% to 10% is often conducive to clinically important risk reduction (244,245). Less well described, but certainly plausible, is similar improvement in those who lower weight less but redistribute weight from fat to lean.

Energy expenditure per unit body mass peaks in early childhood due to the metabolic demands of growth. Total energy expenditure generally peaks in the second decade, and energy intake often does as well. Thereafter, energy requirements decline with age, as does energy consumption. Energy expenditure tends to decline more than energy intake so that weight gain and increasing adiposity are characteristic of aging (see Chapter 31).

It is of interest that the capacity of the body to store excess calories in an energy reserve composed of adipose tissue is adaptive in any environment imposing cyclical caloric deprivation. This tendency becomes maladaptive only when an excess of calories is continuously available. Also of note, the adaptive capacity for weight gain is generally variable among individuals and populations, and it is somewhat systematically variable between men and women.

Men are far more prone than premenopausal women to accumulate excess fat at the belly and within the abdominal viscera, rendering them more susceptible to cardiometabolic sequelae of obesity. As mentioned earlier, the central pattern of obesity, known colorfully as the “apple” pattern, is referred to as android. In contrast, the “pear,” or peripheral, pattern of obesity is gynoid.

There is a potential explanation for the tendency of women of reproductive age to store body fat more innocuously than men in evolutionary biology. Namely, reproduction depends on a woman’s ability to meet both her own caloric needs and those of a developing fetus (see Chapter 27). The capacity to create a large enough energy reserve to help ensure a successful pregnancy may be a critical, and of course uniquely female, adaptation. A final contribution to this admittedly speculative construct is made by the effects in women of reducing body fat content below a critical threshold. Menses ceases, and a state of infertility ensues. This effect is most commonly observed in young female athletes as well as girls with eating disorders, in whom it represents a threat of irreversible osteopenia (see Chapters 14 and 25).

Thermogenesis

Food ingestion increases sympathetic tone, raising levels of catecholamines and insulin. Brown adipose tissue, primarily concentrated in the abdomen, upper back and neck, and along the spinal cord, functions principally in the regulation of energy storage and wastage by inducing heat generation in response to stimulation by catecholamines, insulin, and thyroid hormone. The increase in sympathetic tone postprandially results in thermogenesis (heat generation), which may consume up to 15% of ingested calories. Some researchers even suggest targeting thermogenesis for antiobesity efforts (246,247). A reduced thermic effect of food may contribute to the development of obesity, although this is controversial (248,249). Approximately 7% to 8% of total energy expenditure is accounted for by obligatory thermogenesis, but up to an additional 7% to 8% is facultative and may vary between the lean and overweight.

Insulin resistance may be associated with reduced postprandial thermogenesis. However, obesity apparently precedes this reduction, suggesting that impaired thermogenesis is unlikely as an explanation for susceptibility to obesity. Thermogenesis is, in part, related to the action of b_3-adrenergic receptors, the density of which varies substantially. Reduced thermogenesis may contribute to weight gain with aging, as thermogenesis apparently declines with age, at least in men (250,251).

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Energy consumption generally has risen in industrialized countries over recent decades as both the energy density of the diet, portion sizes, and frequency of snacking have increased. During the same period, energy expenditure generally has fallen, largely due to changes in the environment and the patterns of work and leisure activity. Fewer than 5% of US adults participate in daily physical activity and just one in three achieve the recommended amount of physical activity weekly (252). The majority of Americans do not meet the physical activity recommendations of 30 min of moderate-intensity activities at least 5 days/week (253). A reduction in exercise-related energy expenditure contributes to energy imbalance and weight gain. The attribution of weight gain to physical inactivity is compounded by the associations between sedentary behavior and poor diet (254). For example, data from the *Behavioral Risk Factor Surveillance System* indicate that relative inactivity correlates with a high dietary fat intake (255).

Although there is consensus that physical activity is essential to long-term weight maintenance, the mechanisms of benefit remain controversial. Evidence that physical activity reduces food intake or results in extended periods of increased oxygen consumption is lacking, and there is some evidence to the contrary. Exercise has the potential to increase the BMR by increasing muscle mass. Energy consumption during exercise can help maintain energy balance. For example, 45 min of jogging or 75 min of brisk walking could achieve a caloric expenditure of approximately 500 kcal (see Table 5.4). The efficiency for linking energy consumption to physical work of contracting muscle is approximately 30%; 70% of the available energy is wasted as heat. There is little evidence that the efficiency of work-related energy metabolism differs between leaner and heavier persons.

TABLE 5.4

Energy Expenditure of Some Representative Physical Activities[a]

Activity	METs[b] (multiples of RMR)	kcal/min
Resting (sitting or lying down)	1.0	1.2–1.7
Sweeping	1.5	1.8–2.6
Driving (car)	2.0	2.4–3.4
Walking slowly (2 mph)	2.0–3.5	2.8–4
Bicycling slowly (6 mph)	2.0–3.5	2.8–4
Horseback riding (walk)	2.5	3–4.2
Playing volleyball	3.0	3.5
Mopping	3.5	4.2–6.0
Golfing	4.0–5.0	4.2–5.8
Swimming slowly	4.0–5.0	4.2–5.8
Walking moderately fast (3 mph)	4.0–5.0	4.2–5.8
Playing baseball	4.5	5.4–7.6
Bicycling moderately fast (12 mph)	4.5–9.0	6–8.3
Dancing	4.5–9.0	6–8.3
Skiing	4.5–9.0	6–8.3
Skating	4.5–9.0	6–8.3
Walking fast (4.5 mph)	4.5–9.0	6–8.3

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Swimming moderately fast	4.5–9.0	6–8.3
Playing tennis (singles)	6.0	7.7
Chopping wood	6.5	7.8–11
Shoveling snow	7.0	8.4–12
Digging	7.5	9–12.8
Cross-country skiing	7.5–12	8.5–12.5
Jogging (10- to 12-min-mile pace)	7.5–12	8.5–12.5
Playing football	9.0	9.1
Playing basketball	9.0	9.8
Running (8-min-mile pace)	15	12.7–16.7
Running (4-min-mile pace)	30	36–51
Swimming (crawl stroke) fast	30	36–51

[a]All values are estimates and based on a prototypical 70-kg male; energy expenditure is generally lower in women and higher in larger individuals. MET and kilocalorie values derived from different sources may not correspond exactly.

[b]A MET is the rate of energy expenditure at rest, attributable to the resting (or basal) metabolic rate (RMR). Although resting energy expenditure varies with body size and habitus, a MET is generally accepted to equal approximately 3.5 mL/kg/min of oxygen consumption. The energy expenditure at one MET generally varies over the range from 1.2 to 1.7 kcal/min. The intensity of exercise can be measured relative to the RMR in METs.

Data from Ensminger AH, et al. The concise encyclopedia of foods and nutrition. In: Wilmore JH, Costill DL, eds. Physiology of sport and exercise: Human kinetics. Champaign, IL: publisher, 1994; American College of Sports Medicine. Resource manual for guidelines for exercise testing and prescription, 2nd ed. Philadelphia, PA: Williams & Wilkins, 1993; Burke L, Deakin V, eds. Clinical sports nutrition. Sydney, Australia: McGraw-Hill Book Company, 1994; McArdle WD, Katch FI, Katch VL. Sports exercise nutrition. Baltimore, MD: Lippincott Williams & Wilkins, 1999

There has been a strong national emphasis on the health benefits of physical activity, as evidenced by First Lady Michelle Obama's *Let's Move!* campaign (256) and President Obama's *The Presidents Challenge* (Discontinued June 2018). Overall, however, little progress was made toward *Healthy People 2020* objectives in this category (257). Although the utility of physical activity per se in promoting weight loss is uncertain, lifetime physical activity apparently mitigates age-related weight gain and clearly is associated with important health benefits (258–261). Moreover, the argument that physical activity does not promote weight loss is flawed. Physical activity can indeed promote weight loss and burn fat but only if we engage in enough of it and do not then overeat. The problem is that even those of us who exercise daily are relatively sedentary by historical standards. In the obesigenic environment of the modern world, we are more prone to excessive energy intake and inadequate energy expenditure than any previous generation (262,263).

The issue of whether physical activity and attendant fitness are more important to health than weight control has generated some controversy. Some authors argue that "fitness" is more important than

"fatness," while others defend the alternative view (264–285).

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This dispute, however, is more distracting than helpful. At the population level, most fit people are at least relatively lean, while excess weight and lack of fitness generally correlate. Indeed, even if "fit" trumps "fat" in terms of health effects, fewer than 9% of the population resides in this category of both "fit" and "fat" (286).

Evidence from large cohort studies suggests that fitness and fatness are independent predictors of health outcomes. The combination of fit and lean is clearly preferable over all others.

Evidence from the National Weight Control Registry and other studies suggests that regular physical activity may be an important element in lasting weight control (287,288). Physical activity is among the best predictors of long-term weight maintenance (289–294). It has been estimated that the expenditure of approximately 12 kcal/kg body weight per day in physical activity is the minimum protective against increasing body fat over time (295). The contribution of physical activity to weight maintenance may vary among individuals on the basis of genetic factors that are as yet poorly understood (296,297).

Over recent years, there has been accumulating and encouraging evidence that lifestyle activity, as opposed to structured aerobic exercise, may be helpful in both achieving and maintaining weight loss (298). Such unobtrusive physical activity may be more readily accepted by exercise-averse patients.

Macronutrient Metabolism

There is some degree of metabolic control over the consumption and distribution of macronutrients. Cortisone, galanin, and endogenous opioid peptides stimulate the medial hypothalamus to promote fat intake. Dopamine generally has antagonistic effects, suppressing desire for fat intake (though this depends on the neuroanatomical area of action and associated dopamine receptor subtype). Amphetamines act as dopamine precursors and thereby tend to reduce fat intake. Drugs such as neuroleptics (e.g., phenothiazines) that antagonize dopamine often are associated with increased fat and caloric intake and weight gain. Endogenous opioid peptides and growth hormone-releasing factor may play a role in the regulation of protein intake.

Carbohydrate intake and craving is mediated by effects of *g*-aminobutyric acid, norepinephrine, neuropeptide Y, and cortisol on the paraventricular nucleus of the medial hypothalamus. Activity of this system tends to be high when serum glucose and/or glycogen stores are low. Suppression of carbohydrate craving apparently is mediated by serotonin (see Chapters 34 and 38) and cholecystokinin. Insulin resistance may be associated with carbohydrate craving due to elevations of norepinephrine, cortisone, and neuropeptide Y. The interactions of appetite signaling with macronutrients are further discussed in Chapter 38. The role of macronutrient distribution in weight control efforts is addressed later in this chapter.

Sociocultural Factors

The imbalance between energy intake and energy expenditure fundamental to obesity is largely the product of an interaction between physiologic traits and sociocultural factors. Human metabolism is the product of some 6 million years of natural selection (see Chapter 44), the overwhelming majority of which occurred in an environment demanding vigorous physical activity and providing access to a largely nutrient-dense but energy-dilute diet (299). In such an environment characterized by cyclical feast and famine, metabolic efficiency would be favored, as would a capacity to store nutrient energy in the body against the advent of famine (300).

Such an environment likely would shape behavioral responses as well. The tendency to binge eat, characteristic of modern-day hunter-gatherers and many animal species, is adaptive when food is

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occasionally abundant but often deficient; therefore, such a tendency may be nearly universal in humans (299). The increasing frequency of binge eating disorder (see Chapter 25) likely represents the convergence of this widespread native tendency, with the ever-increasing opportunities to indulge it to harmful excess. Even in the absence of pathology, the constant and abundant availability of tasty food in conjunction with this tendency constitutes a formula for excess energy consumption.

An innate preference for sweet foods has been well documented in humans and other animals (301). Such a preference would likely be adaptive in a primitive environment, as naturally sweet foods (e.g., fruit, honey) provide readily metabolizable energy and are rarely toxic. There is evidence of a strong pleasure response to dietary fat, mediated in part by opioid receptors (302). A strong affinity for dietary fat would have been adaptive in an environment where dietary fat was scarce yet represented a source of concentrated energy and essential nutrients. Similarly, the need for a range of micronutrients and the potential difficulty in consistently finding a variety of foods would likely have cultivated a strong preference for dietary variety. This trait, sensory-specific satiety, becomes maladaptive in an environment providing food in constant variety as well as abundance, favoring excessive intake (303) (see Chapter 38).

The imbalance between energy intake and expenditure is compounded by modern conveniences that have led to a decline in physical activity associated with daily activities (149). The global spread of modern technology is associated with the emergence of obesity as a global public health problem (304). Prevailing patterns of behavior, including use of convenience devices that minimize physical activity (e.g., elevators, remote control devices) and consumption of an energy-dense diet, are generally reinforced at the societal level, often taking on culturally normative implications (305). Sociocultural influences are powerful determinants of both activity and dietary patterns (306,307) and, in the modern context, of obesity.

Both overweight and lean individuals generally underreport calorie intake, but the degree of underreporting tends to be greater in heavier persons. Generally, calorie consumption is higher in heavier, compared with leaner, individuals (308,309), as would be expected.

Other Factors

Endocrinopathy, such as Cushing's syndrome or hypothyroidism, is a rare cause of obesity. Relatively few patients with obesity have hypothyroidism, and most previously lean patients with hypothyroidism do not gain significant weight as a result of the thyroid disease.

An association has been noted between variations in the microbiota (endogenous commensal flora) of the human colon and obesity. A similar association has been cited between adenovirus exposure and obesity (310). These associations may be of a causal nature or may be statistical flukes, and further research is needed. But even if causal, they still have the potential to divert attention from the more important and painfully obvious causes of epidemic obesity: caloric excess and relative inactivity. While the novel associations may tantalize, they should not be exaggerated. When a prevailing excess of calories and prevailing deficiency of physical activity have been eliminated from the formula, if there is any obesity left to explain, the day of the novel theory will have arrived. It will be most welcome.

Genetic Influences on Energy Balance and Weight

There is a strong genetic contribution to obesity, mediated along several important pathways. Genes influence REE, thermogenesis, lean body mass, and appetite. There is, thus, an important potential genetic influence on both energy intake and expenditure. Overall, genetic factors are thought to explain at least 50% of the variation in BMI. Adoption studies demonstrating an association between obesity in a child

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and the biological parents, despite being reared by surrogate parents, and twin studies showing anthropometric correspondence between identical twins reared apart are particularly useful sources of insight in this area (311–314).

Genetic factors are of clinical importance as they help explain individual vulnerability to weight gain and its sequelae and perhaps also individual variability in responsiveness to weight loss interventions. Minimally, an appreciation for genetic factors in energy balance should foster insight and compassion relevant to clinical counseling. Maximally, elucidation of genetic contributions to obesity over time may illuminate novel therapeutic options.

Dozens of genes have been implicated as candidates for explaining, at least partly, susceptibility to obesity in different individuals; gene–gene interactions are highly probable in most cases (315–319). Only in rare instances is a monogenic explanation invoked. Of these, the most common appears to be a mutation in the melanocortin-4 receptor gene (MC4R), which interferes with satiety signals mediated by *a*-melanocyte-stimulating hormone. This mutation may account for up to 4% of severe obesity in humans. A variety of mutations may interfere with leptin signaling, and some of these may prove to be monogenic causes of obesity. One hundred and twenty-seven candidate genes for obesity-related traits were listed in the Human Obesity Gene Map (320) and genetic studies have shown 97 BMI-associated loci in genome-wide association studies (321).

Leptin, produced in adipose tissue, binds to receptors in the hypothalamus, providing information about the state of energy storage and affecting satiety (322,323). Binding of leptin inhibits secretion of neuropeptide Y, which is a potent stimulator of appetite.

The Ob gene was originally identified in mice. Ob/Ob mice are deficient in leptin and, as a result, gain enormous amounts of weight (324). Administration of leptin to Ob/Ob mice results in rapid weight loss. In humans, obesity is associated with elevated leptin levels (325). Nonetheless, the administration of leptin in humans has only been associated with modest weight loss (326), suggesting that leptin resistance rather than deficiency may be an etiologic factor in some cases of human obesity (327). Leptin is the primary chemical messenger that signals adipocyte repletion to the hypothalamus; leptin resistance thus has the potential to delay or preclude satiety. The importance of leptin to the epidemiology of obesity has been reviewed (328–331).

Much of the genetic influence on weight regulation may be mediated by variation in REE (332), and appetite/satiety, addressed in Chapter 38 (333).

While the contribution of genes to obesity deserves both recognition and respect, it should not distract from the ultimate hegemony of environmental influences. Genes help explain varied susceptibility to, and expression of, obesity under any given set of environmental conditions. Stated another way, genes help explain the expanse of the “bell curve” characterizing the distribution of weight in a given population at a given time. Isolating the effects of genes on obesity from obesigenic elements in the environment is a considerable challenge (334); thinking of obesity as a product of gene–environmental interaction in most cases may be the best means of meeting this challenge at present (335,336).

Environmental factors better explain the position of that entire bell curve relative to a range of potential distributions. The genetic profile of US residents today, for example, may be quite similar to the profile 60 years ago, while the weight distributions for those two populations differ dramatically. The explanation for this divergence over time has much more to do with environmental change than with genetic change.

The Gut Microbiome and Obesity

Recent advances have allowed scientists to identify common microorganisms inhabiting the human

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intestinal tract. Initial research done in mouse models (337–339) followed by subsequent studies in humans (340–342) demonstrated distinct gut microbiota in persons with obesity as compared to lean individuals. For example, persons with higher ratios of *Prevotella* to *Bacteroides* species have been shown to lose more weight on calorie-restricted diets (343). Moreover, studies suggest that these differences in gut microbiota may affect energy balance by influencing gastrointestinal absorption of ingested nutrients and energy, such as microbial enzymatic action on otherwise undigestible polysaccharides (344). Interestingly, the effects of the microbiome on obesity seem to be transmissible. In mouse models, "transplantation" of gut microbes from obese mice to normal mice results in greater increases in total body fat as compared to those receiving microbes from lean mice (345). However, as yet there is not clear evidence that prebiotic or probiotic supplementation has any meaningful impact on weight management (346,347). Two straightforward tactics are likely to be beneficial: avoiding overuse of antibiotic treatments, which risks negatively manipulating the microbiome, and consuming sufficient fiber and prebiotic nutrients via a reasonable dietary pattern (348,349).

Environmental Obesigenicity

The term "obesigenic" has been coined to characterize the constellation of factors in the modern environment that contribute to weight gain. Obesigenicity ensues from any influence that contributes to a relative increase in energy intake or a relative decline in energy expenditure. Weight gain and eventually obesity result whenever habitual energy intake exceeds habitual energy expenditure.

Obesigenic elements in modern societies encompass labor-saving technology; energy-dense, low-cost, ubiquitous food; food marketing; reliance on cars; suburban sprawl; time demands that preclude food preparation at home; school policies that curtail physical education; and more.

When contending with obesity and weight control at the level of an individual patient or family, the clinician is well advised to consider the contributory forces at the social level that render obesity so prevalent and relentless. An appreciation for environmental obesigenicity fosters realistic perspectives on the causes and solutions for obesity and protects against the temptation to "blame the victim." The evolutionary context that best highlights the obesigenicity of the modern environment is the subject of Chapter 44. Implications for effective obesity control are addressed in Chapter 47.

Dieting, Dietary Pattern, and Weight Management

Energy intake varies with the macronutrient composition of the diet. Each gram of dietary carbohydrate releases 4 kcal of energy when metabolized, each gram of protein releases slightly less than 4 kcal, and each gram of fat releases approximately 9 kcal on average. There is, of course, variation around these average values among the diverse food sources within each macronutrient category.

Despite significant variability in basal metabolism, it is possible to estimate energy requirements. Several formulas are available to approximate energy needs based on age, body mass, and state of health. The most widely cited of these are the Harris–Benedict Equation and simplifications of it (see Appendix A). Such formulas typically are used to determine the caloric requirements of inpatients receiving total parenteral nutrition, but they are equally applicable to the ambulatory setting. Although it is relatively straightforward to estimate caloric needs, the utility of doing so in the outpatient setting is debatable. Unless a patient is willing to carefully count calories, there is likely to be a substantial discrepancy between a formulaic recommendation and actual practice. The availability of software, internet services, and smartphone apps for tracking nutrition and calorie intake may render determination of energy needs more useful.

Because approximately 70% of calories are spent on basal metabolism, even vigorous physical activity

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may be insufficient to control weight when caloric intake substantially exceeds the needs of REE. Although the energy intake required to maintain weight varies substantially among individuals, the degree of caloric restriction, relative to habitual intake, required to produce weight loss is more predictable. Each pound of body fat represents a repository of approximately 3,500 kcal, as noted previously. To lose a pound of fat requires that energy expenditure be increased by 3,500 kcal or that intake be restricted by a comparable amount (or a combination of the two). To reduce caloric intake by 3,500 kcal over a week requires a daily restriction of approximately 500 kcal. In a 2,000 kcal diet, this represents a 25% reduction in total calorie intake. Therefore, whatever the baseline calorie intake required to maintain weight, a reduction of 500 kcal/day will generally result in approximately 1 lb of weight loss per week initially. However, as noted previously, due to counter-regulatory mechanisms that occur during weight loss this rule of thumb breaks down after a few weeks of sustained energy deficit (228,229). As a result, further reductions may be required to continue this pace of weight loss (see Chapter 47).

Successful dietary approaches to weight loss involve either restricting overall calories or restricting specific foods or macronutrient classes. There is an intuitive rationale for restricting dietary fat in efforts to control weight: It is the most calorically dense macronutrient and the least satiating per calorie. Per gram, fat contains at least twice as much energy as protein or carbohydrate. The fiber, protein, and water content of foods all contribute to their satiating effects, facilitating fullness with fewer calories, whereas fat produces the opposite effect, increasing the calories required to feel satisfied (350). Consequently, every gram of fat removed from the diet would need to be replaced with twice the mass of these other macronutrients to replace the lost calories. In addition, because carbohydrate sources in particular are apt to contain at least some fiber that is noncaloric, the volume differential between fat and carbohydrate to achieve the same calorie load is even greater than the mass difference. At a certain point, volume becomes limiting in calorie intake (this topic is addressed in Chapter 38).

However, there is evidence that fat restriction has important limitations in achieving weight control. Although NHANES data suggest that the proportion of total calories consumed as fat has declined over recent years in the United States, total fat intake has been stable due to increases in the intake of calories from other macronutrient sources, particularly carbohydrate (351). Roughly 49% of calories in the typical American diet come from carbohydrate, roughly 15% from protein, 34% from fat, and 2% from alcohol (a concentrated source of calories, at 7 kcal/g; see Chapter 40).

There is evidence that, in general, portion sizes have been increasing in the United States for several decades at least, leading to an increase in total calories consumed, regardless of the source. The still-booming low-fat and nonfat food industry capitalized on the expectation of the public that fat restriction would facilitate weight control and promote health. For many, the result has been excessive intake of nutrient-poor foods that are high in simple sugars and low in fiber. Although these foods are less calorically dense than their higher-fat predecessors, they are often consumed in excess due to the ostensible “guiltlessness” of the consumer and possibly to lesser effects on satiety; fat-free yet sugary snacks are prototypical. Overindulgence in fat-reduced but energy-dense foods composed principally of simple carbohydrate, and the inevitable effects on weight contributed mightily to the dawn of the recent “low-carb” dieting era. In contrast to the patterns that prevailed, however, the guidance offered regarding low-fat eating always emphasized naturally low-fat foods, such as vegetables and fruits, rather than highly processed snack and dessert items. Such misapplication of dietary guidance appears to be a generalizable vulnerability when guidance is offered in terms of nutrient classes rather than foods (352).

In response to the accelerating obesity pandemic, competing weight-loss diets have propagated; those touting carbohydrate restriction have recently been most in vogue.

There are numerous reviews on the subject of diet for weight loss (59,353–371). The most basic

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conclusion, based on dozens of experimental trials, is that, on average, there appears to be little, if any, difference in weight loss outcomes from one dietary pattern to the next. When considering other health outcomes, in addition to weight loss, (let alone additional tangential outcomes, such as environmental sustainability and "planetary health"), in the aggregate, this literature lends strongest support to sensible, balanced diets abundant in fruits, vegetables, whole grains, and lean protein sources, with limited intake of ultra-processed foods and moderation of intake of dietary fat, simple sugars, and refined starches. Weight-loss approaches popular over recent years will be discussed in the next section, including fat-restricted diets, carbohydrate-restricted diets (including the Paleo and ketogenic diet), low-glycemic diets, and Mediterranean and other largely plant-based diets.

Fat-Restricted Diets

High dietary fat intake has historically been a powerful predictor of weight gain (372). Epidemiological studies have consistently shown that increasing dietary fat is associated with increased prevalence of obesity (373). Transcultural comparisons dating back at least to the work of Ancel Keys suggest that higher intake of dietary fat is associated with higher rates of obesity and chronic disease (374–376). Most authorities concur that high intake of dietary fat contributes to obesity at the individual and population levels. The theoretical basis for weight loss through dietary fat restriction is strong, given the energy density of dietary fat (377), which is the most energy dense and least satiating of the macronutrient classes on a calorie-by-calorie basis (378–380).

When fat restriction is in accord with prevailing views on nutrition (i.e., achieved by shifting from foods high in fat to naturally low-fat foods), the results are consistently favorable with regard to energy balance and body weight. A review of the results from 28 clinical trials showed that a reduction of 10% in the proportion of energy from fat was associated with a decrease in weight of 16 g/day (381). A 2-year randomized weight-loss trial comparing a very low-fat vegan diet to a more moderate low-fat diet found that both diets led to weight loss, but the subjects on the vegan diet incurred significantly greater weight loss at both 1 year (4.9 vs. 1.8 kg) and 2 years (3.1 vs. 0.8 kg) (382). In a recent review of 37 published studies in which participants were randomized to lower or higher fat dietary patterns but without intention to lose weight, those consuming lower fat intake consistently had improvements in weight, waist circumference, and body composition (383). In a meta-analysis of 32 controlled, isocaloric feeding studies energy expenditure and fat loss were greater with lower-fat diets compared with low-carbohydrate diets (384).

Despite the extensive literature supporting dietary fat restriction for weight loss and control, there are dissenting voices (385). For the most part, dissent is predicated on the failure of dietary fat restriction to achieve population-level weight control in the United States. Recent trends in the United States suggest that fat intake over recent decades has held constant, not been reduced, and that intake of total calories has risen to dilute the percentage of food energy derived from fat; increased consumption of highly processed, fat-reduced foods is the principal basis for these trends (386). Thus, the failure of dietary fat restriction to facilitate weight control is likely more a problem of how the guidance has been applied than errancy in the guidance itself (387).

In response to the public's interest in fat restriction, the food industry generated a vast array of low-fat, but not necessarily low-calorie, foods over the past two decades. The increase in calories was driven by increased consumption of calorie-dense, nutrient-dilute, fat-restricted foods, contemporaneous with a trend toward increasing portion sizes in general (350,388–391). Lowering the fat content of processed foods while increasing consumption of simple sugars and starch is not consistent with the long-standing recommendations of nutrition authorities to moderate intake of dietary fat. Yet, it is this distorted approach

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to dietary fat "restriction" that best characterizes secular trends in dietary intake at the population level and that subtends the contention that dietary fat is unrelated to obesity.

Carbohydrate-Restricted Diets

The popularity of carbohydrate-restricted diets for weight loss has reshaped the US food supply. While recent preoccupation with this dietary practice has been particularly intense and widespread, it is worth noting that interest in carbohydrate restriction for weight loss is not new; Atkins' *Diet Revolution* was first published in 1972 (392) and it followed several low-carb dieting fads in the century preceding this publication. The degree of carbohydrate restriction is often designated as low-carbohydrate (daily carbohydrate intake of 60–130 g) or very low carbohydrate (less than 60 g/day).

Review of low-carbohydrate diets to date suggests that short-term weight loss is consistently achieved, but proving sustainability of the early weight loss has been more challenging. This may be due, in part, to the tendency for much of the initial weight loss on low-carbohydrate diets being caused by fluid loss secondary to glycogen breakdown (393–398). Brehm et al. (399) examined weight loss, cardiac risk factors, and body composition in 53 women with obesity randomly assigned to a very-low-carbohydrate diet or a calorie-restricted, balanced diet with 30% of calories from fat. Subjects assigned to the very-low-carbohydrate diet group lost more weight (8.5 ± 1.0 vs. 3.9 ± 1.0 kg; $p < 0.001$) and more body fat (4.8 ± 0.67 vs. 2.0 ± 0.75 kg; $p < 0.01$) than those assigned to the calorie-restricted, balanced diet group; cardiac risk measures improved comparably in both groups at 6 months. Sondike et al. ran a 12-week weight-loss trial comparing low-carbohydrate to moderately fat-restricted diets in 30 overweight adolescents. There was significantly greater weight loss with the low-carbohydrate assignment. However, LDL cholesterol levels improved with fat restriction but not with carbohydrate restriction (400). In a meta-analysis of Randomized Controlled Trials (RCTs) of low-fat versus low-carbohydrate diets, the slightly greater weight loss achieved in the low-carbohydrate group at 6 months vanished by month 12 (401). A systematic review published in *Lancet* in 2004 found that weight loss achieved while on low-carbohydrate diets was associated with the duration of the diet and restriction of energy intake but not with restriction of carbohydrates per se (402).

Carbohydrate restriction does appear to improve satiety and decrease hunger, perhaps lending to its greater success in short-term weight loss. One study investigating carbohydrate and fat restriction effects on hunger perception in overweight premenopausal women suggested that a greater decrease in hunger perception may lead to a greater weight loss observed in the carbohydrate-restriction group (403). A recent systematic review of RCTs of low-carbohydrate diets did find that across the board there was a higher attrition rate in the low-fat groups compared to low-carbohydrate groups (404), supporting this theory.

However, the anorexic effect of a lower-carbohydrate diet may in fact be related to the increased protein content, not the restriction of carbohydrates; protein is noteworthy for its high satiety index (405,406). In 1999, Skov et al. (407) reported an interesting variation on the low-carbohydrate diet theme by comparing two fat-restricted (30% of calories) diets, one high in carbohydrate (58% of calories) and the other high in protein (25% of calories). The researchers followed 65 overweight adults for 6 months and gave them diets strictly controlled with regard to nutritional composition but unrestricted in calories. More weight was lost with high protein (8.9 kg) intake than with high carbohydrate (5.1 kg) intake; no weight loss occurred in a control group. Furthermore, a recent meta-analysis comparing isocaloric low-fat diets differing only in proportion of carbohydrates and protein have found increased weight loss with high-protein, lower-carbohydrate diets than with high-carbohydrate, lower-protein diets (407,408).

While interest in the Atkins and South Beach diet has slowed, new interest in the so-called Paleolithic

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diet and the plant-based "eco-Atkins" diets (409) has brought new popularity to the high-protein, lower-carbohydrate approach. These diets emphasize consumption of foods found in the supposed "native" human environment—plants, nuts, seeds, legumes, eggs, and in the case of the Paleo diet, fish and lean meats—while eschewing all grains and sugar. While evidence is limited, one small 3-month pilot study of patients with type 2 diabetes found improved glycemic control and increased weight loss when subjects adhered to the Paleo diet compared to a conventional diabetes diet (410). Recent hype aside, benefits likely increase when adherents use it as guidance away from high carbohydrate, processed foods, and weight loss will likely follow the same pattern seen in many of the existing low-carbohydrate studies (411), with unclear health benefits unless following the equally "Paleo" practices of our Stone Age ancestors of consuming as much as 100-g fiber daily and burning up to 4,000 cal/day through vigorous activity.

Two studies of low-carbohydrate diets that received widespread attention are those by Samaha et al. (412) and Foster et al. (413), published in the same issue of the *New England Journal of Medicine* in 2003. Samaha et al. compared a very-low-carbohydrate diet (<30 g carbohydrate/day) to a fat- and calorie-restricted diet in 132 adults with BMI of 35 or above over a 6-month period. The carbohydrate-restricted diet resulted in greater weight loss at 6 months than the low-fat diet, but was also associated with a far greater reduction in daily calorie intake (a mean reduction of 271 kcal/day for the low-fat diet and 460 kcal for the low-carbohydrate diet). Foster et al. compared the Atkins diet, as described in *Dr. Atkins' New Diet Revolution* (414), to a fat- and calorie-restricted diet in 63 adults with obesity followed for 12 months. The low-carbohydrate diet produced significantly greater weight loss at 6 months but not 12 months. Calorie intake was not reported. In both studies, attrition and recidivism were high; Samaha et al. noted that their trial was unblinded, whereas Foster et al. made no mention of blinding. Foster published a follow-up study in 2010 again comparing a low-carbohydrate diet to a low-fat diet, this time for 2 years. The low-carbohydrate diet produced just slightly greater weight loss at 12 months, with no difference compared to the low-fat diet by year 2 year of follow-up (415).

In a widely publicized study comparing the effectiveness and adherence rates of four popular weight-loss diets among overweight subjects with hypertension, dyslipidemia, or fasting hyperglycemia, Dansinger et al. (207) found no significant difference in mean weight loss between groups at 1 year (416). Predictably, the study reported no significant differences in mean total calorie reduction between groups, lending support to the widely accepted notion that total calorie consumption, regardless of macronutrient content, is of prime importance in weight-loss efforts. All diet groups (Atkins, Weight Watchers, Ornish, and Zone) had poor adherence rates, with no significant difference between groups. In all diet groups, greater adherence to the diet resulted in improved weight outcomes; participants in the top tertile of adherence had a mean loss of 7% body weight. No significant differences in cardiac risk factors were noted across groups; in each group, the amount of weight loss predicted improvements in several risk factors.

Fairly similar results were seen in a study by Gardner et al. (417) published in 2007. These investigators randomized just over 300 premenopausal women to one of four diets: the Atkins diet, the Zone diet, the Ornish diet, or the LEARN cognitive behavioral therapy program. At 12 months, weight loss was greatest in the Atkins group, differing significantly only from the Zone diet. Cardiac risk factors assessed included lipids, blood pressure, insulin, and glucose and were fairly similar across treatment categories. Media attention to the study was intense and generally ignored several salient limitations. First, weight loss was limited in all four diet groups; the Atkins group lost a mean of roughly only 10 lb in a year. Second, the Atkins group was gaining back weight faster than the other groups at the 12-month mark. Third, the two treatment assignments that differed most in outcomes (Atkins and Zone diets)

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differed least in dietary composition, obviating any simple conclusions about the association between macronutrient profile and weight loss.

Yancy et al. (418) compared a low-carbohydrate diet plus nutritional supplementation to a low-fat diet with calorie deficit of 500 to 1,000 cal/day among 120 overweight subjects with hyperlipidemia. Both groups received exercise recommendations and attended group meetings. The low-fat diet group lost significantly less weight than the low-carbohydrate diet group at 6 months (mean change, −12.9% vs. −6.7%; $p < 0.001$). The low-carbohydrate group had lower attrition, yet the low-fat group appeared to have better adherence to the diet.

Brinkworth et al. (419) compared the effectiveness at 68 weeks of two calorie- and fat-controlled 12-week diets: a standard protein group (15% protein, 55% carbohydrate) and a high-protein group (30% protein, 40% carbohydrate). Results indicated no significant difference in weight loss between groups; however, neither group had high compliance with the diet. Both diets significantly increased HDL cholesterol concentrations ($p < 0.001$) and decreased fasting insulin, soluble intercellular adhesion molecule-1 (sICAM-1), and C-reactive protein (CRP) levels ($p < 0.05$).

In a small group of patients with obesity and type 2 diabetes that consumed habitual diets for 7 days followed by a low-carbohydrate diet for 14 days, Boden et al. (420) found that the two-week low-carbohydrate diet resulted in spontaneous reduction in energy intake by almost one third, from 3,111 kcal/day to 2,164 kcal/day; weight loss during this period was completely accounted for by reduced caloric intake. This study highlighted the calorie reduction associated with carbohydrate restriction that, while providing an obvious mechanism for inducing weight loss, is frequently left unmentioned (421). Several other studies comparing low-carbohydrate to low-fat or conventional diets with durations ranging from 6 to 12 weeks were reviewed. Studies using comparable energy intake among subjects across groups consistently reported comparable weight loss, regardless of the target population (422–426).

Another study examining isocaloric diets differing only in carbohydrate composition came to similar results. Golay et al. (424) assigned 68 overweight adults to approximately isocaloric low- (25% of calories) and moderate- (45% of calories) carbohydrate diets for 12 weeks; they observed comparable losses of weight, waist circumference, and body fat in both groups. For the most part, metabolic indices were favorably and comparably influenced by both diets as well.

Poppitt et al. (427) achieved significant weight loss among 46 adult subjects with metabolic syndrome followed for 6 months by substituting carbohydrate for fat. Complex carbohydrate substitution for fat was associated with both weight loss and amelioration of the lipid profile; the substitution of simple carbohydrate for fat did not result in weight gain.

Most recently, the so-called “carbohydrate-insulin model of obesity” has been proposed, in which it is theorized that increased insulin secretion caused by higher carbohydrate intake drives fat accumulation in adipose tissue and away from oxidation, thereby causing a state of “cellular starvation,” which leads to increased hunger and suppression of energy expenditure (428). Carefully controlled experimental trials have failed to support this hypothesis, and a meta-analysis of 32 controlled feeding studies found that energy expenditure was lower with low-carbohydrate diets (384,429).

The recent preoccupation with carbohydrate restriction appears to be reactionary to the prior era during which fat restriction was hyped. The popular press and media reports suggest that the public feels misled by promises that fat restriction would lead to weight loss. In particular, the widely known US Department of Agriculture (USDA) food guide pyramid came under attack as a contributor to worsening obesity rates (430) and was replaced by MyPlate (431), which was still criticized as vague, not representative of the best available evidence, and influenced by special interest groups (432). The adulteration of messages in the pyramid under the influence of special interest groups is the subject of a

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popular book (433). As this edition of Nutrition in Clinical Practice is being prepared, the 2020 Dietary Guidelines for Americans has been released and rightly avoids recommending specific macronutrient profile diets but rather emphasizes the synergistic properties of dietary patterns as a whole. The competition between low-fat and low-carbohydrate diets for weight loss has in some ways polarized debate beyond the point of reason or utility (421,434). There is little to suggest that the selective vilification of a macronutrient class is prudent or useful in the pursuit of sustainable weight loss.

In contrast with indiscriminate restriction of carbohydrates, lowering carbohydrate intake while focusing on healthier sources of fats and proteins may improve cardiovascular risk. In two large cohort studies that followed nearly 130,000 adults over more than two decades, low carbohydrate intake of primarily vegetable sources of protein and fats was associated with approximately 20% lower overall and cardiovascular mortality and low-carbohydrate diets based primarily on animal sources were associated with higher mortality rates (435).

During 26 years of follow-up of women in the Nurses' Health Study and 20 years of follow-up of men in the Health Professionals' Follow-up Study, low-carbohydrate diets in the highest versus lowest decile for vegetable proteins and fat were associated with lower all-cause mortality (hazard ratio [HR] 0.80, 95% CI 0.75–0.85) and cardiovascular mortality (HR 0.77, 95% CI 0.68–0.87) [30]. By contrast, low-carbohydrate diets in the highest versus lowest decile for animal protein and fat were associated with higher all-cause (HR 1.23, 95% CI 1.11–1.37) and cardiovascular (HR 1.14, 95% CI 1.01–1.29) mortality. (See “Dietary fat” and “Overview of primary prevention of cardiovascular disease,” section on “Healthy diet.”)

Low-Glycemic Diets

Advocates of low-carbohydrate diets often share a common rationale pertaining to minimizing the glycemic index (GI) or glycemic load (GL) of the diet. The GI of a food is a measure of how much its ingestion raises blood glucose levels postprandially, measured as the area under the glucose curve (436). Carbohydrate-containing foods can be ranked according to the typical postprandial glycemic response they induce (437). The GI, developed by Dr. David Jenkins et al. (438) at the University of Toronto in 1981, compares foods on the basis of a fixed and equal dose of intrinsic carbohydrate, customarily 50 g. This fixed-dose comparison is a weakness of the index when it is applied to dietary guidance. Nearly 10 medium-sized carrots are required to produce a 50-g dose of carbohydrate, as compared to 1 cup of vanilla ice cream. Ice cream consequently has a markedly lower GI than carrots (see Table 5.5). This deficit led to the development of the GL. Taking both GI and standard serving sizes into account, the GL is the weighted average GI of a food multiplied by the percentage of energy from carbohydrate (439,440) and is believed to better predict the glycemic impact of foods under real-world conditions (437).

TABLE 5.5

Glycemic Index of Some Common Foods

Food Group	Food	Glycemic Index
Breads	White bread*a*	100
	Whole-wheat bread	99
	Pumpernickel	78
Cereal products	Cornflakes	119
	Shredded wheat	97

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	Oatmeal	85
	White rice	83
	Spaghetti	66
	Bulgur wheat	65
	Barley	31
Fruit	Raisins	93
	Bananas	79
	Oranges	66
	Grapes	62
	Apples	53
	Cherries	32
Vegetables	Parsnips	141
	Baked potato	135
	Carrots	133
	Corn	87
	Boiled potato	81
	Peas	74
	Yams	74
Legumes	Lima beans	115
	Baked beans	60
	Chick peas	49
	Red lentils	43
	Peanuts	19
Dairy products	Yogurt	52
	Ice cream	52
	Milk	49
Sugar	Sucrose	86

[a]*Reference standard.*

Adapted from Jenkins DJ, Jenkins AL. The glycemic index, fiber, and the dietary treatment of hypertriglyceridemia and diabetes. J Am Coll Nutr. 1987;6:11–17.

The relationship between weight and BMI is roughly analogous to the relationship between GI and GL. Weight may be high, but a person may still be lean if they are tall. Similarly, the GI may be high, but the glycemic effect of that food may be modest if the carbohydrate content is relatively dilute. An expansive table of GI and GL values of common foods, published in 2002, is available at www.ajcn.org (441). A few foods representing the range of potential divergence between GI and GL are shown in Table 5.6.

TABLE 5.6

Glycemic Index and Glycemic Load of a Few Foods that Demonstrate How the Values May Diverge[a]

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Food	GI	Serving Size	Carbohydrate Dose (g)	GL
Chickpeas	51	150 g	30	11
Vanilla ice cream	54	50 g	9	3
Strawberries	57	120 g	3	1
Orange	69	120 g	11	5
Whole-wheat bread	73	30 g	13	7
Orange juice	81	250 mL	26	15
Coca-Cola	90	250 mL	26	16
Plain bagel	103	70 g	35	25
Doughnut	108	47 g	23	17
Carrots	131	80 g	6	5

[a]*The foods are listed from lowest to highest GI.*

GI, glycemic index; GL, glycemic load.

Data from Foster-Powell K, Holt SH, Brand-Miller JC. International table of glycemic index and glycemic load values: 2002. Am J Clin Nutr. 2002;76:5–56.

A review suggests that low-GL diets are associated with marked weight benefits and loss of adiposity in ad libitum studies of adults and children (442). Some studies suggest that the primary mechanisms by which low-GI foods may facilitate weight loss is through their ability to increase satiety and reduce subsequent food intake (443,444). However, a meta-analysis that included 183 participants involved in 11 clinical trials revealed no difference between high-GI or low-GI breakfasts on intake at the subsequent meals (445).

A trial by Ebbeling et al. (446) reveals some of the potential distortions introduced when means of improving dietary intake pattern are considered as mutually exclusive of one another. This group of investigators compared a diet reduced in GL, with 30% to 35% of calories from fat, to a diet termed “conventional” in which fat was restricted to 25% to 30% of calories, but the quality of the carbohydrate choices was unaddressed. The reduced-GL diet resulted in slightly greater weight loss and control of insulin resistance than the control diet in the 16 adolescents with obesity followed. What seems most noteworthy, however, is that the range of fat intake for the low-fat and low-GL diets was actually contiguous. Thus, this study actually compared two diets that differed little with regard to fat content, one in which GL was controlled, the other in which it was not. This is very much like comparing complex to simple carbohydrate and finding that complex carbohydrate has preferable health effects. Regrettably, in the rush to defend competing dietary claims, this simple message is obscured.

Overall evidence suggests that with regard to weight loss, both high- and low-GI or GL diets will produce equivalent weight loss over 6 months, assuming equivalent dietary fat and carbohydrate intake. Two short-term trials investigating the role of GI on energy intake, weight, and risk factors for chronic disease found no significant differences between groups in energy intake, body weight, or fat mass (447,448). Longer-term studies are mixed. Data from three cohort studies comprising 120,784 men and women followed over 16 years suggested a small increase in weight gain in those who tended to consume higher-GL diets (449). In this and other studies, it is likely that weight loss from low-GI/GL dietary patterns is more likely to be caused by higher fiber and/or protein intake, which both tend to increase

satiety (450).

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Low-GL diets may support children in obesity prevention. In 2000, Spieth et al. (451) reported the results of a retrospective cohort study comparing a low-GI diet to a low-fat diet for weight loss in 107 children with obesity. Greater reduction in the BMI was observed at approximately 4 months in the low-GI group (−1.53 kg/m^2 [95% CI, −1.94 to −1.12]) than in the low-fat diet group (−0.06 kg/m^2 [−0.56 to +0.44], $p < 0.001$).

While low-GL diets may not have any unique bearing on weight loss compared to other approaches, they do appear to have positive benefits on metabolic markers and glycemic control. In a 2002 study by Heilbronn et al. (452), 45 overweight subjects with type 2 diabetes were randomly assigned to either a high- or low-GI diet following 4 weeks of a high-saturated-fat diet. All diets were energy restricted. Weight loss did not differ between treatments; however, a significantly greater reduction in LDL was observed on the low-GI diet. A 6 month trial of Asian women without diabetes and a history of gestational diabetes randomized into a high-GI or low-GI group; significant reductions in body weight, BMI, and WHR were observed only in the low-GI group ($p < 0.05$), as were significant improvements in glucose tolerance (453).

A recent review suggests that low-GL diets are associated with marked weight benefits and loss of adiposity in ad libitum studies of adults and children (454).

Few authors have explicitly addressed the fact that there are various means of achieving a diet with a low GL overall. McMillan-Price et al. (455) did so in a randomized trial of roughly 130 overweight adults. Two diets relatively high in carbohydrate and two diets relatively high in protein (and thus, lower in carbohydrate) were compared on the basis of differing GLs. The study showed, as most do, that restricting calorie intake by any means led to roughly comparable weight loss in the short term, although trends hinted at a benefit of low GL. The percentage of subjects achieving a weight reduction of at least 5% was significantly greater on the low-GL diets irrespective of whether they were high-carbohydrate or high-protein diets than on their higher-GL counterparts. Similarly, body fat loss was enhanced, at least among women, by the low-GL diets. Whereas LDL cholesterol decreased significantly on the high-carbohydrate, low-GL diet, it actually increased on the high-protein, low-GL diet.

Aggregated, these findings point strongly toward the importance of food choices, rather than choices among macronutrient categories, as a major arbiter of cardiac risk. A low-GL diet can be achieved by minimizing carbohydrate intake, but this approach is apt to “toss out the baby with the bathwater.” High-carbohydrate foods such as most whole grains, beans, legumes, vegetables, and even fruits can contribute to a low-GL dietary pattern. Such foods also provide a diversity of micronutrients of potentially great importance to overall health, and cardiovascular health specifically, antioxidant flavonoids and carotenoids noteworthy among them.

By demonstrating that a high-carbohydrate, low-GL diet may offer particular cardiac benefit, this study points toward a diet in which choice within macronutrient categories is given at least as much consideration as choice among those categories. This perspective is concordant with a large volume of research suggesting that cardiac risk may be mitigated by reducing dietary fat and by shifting fat intake from saturated and trans fatty acids to monounsaturates and polyunsaturates. Cardiac health at the population level will likely be well served when dietary guidance is consistently cast in terms of healthful, wholesome foods rather than competition among the three macronutrient classes from which a diet is composed.

Mediterranean Diets

The Mediterranean diet differs from the typical US diet in the quantity and quality of fat and the quantity

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of unrefined grains, vegetables, fruit, and lean protein sources (456). The Mediterranean dietary pattern is low in saturated fat and high in monounsaturated fatty acids, high in antioxidants including vitamins C and E, and high in fiber and folic acid. Olive oil is the dominant fat source, and consumption of fruits and vegetables, grains, fish, and legumes are moderate to high. Wine is commonly served with meals (457). Although there is variation in the Mediterranean diet, depending on country and region due to cultural, ethnic, religious, economic, and agricultural production differences (456,458–460), the dietary characteristics common to the region have been consistently associated with good health and longevity. Of note, many of the Mediterranean populations enjoying good health have traditionally high rates of physical activity compared to Western societies (461), potentially confounding comparisons based on dietary pattern.

The Mediterranean diet is relatively high in total fat. Some have expressed concerns that adherence to this diet may promote weight gain (462). However, because of the overall pattern of foods in this diet, i.e., its emphasis on whole foods and vegetarian protein sources, it is not based largely on energy-dense foods as most higher-fat diets tend to be. Data from a population-based study of 23,597 adult men and women suggest that adherence to a traditional Mediterranean diet is unrelated to BMI in both sexes, after adjusting for total energy intake. Rising obesity rates observed in Mediterranean populations have been ascribed to falling levels of physical activity in conjunction with new dietary influences from the United States, contributing to increased energy intake (463).

Evidence from cross-sectional studies generally supports a beneficial association between weight status and the traditional Mediterranean dietary pattern (464,465). Based on a sample of more than 3,100 Spanish men and women, Schroder et al. found that obesity risk decreased in men and women with increasing adherence to the traditional Mediterranean dietary pattern ($p = 0.01$ and $p = 0.013$, respectively) (464).

The evidence is convincing that energy-dense foods generally contribute to weight gain. However, it is also clear that when energy restriction can be achieved on a diet relatively high in fat content, weight loss is achieved (466). A Mediterranean diet, which is high in monounsaturated fatty acids but not predominantly composed of energy-dense foods, may be more effective at long-term weight loss than a diet based predominantly on restriction of total fat because it may be more palatable and therefore better sustained.

McManus et al. (467) evaluated a calorie-controlled, moderate-fat Mediterranean diet compared to a standard low-fat diet (also calorie controlled). The Mediterranean diet resulted in superior long-term participation and adherence, leading to greater weight loss. The moderate-fat group lost a mean of 4.1 kg, reduced BMI by 1.6 kg/m^2, and lowered waist circumference by 6.9 cm, compared to increases in the low-fat group of 2.9 kg, 1.4 kg/m^2, and 2.6 cm, respectively, at 18 months ($p < 0.001$) (467). A 2004 study by Flynn et al. (468) demonstrated weight loss along with a reduction in cholesterol levels and increased feelings of well-being among 115 postmenopausal women after 15 months on a Mediterranean diet. The intervention involved a weekly cooking class for 1 year, with professional chefs providing training in the correct use of natural ingredients of traditional Mediterranean cuisine.

Esposito et al. followed 3,000 women and 3,600 men for 4 years as half adhered to a Mediterranean-style diet and half to a low-fat diet based on AHA guidelines. At year 1, subjects in the Mediterranean arm had lost significantly more weight than their low-fat dieting counterparts (−6.2 vs. −4.2 kg). This difference was attenuated by the end of the 4-year study (469). One important limitation of this study and others is that diet was self-reported.

There is some evidence that in addition to facilitating weight loss, a moderately hypocaloric

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Mediterranean diet may also improve body composition and health outcomes, improving metabolic profile and preventing loss of fat-free mass (470). A meta-analysis of 20 RCTs evaluating different dietary approaches to weight loss in people with type 2 diabetes found that the Mediterranean diet had the greatest effect on glycemic control of any dietary approach, and along with a low-carbohydrate diet led to the greatest weight loss in subjects (471). Another meta-analysis found that Mediterranean diets appear to be more effective than low-fat diets in improving cardiovascular risk factors such as high blood pressure, dyslipidemia, and inflammatory markers (472). Most notably, a multicenter randomized trial of 7447 persons at high risk for cardiovascular disease followed for nearly 5 years showed 30% reduced hazard ratio for major cardiovascular events in those assigned to a Mediterranean diet supplemented with extra-virgin olive oil or mixed nuts, compared with a control group that was advised to reduce dietary fat intake (473).

It is worth noting that although many studies have demonstrated successful weight control and health improvements with adoption of the Mediterranean diet (467,470), some have included supports such as cooking classes to ensure that participants learn how to correctly use the natural ingredients of traditional Mediterranean cuisine (468). More research is needed to determine whether the Mediterranean diet can be realistically and reliably implemented and sustained among free-living populations in the United States, given the current state of ubiquitous access to, and American affinity for, energy-dense snacks and fast foods. Continuing to eat oversized servings of “French fries,” but adorning them with olive oil, does not qualify as a healthful application of the Mediterranean diet.

Weight-Loss Diets and Body Composition

One of the most tantalizing claims of popular weight-loss diets is that weight loss can be achieved or facilitated by means other than energy deficit. Deemphasizing calories is, in fact, quite characteristic of popular weight-loss approaches. Proponents of carbohydrate restriction contend that limiting intake of carbohydrate allows for weight loss, regardless of calorie intake (474). At least one study reported at the 2003 meeting of the North American Association for the Study of Obesity (475) suggested greater weight loss over a 12-week period among subjects on a low-carbohydrate diet than among those on a low-fat diet, despite 300 more cal/day on the carbohydrate-restricted assignment.

However, only limited data are available to date on the effects of carbohydrate restriction on body composition. There is clear evidence of a dehydrating effect of very-low-carbohydrate diets, and of ketosis, in the short term (59); thus, some of the early weight loss on low-carbohydrate diets is almost certainly water. This may explain why low-carbohydrate diets often show increased weight loss in the short term, yet long-term trials fail to show persistent differences in weight loss compared to low-fat or Mediterranean diets (471). An association between increasing dietary fat and increasing body fat has been noted (463). Nelson et al. (476) reported a positive association between dietary fat and body fat and negative associations with body fat for both total and complex carbohydrate.

Hays et al. (477) reported that a diet rich in complex carbohydrate resulted in an increase in lean body mass and a decrease in body fat among 34 subjects with impaired glucose tolerance. Similar results have been observed by other groups (478). Volek et al. (479), however, reported a loss of body fat and an increase in lean body mass with carbohydrate restriction in 12 volunteers followed for 6 weeks. The effects of physical activity on body composition are, of course, clear and noncontroversial, with increased activity leading to relative increases in lean body mass at the expense of body fat (53,480).

Recent focus in the specific metabolic properties of fructose has led to vilification of fructose, especially high-fructose corn syrup, for its role in the obesity epidemic (481). Indeed, Americans consume too much sugar, and added dietary sugar has been linked to weight gain (482). There may be

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important physiologic distinctions in the way fructose is metabolized in the liver compared to sucrose (483). However, available evidence suggests that similar decreases in weight and body fat result from hypocaloric diets whether the primary sugar content is fructose or glucose (484), arguing against claims that the replacement of sucrose with high-fructose corn syrup is the biggest contributor to the rise in obesity. Furthermore, fructose as found naturally in whole fruit, in typical dietary consumption, has been shown to support weight loss and reduction of cardiovascular risk factors (485). Recommendations should therefore focus on reducing all refined sugar and processed simple carbohydrates, not replacing fructose with glucose or developing novel products such as "fructose-free" soda (483).

Overall, there is little evidence to support a claim that loss of body fat is achieved preferentially by redistributing macronutrients at isoenergetic levels (374,486). Worth noting, once again, is that a pound of body fat represents an energy reserve of over 4,000 kcal; a pound of muscle, a reserve of roughly 1,800 kcal; and a pound of water, no latent energy whatsoever. While each weighs a pound, each requires a markedly different energy deficit to be lost; water can be lost with no energy deficit. Thus, until proved otherwise, the most plausible explanation for enhanced weight loss at any given level of energy intake is the loss of body compartments that represent lesser energy reserves. Such losses of water and muscle protein are undesirable.

Popular Diets

A web search on Google using the terms "diet," "weight loss," and "weight control" yields 1.34 billion, 2.86 billion, and 2.32 billion entries, respectively (487). As impressive as the sheer magnitude of these results is the pace of growth: The same web search in 2013 in preparation for the 3rd edition of this text yielded "just" 134 million, 326 million, and 219 million entries, respectively (489). Thus, it is far beyond the scope of this or any other text—or even plausibility—to characterize even a representative sample of weight-loss diets, programs, and products being promoted to the general public.

The best that can be done to characterize these myriad claims on the basis of evidence is to apply a process of exclusion. In a systematic review of the obesity-prevention and obesity-control literature (488), strategies that emerge as most promising with regard to lasting weight control involve achieving an energy-controlled and balanced diet along with regular physical activity. Fundamentally, claims for virtually any other approach to sustainable weight loss are unsubstantiated. More recently, extensive literature analyses and systematic reviews on diets and dietary approaches for weight loss have time and again reinforced this, not least of which include those conducted by the NIH, American Heart Association, American College of Cardiology, and The Obesity Society as part of the NHLBI obesity management guidelines (489); the American Association of Clinical Endocrinologists, as part of their society's obesity guideline process (490); and the 2020 Dietary Guidelines for Americans Advisory Committee, as preparation for the most recent iteration of the Dietary Guidelines for Americans (491). There is little or no scientific evidence to support the contentions of the most popular diets, including those based on carbohydrate restriction (e.g., the Atkins diet), those based on preferentially increasing fat intake (e.g., the "keto" diet), those based on food combination or food proportioning (e.g., the Zone diet), those based on the GI (e.g., the South Beach diet, the GI diet), or those based on altering the timing of food intake (e.g., time-restricted feeding, intermittent fasting) (486). There is, of course, no shortage of anecdotal support and testimonials for virtually all the popular diets.

Due to recent popularity, "intermittent fasting" and the "keto" diet bear mention. Intermittent fasting loosely includes a range of strategies aimed at limiting certain days in which food is consumed (such as "alternate-day fasting") or limiting certain hours in which intake is allowed (known as time-restricted feeding). Though theories positing potential mechanisms of benefit of intermittent fasting abound, ranging

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from aligning circadian rhythms with meal patterns to improved fatty acid metabolism and others, there is little definitive data supporting unique timings of food intake with improved weight outcomes. While some rodent studies have suggested that intermittent fasting may increase metabolism and weight loss, human studies have largely failed to support this. In a trial of 100 persons with obesity, those who were randomized to an alternate-day fasting protocol and those who followed a standard calorie restriction diet had similar weight loss after 6 and 12 months (492). Among 116 participants randomized to time-restricted feeding, in which they were allowed to eat only from noon to 8 pm, or a traditional meal plan of three structured meals throughout the day, there was no difference in weight loss or cardiovascular risk factors between these groups during the 12 week trial (493). A meta-analysis of six controlled trials of intermittent fasting strategies lasting between 3 and 12 months found no difference in weight loss, compared with standard caloric reduction (494). It remains to be seen if certain types of intermittent fasting protocols are found to be of benefit for weight or other outcomes. For example, several (495–497) studies suggest that early-day time-restricted feeding, in which a greater part of daily intake is consumed in the early parts of the day may have weight management and health benefits, whereas late-day time-restricted feeding does not appear to have such benefits and may in fact worsen cardiometabolic health indicators, including glycemic control, insulin levels, blood pressure, and lipids (498,499). While this interesting outcome warrants additional study, it would seem prudent to characterize this support for the age-old wisdom of eating breakfast like kings and dinners like paupers, rather than a newfound magical way of timed eating. Ketogenic diets for weight loss, or “keto,” have jumped in popularity since the last edition of this text. The diet itself is not new, however, as published reports of ketogenic diets, which classically are composed of high-fat, moderate protein, and low-carbohydrate intakes, as treatment for epilepsy date to the early 20th century. A variant of carbohydrate-restricted diets, typical keto diet prescription includes at least 70% of calories from fat and approximately 20% and 10% from protein and carbohydrate, respectively. As with other carbohydrate-restricted diets, quick weight loss is not uncommon and may exceed what is achieved with a moderate- or high-carbohydrate dietary intake, but beyond the initial few months, weight loss outcomes do not appear to be different from other dietary patterns (500). As noted in the paragraph earlier, there is no consistent evidence supporting the superiority of ketogenic diets for weight management. Indeed, the recently published report of the Dietary Guidelines Advisory Committee did not even include a single mention of “keto” or “ketogenic” diets, despite thorough investigation during its review process.

Worth noting is that a modest proportion of the books on the subject of diet address not so much the *what* of weight loss as the *how*, describing strategies for achieving a diet and lifestyle that evidence indicates to be associated with both lasting weight control and good health. Among the offerings in this category are approaches based on energy density (501,502), water and fiber content (503), and the array of skills and strategies needed to navigate through the modern, “toxic” nutritional environment (504). Related to these are books dedicated to the same goal for children and/or families (505).

Potential Hazards of Popular Weight-Loss Diets

There is little to suggest that dietary fat restriction as a weight-loss or weight-control method poses any likelihood of harm, even if restriction of total fat is other than optimal. Perhaps because societies subject to high rates of obesity also tend to consume excessive quantities of harmful fats, the literature generally indicates that restriction of dietary fat is both conducive to weight loss and health promoting (506,507). Many cultures recognized for good health and longevity have native diets very low in fat (68); few free-living societies adhere to dietary patterns low in carbohydrate. The worst that can be said of fat restriction for weight loss is that if extreme, it may not be optimal for health (508). Even critics of dietary

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fat restriction appear to agree that low-fat diets offer health benefits relative to the typical American diet, which is high in saturated and trans fats.

Carbohydrate restriction, in contrast, when extreme, is actually or potentially linked to an array of adverse health effects (59). These adverse effects stem from wholesale reductions in carbohydrate intake and do not pertain to shifting calories within the carbohydrate class from sugars and refined grains to whole grains, fruits, and vegetables, a practice with widespread support.

There is evidence that weight loss attributable to carbohydrate restriction is in part body water loss. Gluconeogenesis consumes water along with glycogen, and ketone bodies cause increased renal excretion of sodium and water (509). Studies indicate that dizziness, fatigue, and headache are common side effects of ketosis (510).

Ketosis is potentially harmful, with possible long-term sequelae, including hyperlipidemia, impaired neutrophil function, optic neuropathy, osteoporosis, and protein deficiency, as well as alterations in cognitive function. Children on ketogenic diets as part of an antiseizure regimen have developed dehydration, constipation, and kidney stones. In response to ketosis, renal calcium excretion increases. To make up for the loss of calcium in urine, it is mobilized from bone to circulation (509). One study of adolescents on a ketogenic diet showed decreased bone mineral density after just 3 months, despite vitamin D and calcium supplementation (510). Sustained ketosis causes bone resorption, suggesting a risk for osteoporosis (511).

A comparison of eight high-protein, low-carbohydrate diets indicates that the Atkins diet had the highest level of total fat, saturated fat, and cholesterol (512). Consuming a diet high in saturated fat may raise total and LDL cholesterol levels, both of which contribute to cardiovascular disease. A significant increase in LDL has been reported among subjects on the Atkins diet, although this finding is inconsistent and is often accompanied by a potentially countervailing rise in HDL. An increase in CRP on the Atkins diet has been observed, suggesting an inflammatory response. A high intake of saturated fat generally increases the risk of insulin resistance (510), contradicting the contention of low-carbohydrate diet proponents that carbohydrates are to blame for insulin resistance (474). High-fat diets may also predispose to cancer (512).

High protein intake may negatively affect renal function and accelerate renal disease in patients with diabetes. In patients with renal dysfunction on a high-protein diet, there is glomerular damage causing spillage of plasma proteins and resultant tubular injury and fibrosis (510). Urinary calcium excretion is also increased, and hypercalciuria may ensue, predisposing to calcium stone formation (509). High protein intake imposes a metabolic burden on both the liver and kidneys, requiring additional excretion of urea and ammonia (513).

Extreme carbohydrate restriction is potentially associated with increased risk of dysthymia, if not depression, through a serotonergic mechanism (514). The production of serotonin in the brain requires delivery and uptake of tryptophan, which is influenced by both the availability of tryptophan and the actions of insulin. With very low carbohydrate intake and blunted insulin release, tryptophan delivery to the brain is impaired, serotonin production is limited, and mood instability has been reported to ensue (515); the public health significance of this mechanism remains uncertain.

Finally, high-protein, low-carbohydrate diets simply do not allow for adequate intake of fruits (and to a lesser extent, vegetables), restricting nutrient and fiber-rich foods shown to be protective against a wide array of chronic diseases (516–519). Soluble fiber lowers cholesterol, reducing the risk for cardiovascular disease, and lowers insulin secretion after meals by slowing nutrient absorption (510,520). By several mechanisms, fiber is thought to contribute to satiety and calorie control. Fruit and vegetable intake has long been, and remains, well below recommended levels in the United States

(521,522).

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The known and potential hazards of extreme carbohydrate restriction are summarized in Table 5.7.

TABLE 5.7

Known and Potential Adverse Effects of Extreme Restriction of Dietary Intake of Carbohydrate

Adverse Effect	Mechanism
Constipation	An established effect attributable to low intake of dietary fiber.
Dehydration	Gluconeogenesis consumes water along with glycogen, and ketone bodies cause increased renal excretion of sodium and water.
Depression/dysthymia	A theoretical risk due to impaired delivery of tryptophan to the brain and impaired serotonin production.
Halitosis	An established effect of ketosis.
Hepatic injury	A potential sequela of high protein intake over time.
Increased cancer risk	A potential sequela of increased consumption of animal products and decreased consumption of grains and fruit.
Increased cardiovascular disease risk	A potential sequela of increased consumption of animal products and decreased consumption of grains and fruit.
Nausea	An established side effect of ketosis.
Nephropathy	A potential consequence of high intake of protein over time.
Osteopenia	An established effect of ketosis. Hypercalciuria is induced by high intake of dietary protein.
Renal calculi	A known sequela of ketosis. Risk is increased by dehydration.

Adapted from Pagano-Therrien J, Katz DL. The low-down on low-carbohydrate diets: responding to your patients' enthusiasm. Nurse Pract. 2003;28:5,14.

Weight Loss Sustainability

As opposed to most people who commit a lifetime to sequential dieting, the literature on long-term weight loss success is thin; frequency of dieting is a negative predictor of lasting weight control (523). The best available data are from observational studies (524), transcultural comparisons, and the National Weight Control Registry (525). The Registry was established to characterize the behavioral patterns of individuals successful at long-term maintenance of considerable weight loss (an average loss of 30 kg maintained for over 5 years).

Registry data indicate that a relatively low-fat, and therefore energy-dilute, diet is a mainstay of successful weight maintenance, as is regular physical activity (526–529). Fundamentally, people successful at lasting weight control tend to subscribe to a pattern of behaviors highly concordant with prevailing recommendations for overall good health (288,526–528,530–532). Limited time spent watching television is also characteristic of long-term weight control (533). There is nothing to suggest that any other approach to weight loss, no matter the apparent advantages at the start, can compete with a healthful, balanced diet and regular physical activity in the long run.

Dietary Pattern and Health

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In the Diabetes Prevention Program, a low-calorie, low-fat diet coupled with moderately intense physical activity for at least 150 min/week reduced the incidence of type 2 diabetes by 58% (534). Similarly, the DASH Collaborative Research Group has shown that hypertension can be prevented and treated by reducing intake of saturated and total fat and adopting a diet rich in fruits, vegetables, grains, and low-fat dairy (535,536). Cardiovascular disease prevention has been demonstrated with both low-fat (537) and Mediterranean dietary patterns (538). Weight loss is a common element in all of these successful interventions.

Reviews of diet for optimal health do not necessarily demonstrate complete accord on all points but are nonetheless substantially confluent with regard to fundamentals (182). Diets primarily comprise unprocessed, whole foods, rich in fruits, vegetables, and whole grains; restricted in animal fats and trans fat from processed foods; limited in refined starches and added sugar; providing protein principally from lean sources; and offering fat principally in the form of monounsaturated and polyunsaturated oils are linked to good health (218,539–545). With regard to diet and optimal health, debate is substantially limited to variations on this basic theme rather than any fundamental departures from it. This topic is addressed at greater length in Chapter 45.

Health Implications of the "Native" Human Diet

A noteworthy contribution is made to considerations of dietary pattern and human health by the anthropology literature. Quite distinct from biomedical research, a fairly extensive body of work characterizes what is and is not known about the native nutritional habitat of our species. While there is debate about many details, there is general consensus that humanity adapted over eons to an environment in which calories were relatively scarce and physical activity demands were high (546). Saturated and trans fat intake were low and negligible, respectively; micronutrient intake was high; and protein intake was from lean sources (297,547).

The traditional human diet was of course low in both starch and sugar, but it was rich in complex carbohydrate from a variety of plant foods (297). Many, but not all, anthropologists suggest that we were more gatherers than hunters and that meat likely contributed less to our subsistence than did the gathering of diverse plant foods (548,549). That this should be relevant to human health requires nothing more than acknowledging that human beings are creatures. For all other species under our care, epitomized by zoological parks, the diet we provide is an adaptation of the diet consumed in the wild. The "native" human diet appears to have provided roughly 25% of calories from fat, 20% to 25% of calories from protein, and the remainder from complex carbohydrate (297); this pattern is remarkably confluent with that demonstrating compelling health benefit in clinical trials (534,535).

Dietary Guidelines for Weight Control, Health Promotion, or Both

On the basis of its review of evidence linking dietary pattern to health outcomes, the USPSTF advises clinicians to endorse to all patients over the age of 2 a nutrient-dense diet low in saturated fats, added sugars, and sodium, while abundant in fruits, vegetables, and whole grains (550,551). These recommendations are highly concordant with those of the National Heart, Lung, and Blood Institute at the NIH (552).

In 2010, the IOM released updated dietary guidelines reiterating its recommendations for 45% to 65% of calories from carbohydrate, 20% to 35% from fat, and 10% to 35% from protein, in conjunction with 60 min each day of moderately intense physical activity (553). The IOM guidelines further emphasize the restriction of saturated and trans fat and their replacement with monounsaturated and polyunsaturated fat. The American College of Preventive Medicine has formally adopted a position in support of dietary

recommendations within the IOM ranges since 2002 (554).

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The Dietary Guidelines for Americans, updated in 2020, reaffirm its core tenets, which have not changed substantially for years, including recommendations to choose a variety of nutrient-dense foods and beverages and to limit intake of saturated and trans fats, added sugars, salt, and alcohol (**Figure 5.3**). (555) The 2020 Dietary Guidelines for Americans can be found at https://www.dietaryguidelines.gov/ and the Scientific Report that summarizes the current evidence base can be found at https://www.dietaryguidelines.gov/2020-advisory-committee-report.

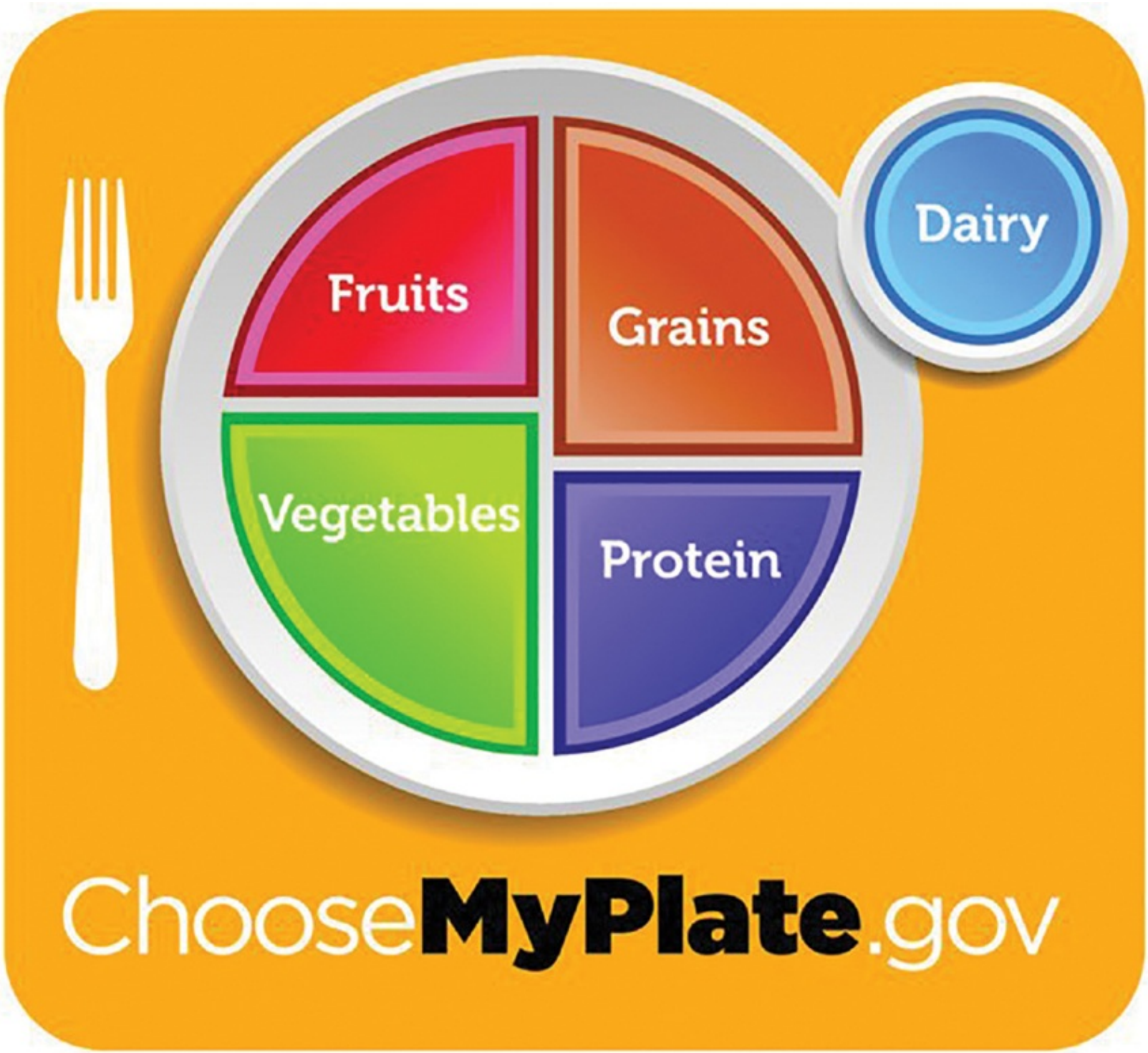

FIGURE 5.3 MyPlate illustrates the five food groups that make up a healthy diet. Use the image to help build a healthy plate at every meal. (From http://www.choosemyplate.gov/.)

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The Centers for Disease Control has partnered with the nonprofit Produce for Better Health Foundation to develop the Fruit & Veggies—More Matters initiative to encourage Americans to increase fruit and vegetable consumption (556), similar to the National Cancer Institute's "5-a-day" program encouraging fruit and vegetable intake and endorses dietary guidelines (557). The American Heart Association offers dietary guidelines that call for balancing caloric intake and physical activity to maintain healthy body weight, with a diet rich in vegetables and fruits, whole grains, omega-3 rich fish, and a limited intake of saturated fat (<7% of total calories) and minimal to no trans fat (558). Both the American Dietetic Association and the American Diabetes Association support the USDA/IOM dietary guidelines and both recommends an emphasis on whole grains, at least five servings of fruits and vegetables daily, restriction of saturated fat and cholesterol, and limited sugar and sweet consumption (559,560). Differing only in detail, all these recommendations are substantially congruent.

Both health and weight control appear to be facilitated by a mixed, balanced diet that is based on healthful, wholesome foods within each nutrient class rather than by choosing a nutrient class to abandon (Table 5.8) (561–563).

TABLE 5.8

Comparison of Diets Recommended for Health Promotion

	Low Carbohydrate	Low Fat/Vegetarian/Vegan	Low Glycemic	Mediterranean	Mixed/Balanced	F
Health benefits relate to	Emphasis on restriction of refined starches and added sugars in particular.	Emphasis on plant foods direct from nature; avoidance of harmful fats.	Restriction of starches, added sugars; high fiber intake.	Foods direct from nature; mostly plants; emphasis on healthful oils, notably monounsaturates.	Minimization of highly processed energy-dense foods; Emphasis on wholesome foods in moderate quantities.	M o p fo E o p a m
Compatible elements	Limited refined starches, added sugars, processed foods; limited intake of certain fats; emph whole-plant foods, with or without lean meats, fish, poultry, seafood.					
And all potentially consistent with	**Food, not too much, mostly plants.**[a,b,c]					

[a]Pollan M. 2007. *Unhappy meals*. *New York Times Mag*. January 28. http://www.nytimes.com/2007/01/28/magazine/28nutritionism.y.html?pagewanted=all

[b]*Portion control may be facilitated by choosing better-quality foods which have the tendency to promote satiety with fewer calories.*

[c]*While neither the low-carbohydrate nor Paleolithic diet need be "mostly plants," both can be.*

Source: Katz DL, Meller S. Can we say what diet is best for health? Annu Rev Public Health. 2014;35:83–103.

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CLINICAL INTERVENTIONS FOR OBESITY: LIFESTYLE COUNSELING, PHARMACOTHERAPY, BARIATRIC SURGERY, AND MEDICALLY SUPERVISED DIETS

Lifestyle Counseling

The primary clinical intervention for weight management is lifestyle counseling, addressed more fully in Chapter 47.

The most recent iteration of the USPSTF statement on weight loss counseling recommends that clinicians offer or refer adults with obesity to intensive, multicomponent behavioral counseling interventions (564). This is especially notable in that prior USPSTF recommendations stated that the evidence of benefit for weight loss counseling was only sufficiently strong in those patients who had both obesity and hypertension, hyperlipidemia, cardiovascular disease, or diabetes (550,551,565).

Worth noting in societies such as the United States, which has both highly prevalent obesity and preoccupation with slimness, is a tendency for even normal-weight individuals to “diet.” In addition, such injudicious practices as smoking may be used as a means to maintain body weight (566). The clinician should be equally prepared to discourage ill-advised weight control practices as to encourage salutary ones. There is some evidence that patients who discuss weight control with their healthcare providers are more apt to pursue weight loss and control by healthful and prudent means (567,568). Also, noteworthy is increasing recognition of the need to reform clinical practice patterns on the basis of both available evidence and professional judgment. A regional plan for obesity control in the New England states, developed by the New England Coalition for Health Promotion (NECON) includes guidance for physician counseling based on such considerations (569).

Theories of behavior modification and their adaptation into the primary care setting for the promotion of healthful eating, physical activity, and weight control are addressed in Chapter 46. Several salient principles warrant particular emphasis. First, given the prevalence of obesity, counseling for weight control should be universal. Second, given the popularity of weight-loss approaches that diverge from well-established practice for health promotion, the principal focus of weight control efforts should, in fact, be health. Recent guidelines have begun to more formally explicate this central point (570). As noted earlier in this chapter, the best available evidence links dietary and activity patterns conducive to health with long-term maintenance of weight. Third, given that obesity is epidemic in both adults and children, the unit to which counseling should be aimed is the family or household rather than the individual patient. Adult patients have a responsibility to engage their children in healthful lifestyle practices, and they will find lifestyle change easier and more sustainable for themselves when the effort involves household-wide solidarity. Finally, weight control efforts should be directed toward long-term sustainability rather than the fast start that seems perennially tantalizing to patients.

Technology for Lifestyle Intervention

There has been an explosion of interest in digital and internet-delivered technologies for weight management, including web-based platforms, mobile device apps, and wearable devices, among others. The interest is for good reason, as technologies may improve scalability of weight loss interventions, lower costs, increase convenience, and improve resource utilization. Extensive evidence suggests these can be effective interventions for weight loss (though somewhat less effective than in-person, face-to-face counseling), particularly when developed in academic settings and include comprehensive approaches with personalized feedback (571). As with traditional interventions, outcomes improve with greater the

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intensity of treatment and frequency of interaction. (572–575) Perhaps the most notable internet-delivered programs for lifestyle intervention are those certified by CDC to deliver nutrition education and behavioral counseling platforms based on the Diabetes Prevention Program curricula. One such program, Omada Health, reported sustained weight loss and A1c improvements over 3 years among 220 patients with obesity and prediabetes who enrolled in the 16-week weight loss intervention followed by ongoing weight maintenance support (576). Private health insurers are beginning to cover these programs and it is expected that Medicare will soon do so, as well.

Nutrigenomics/Nutrigenetics

Though we remain in the infancy of these budding fields, the potential for nutrigenomics and nutrigenetics to inform the fields of nutrition and weight management is immense. Nutrigenomics refers to the relationship between genes and nutrition, including the effect on weight and weight-related behaviors. Nutrigenomics involves the impact of diet and nutrition on gene expression (577). As our understanding of the interactions between our genetic makeup and nutritional intake improves, it should be possible to determine the impact of unique differences in genetic makeup on physiologic responses to dietary intake. For example, in a 2-year randomized controlled trial evaluating varying dietary patterns on weight loss and body composition changes, those participants who carried a specific risk allele (*FTO rs1558902*) in the fat mass and obesity-associated (FTO) gene had significantly greater reduction in weight and improvements in body composition and fat distribution in response to higher protein intake, compared with the overall population studied (578). Another trial showed that another allele (*FTO rs9939609*) also conferred improved benefits in response to higher protein intake, in this case a reduction of food cravings and appetite (579). Studies such as these offer much hope that we will soon have progressively improved science to inform nutrition recommendations. Ultimately, it is hoped that one day these emerging fields will be able to provide comprehensive pictures of each person's integrated metabolism so as to construct a truly personalized diet to greatly improve health and prevent nutrition- and behavior-related disease, including obesity. Nutrigenomics is also discussed briefly in Chapter 45.

Pharmacotherapy

Unquestionably, healthful nutritional intake, regular physical activity (and other healthful lifestyle behaviors and patterns), and supportive behavioral counseling are the cornerstones of weight management. However, the prevalence of obesity remains unconscionably high—despite decades of public messaging about nutrition and health risks of overweight and obesity, and achieving and maintaining significant weight loss is challenging for most—in part due to adaptive physiological responses to weight loss in which appetite and metabolic efficiency increases thereby counteracting weight loss and contributing to weight regain. As such, availability and access to treatment options beyond diet and exercise is important for those affected persons who have not been able to sufficiently manage their weights, health risks, and health outcomes with behavioral modification alone.

As with other chronic, nutrition-related medical conditions (such as hypertension or diabetes), pharmacotherapy is a treatment option that can be utilized to reinforce behavior modification and assist with weight loss and sustained weight maintenance. Pharmacotherapy for obesity is approved as an adjunct to behavioral counseling for individuals with BMI ≥30 kg/m^2 (or BMI ≥27 kg/m^2 alongside weight-related comorbidities). We caution against use of medications for cosmetic reasons; rather, use of pharmacotherapy should generally be reserved for more severe obesity or weight-related health conditions, such as diabetes and hyperglycemia, hyperlipidemia, hypertension, obstructive sleep apnea,

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non-alcoholic fatty liver disease, arthritis of weight-bearing joints, and cardiovascular disease. Pharmacotherapy should be considered only after exhausting reasonable attempts at conservative management, including nutrition education and behavioral counseling. Moreover, pharmacotherapy should be utilized in tandem with behavioral counseling, as numerous studies confirm that combining medication and counseling leads to significantly more weight loss and better health outcomes, compared with either pharmacotherapy or behavioral counseling alone (580–582). Lastly, avoid conflating obesity pharmacotherapy, which has extensive oversight, requires Food and Drug Administration (FDA) approval prior to marketing, and for which claims are carefully regulated, from dietary supplements, which has little regulatory oversight or evidentiary requirements, need not be approved by FDA, and frequently make inflated, if not absurd, claims for weight loss and other purported benefits.

Several medications are approved by FDA for weight management. Older medications approved prior to the mid-1990s are indicated for short-term use, generally described as <12 weeks. The most notable and most widely prescribed medication of this category is phentermine, which was initially approved in 1959. (Three additional noradrenergic medications—diethylpropion, phendimetrazine, and benzphetamine—are also available in the United States, but data on these agents are minimal, they are prescribed much less frequently than other approved medications, and there is are no clear advantages of these over phentermine.) Newer generations of obesity pharmacotherapy are approved for long-term use, as the FDA now appreciates the chronic nature of obesity. Currently available medications indicated for long-term use include orlistat, phentermine/topiramate extended-release (ER), naltrexone/bupropion ER, and liraglutide 3.0 mg. All but orlistat have primary mechanisms of action in the brain, so as to decrease appetite, increase satiety, and/or manage food cravings. Several additional medications are likely to be approved in the near future.

Available medications—particularly those approved in the past two decades, during which the FDA has extensively expanded evidentiary requirements for safety and efficacy required for approval for obesity and diabetes medications—are extensively studied for safety and efficacy (583,584). There are no “magic pills,” to be sure, though currently available medications are reasonably helpful when used appropriately. Average weight loss is typically in the range of 5% to 10% of baseline body weight. However, formal FDA recommendations and prudent clinical practice dictate that patients who are not getting sufficient benefits should discontinue the medication after a reasonable trial of a few weeks or months of use. This clinical practice both avoids unnecessary exposure to persons who are not likely to have benefits and also highlights the significant benefits in those who respond to the medication. Among patients who achieve early benefit—often known as clinical “responders,” average weight loss is closer to 15% weight loss (measured after 1 year of treatment) (585). Because this is impressive magnitude that generally leads to extensive improvements in health and quality of life, it is recommended that these patients continue using the medications. Responders will usually see improvements in weight-related cardiovascular risk factors, including glycemic control, lipids, and blood pressure. In addition to weight loss, the newer medications have also been shown to support maintenance of lost weight in responders who continue using the medications over time.

Phentermine has long been the most frequently prescribed medication for obesity in the US and much of the world. It is approved for short-term use (up to 12 weeks), as the clinical trial requirements for FDA approval in the mid-20th century did not include long-term safety studies. (However, longer trials of phentermine in combination with topiramate have been published, and the combination was approved by FDA in 2012 with allowance for long-term use, as discussed in the following section). Phentermine is an adrenergic agent that suppresses appetite and may, albeit modestly, increase REE. Phentermine can be prescribed at dosages up to 37.5 mg daily, though as little as 4 to 8 mg can be effective, and the dose

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should be individualized to achieve response with the lowest necessary dose. At lower doses, side effects are unlikely. As doses increase, potential side effects may include increased heart rate, headache, insomnia, or dry mouth (586).

Orlistat, which was approved by the FDA in 1999 (and later became available for over-the-counter use), was the first medication for obesity to be approved for long-term use (587,588). Unlike other pharmacotherapy options, it is not absorbed from the gastrointestinal tract and does not have central nervous system mechanisms of action or effects on appetite. Instead, orlistat acts peripherally in the gut by inhibiting pancreatic and gastric lipases, thereby decreasing absorption of roughly 30% of ingested fat when administered with meals. As a result, orlistat generally affords lower weight loss than other obesity medications. Gastrointestinal side effects are related to fat malabsorption, especially at higher doses and when administered with high-fat meals, and may include abdominal discomfort, diarrhea or steatorrhea, or fecal urgency or incontinence, and abdominal discomfort. Importantly, orlistat can decrease the absorption of fat-soluble vitamins and medications, such as levothyroxine and warfarin. It is recommended that patients using this medication take a multivitamin at bedtime.

Phentermine/topiramate ER was approved by FDA in 2012, though its constituent parts have been on the market for many decades (589). Topiramate has been approved as monotherapy for epilepsy since 1996 and for migraine prophylaxis since 2004. With multiple central nervous system effects, including inhibition of carbonic anhydrase, antagonism of glutamate, and modulation of gamma-aminobutyric acid receptors, topiramate complements phentermine to increase the magnitude and sustainability of weight loss, compared with phentermine alone. Phentermine/topiramate ER is available in four doses (3.75/23 mg, 7.5/46 mg, 11.25/69 mg, 15.0/92 mg), which should be prescribed using a dose-escalation protocol. Side effects are uncommon at lower doses and increase proportionally with escalating dose; the most common ones are paresthesia, altered taste perception, insomnia, and headache. While all obesity medications should be avoided during pregnancy, this medication is the only one that has clear evidence of teratogenicity, in that topiramate has long been known to increase risk for orofacial clefts in infants exposed to the medication during the first trimester of pregnancy.

Naltrexone/bupropion ER, approved in 2014, is a combination medication that includes novel preparations of bupropion, which has previously been approved as an antidepressant in 1989 and as an aide for smoking cessation in 1997, and naltrexone, an opioid antagonist that has long been used for opioid dependence, alcohol abuse, and other addictions (590). The combination of the two agents reduces appetite and food cravings by simultaneously targeting both the hypothalamic appetite neurons and mesolimbic dopamine reward circuits. The most common side effect is nausea, which leads to discontinuation in approximately 5% of those prescribed the medication; much less frequently, vomiting, constipation, and elevated blood pressure may occur. Of note, because antidepressant medications, including bupropion, carry warnings for suicidality among persons under age 24, the same warning is listed for this medication as well.

Liraglutide was initially approved in 2010 for the treatment of type 2 diabetes at a dosage of up to 1.8 mg daily, and it has subsequently been approved for cardiovascular risk reduction in patients with type 2 diabetes (591). The 3.0 mg dose has since been approved by FDA specifically for weight management. Liraglutide is an agonist of the incretin hormone, glucagon-like peptide-1 (GLP-1), which is released from enteroendocrine cells in the small bowel in response to nutrient availability following food intake. Administered as a daily subcutaneous injection, liraglutide acts centrally via modulation of anorexigenic and orexigenic neurons in the hypothalamus, as well as peripherally by delaying gastric emptying. The most common side effects are nausea, vomiting, diarrhea and constipation.

Pharmacotherapy is increasingly viewed as a potentially important adjunct to lifestyle interventions in

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the control of obesity (592–594). As weight generally is regained when pharmacologic agents are discontinued, the need for agents that are safe in the long-term and/or robust behavioral interventions that can sustain the weight loss achieved with short-term medication use is clear. Clinicians should be prepared to consider long-term use of pharmacologic agents, as is commonly done with other conditions that are somewhat responsive to diet, such as hypertension and hyperlipidemia. Weight loss during pharmacotherapy should perhaps not be considered an indication for cessation of treatment, any more than the treatment of diabetes, hypertension, or hyperlipidemia to goal levels of glucose, blood pressure, or LDL indicate discontinuation of therapy. However, to apply the same standard in obesity treatment, the long-term safety of pharmacologic agents will need to be assessed. In the meantime, as stated earlier, pharmacotherapy generally should be reserved for more severe obesity or obesity associated with metabolic, psychological, or functional complications, so pharmacotherapy is likely to be associated with greater net benefit than risk. The use of prescription pharmacotherapy for purely cosmetic weight control is, on the basis of currently available evidence, generally ill advised.

Surgery

Bariatric surgery has traditionally included an array of procedures that manipulate parts of the gastrointestinal tract (595), though today nearly all primary surgical obesity procedures are either vertical sleeve gastrectomy (VSG) or Roux-en-Y gastric bypass (RYGB). The most familiar aspects of these procedures—a smaller stomach and nutrient malabsorption—are largely incidental. Rather, these procedures primarily induce weight loss by altering endocrine influences on appetite and satiety, such as ghrelin signaling from the stomach and GLP-1 signaling from the small intestine (596,597). By contrast, laparoscopic banding, a reversible medical device that does not manipulate the gut tissue thereby limiting the volume of food eaten without affecting endocrine signaling, has rapidly fallen out of favor over the past decade as long-term benefits are relatively small—compared with nearly 50 percent of bariatric surgeries a decade ago, today laparoscopic banding accounts for only 2% of bariatric surgeries in the United States (598).

Overall, bariatric surgery is well established as the most effective treatment for severe (stage III) obesity (599,600). The effectiveness of the procedure, in conjunction with the rising prevalence of obesity in general and severe obesity in particular, has resulted in a rapid increase in the number of procedures performed annually; bariatric surgery is now one of the most common gastrointestinal surgeries performed, with an estimated 228,000 procedures performed in the US in 2018 (598). The bariatric surgery experience and literature are increasingly encompassing adolescents (601–603) and children (604,605), along with older adults (606–608).

Surgery generally is indicated only for the management of severe obesity, and then only if other therapies have been tried and have proved ineffective (609,610). A BMI greater than 40, previously referred to as “morbid” obesity and preferably referred to as stage III obesity, or “severe” obesity, should raise the consideration of surgical management. Patients with lesser degrees of obesity may be candidates for surgery if refractory to other interventions and experiencing morbidity (especially type 2 diabetes) or reduced quality of life due to the obesity (611–613). Several studies have shown substantially increased weight loss, greater likelihood of type 2 diabetes remission, and improved long-term mortality outcomes following bariatric surgery, compared with conventional medical therapy (614–618) It should be noted, however, that studies tend to compare bariatric surgery treatment to general medical treatment or low-intensity diet and exercise counseling, rather than intensive nonsurgical obesity treatment; a more relevant control group might instead be a multicomponent lifestyle intervention involving residential treatment for medically supervised rapid weight loss, prepared meals at home, obesity pharmacotherapy as indicated,

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and regular counseling via behavioral, nutrition, and physical activity specialists (619). Nonetheless, the exorbitant value of bariatric surgery cannot be denied.

Weight loss of up to 33% has been maintained after gastric bypass surgery for up to 10 years, an outcome superior to nonsurgical approaches (620); loss of 50% or more of excess weight is commonly achieved within the first postoperative year, with up to 65% to 70% average excess weight loss maintained at 3 to 5 years (621).

Complications and mortality depend on the procedure performed. Surgical mortality in skilled hands generally is as low as 0.1% to 0.3% (612,620,622), usually related to pulmonary emboli and anastomoses leaks; postoperative complications were as high as 40% in 2001 (623), but recent increases in laparoscopic and banding techniques have reduced serious complication rates to approximately 5% (622).

Candidates for bariatric surgery require thorough preparation for the effects of such surgery on lifestyle and dietary pattern. All patients should receive supportive behavioral counseling, both prior to and following the procedure, as well as long-term assistance, such as nutritional counseling and small-group support classes (620). Postoperative challenges include nutrient deficiencies related to malabsorption, psychological adjustment, and alterations in dietary pattern required to accommodate restrictive effects of the procedure. These issues indicate the importance of ongoing monitoring by an experienced and multidisciplinary medical team (597,621,624–626). Bariatric surgery is generally deemed cost-effective for suitably selected patients (627).

In addition to commonly used bariatric surgery procedures, several minimally invasive medical devices and experimental procedures have been developed. These include gastric balloons, vagus nerve stimulation, gastric artery embolization, and others, though none have heretofore shown sufficiently positive outcomes to warrant regular use and these are rarely covered by insurance.

Medically Supervised Structured Diets

Low-calorie diets typically restrict energy intake to between 1,000 and 1,200 kcal/day. Such diets can be constructed to provide balanced nutrition or to be unbalanced in favor of a particular macronutrient class. Evidence of a benefit of unbalanced low-energy diets is, for the most part, lacking, and differences in weight loss are largely attributable to differences in diuresis (628). Evidence for emphasizing a particular macronutrient class is discussed elsewhere in this chapter. Generally, low-calorie diets pose a threat of micronutrient deficiency, and a multivitamin/mineral supplement is appropriate. As a balanced, energy-restricted diet is compatible with both weight-control and health-promotion goals, such an approach to obesity is widely applicable.

Very-low-energy diets used in the 1970s provided inadequate protein and resulted in visceral protein losses. Cardiac protein mobilization was associated with dysrhythmia and sudden death (628). More recently, with attention to the quantity and quality of protein and micronutrients provided, it has been shown that very-low-energy diets can be administered safely; such diets typically are referred to as “protein-sparing modified fasts” and provide approximately 800 to 1000 kcal/day (628). Very-low-calorie diets (VLCDs) can be based on a narrow range of proteinaceous solid foods (e.g., lean meat, fish, poultry) or commercial protein supplements, such as protein bars or shakes. VLCD is frequently used prior to bariatric surgery to decrease perioperative risk (629).

Though medically supervised diets are traditionally limited to specialized obesity treatment centers, several recent studies have successfully implemented variations in primary care settings (630–632). In each of these large studies, participants who were treated with medically monitored structured diets achieved substantially greater weight loss and improvement in glycemic control, diabetes remission, and

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other weight-related endpoints, compared with control groups. Moreover, subjects maintained significant benefits even over a relatively long period of follow-up (2 years). Nonetheless, these results are not typical, and, although very-low-energy diets induce substantial weight loss (e.g., 44 lb in 12 weeks), they are generally ineffective at maintaining such losses over the long term (628) without ongoing counseling and support. For example, Ryttig et al. (633) compared two 24-month weight-loss programs in university students, one commencing with a very-low-calorie induction diet and the other relying on a balanced, energy-restricted diet throughout. Although the initial weight loss was substantially greater in the VLCD group, weight loss at 2-year follow-up did not differ. A meta-analysis of six RCTs showed no difference in long-term (1–5 years) weight loss between VLCD and modest low-calorie diets, despite substantially greater short-term weight loss in the VLCD groups (634).

While these types of intensive diets can be helpful when carefully implemented, they are generally only indicated in the management of severe obesity or in situations where rapid, large amounts of weight loss is important, such as prior to bariatric and some orthopedic surgeries. In many cases less severe calorie restriction (i.e., the strategic use of protein meal replacements as part of a strategy to reduce calories more moderately) is preferred as a less restrictive, less cumbersome, and more sustainable approach (634,635).

Commercial Weight-Loss Programs

The commercial weight loss industry is a $200 billion/year market, with many dubious claims, practitioners, products, and services. Overall, there is limited evidence that commercial weight-loss programs produce sustainable weight loss. As systematic reviews report little evidence suggesting that any of the 32 best known commercial weight loss program has superior results than the rest and few commercial programs have solid evidence supporting their weight loss approaches and claims. Most of the published studies were too small, too short, had too high attrition, and/or had poor methodologies to be of reputable value (636–638). Another study shows few commercial weight loss programs follow evidence-based clinical guidelines for obesity management (639). Interestingly, only about half of those listed in the National Weight Control Registry report using a commercial weight loss program (640).

Overall, the literature on outcomes in commercial weight-loss programs is sparse (641). A multibillion-dollar industry would doubtless be supporting the generation of publications were there good news to report. However, as programs adopt new methods, they may be contributory to efforts to achieve lasting changes in lifestyle that help control weight. One notable program with strong supporting evidence is the CDC’s National Diabetes Prevention Program (642). Modeled after a landmark clinical trial that showed a moderate lifestyle intervention for patients with obesity and prediabetes resulted in nearly 70% reduced incidence of diabetes, this small-group program focuses on evidence-based moderate lifestyle changes and weight loss goals to improve health and prevent diabetes. It has since been adopted by the Centers for Medicare and Medicaid Services as a covered benefit for Medicare beneficiaries to manage obesity and prevent diabetes.

One arena for medically supervised, commercial weight-loss programs includes weight-loss “camps” and alternative schools, which aim to provide education and training in healthful lifestyle practices in an immersive, supportive environment (643). Further studies are needed to determine long-term effects. Another promising area of development is electronic and virtual weight loss services, including several modeled after the National Diabetes Prevention Program. At present, however, the clinician is well advised to consider such programs with an open-minded skepticism. Assessment should be based in part on whether the program provides knowledge or skills that will support lifelong efforts to control weight rather than the short-term management of the patient’s diet. The limited evidence available offers some

support for the Weight Watchers program specifically and self-monitoring in general (644–650).

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RELATED TOPICS OF INTEREST

Nutrients, Nutriceuticals, and Functional Foods

There are, in general, few substantiated claims for micronutrients or dietary supplements that facilitate weight loss (651). In spite of this, use of supplements for weight loss is a popular practice (652–654). Clinicians are encouraged to inquire routinely about their patients' practices in this area. The well-publicized toxicity of ephedra (655,656) is a precautionary tale highlighting the potential dangers in reliance on nutriceuticals and botanicals for weight loss. The Federal Trade Commission generated a report highlighting deception in the advertisements for weight-loss products in 2002 (657). While caution and skepticism in this area are warranted, some promising leads in the literature deserve the practitioner's consideration. It may be useful to mentally categorize the plethora of weight-loss products by purported mechanism in order to better advise patients of potential hazards versus benefit.

Increase Energy Expenditure

This category includes the popular but dangerous ephedra alkaloids, as well as caffeine-containing foods and supplements. At safe doses, caffeine and catechins in foods like green tea (658) likely do support some degree of short-term weight loss, though the magnitude of effect is small and there is no evidence that they can help in the maintenance phase of weight loss. Caution is advised.

Modulate Carbohydrate Metabolism

Chromium is a cofactor in insulin metabolism, and its supplementation may lower insulin levels in insulin-resistant individuals (see Chapter 6). There is as yet no definitive evidence of a role for chromium in weight management per se, but an argument for supplementation in the insulin-resistant patient with obesity could be made on theoretical grounds. A Cochrane review suggests favorable effects of chromium on weight loss from a small number of trials (659); further research into the effects of chromium picolinate supplementation on insulin sensitization and weight management are thus needed and warrant close attention (660–663).

Increase Satiety

The popularity of natural plant extracts that purport to increase satiety has skyrocketed in recent years. Examples include *Hoodia gordonii*, a plant chewed by indigenous peoples of the Kalahari Desert, and *Garcinia cambogia*, made from the tamarind fruit rind. While there is some research to suggest that these effects are plausible (664), the overwhelming evidence thus far does not support most of these plant extract diet supplements as either effective or safe (665). Thus, despite public and media interest (666), other than fiber supplementation, which has consistently been shown to cause small amounts of weight loss, the use of such products for weight management would be premature at best. Rigorous studies of safety and efficacy are warranted.

Increase Fat Oxidation or Decrease Fat Synthesis

Conjugated Linoleic Acid (CLA), a family of isomers of an 18-carbon polyunsaturated fatty acid found in meat and dairy, has generated interest as a potential aid in weight loss. Despite some promising findings in animal studies, human evidence is at best mixed (666–670); several short-term studies have found

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reductions in body fat with CLA supplementation, with a theoretical mechanism involving adipocyte apoptosis or increased fat oxidation (671,672). Nevertheless, adverse health effects of this group of fats, including potentially deleterious effects on insulin sensitivity (673), cannot be excluded with confidence.

Block Fat Absorption

Olestra, or sucrose polyester, is a nonabsorbable fat substitute approved by the FDA in 1996 for use as a food additive in snack foods; it is discussed in detail in Chapter 42. To date, there is no convincing evidence that olestra in the food supply leads to sustainable weight loss or prevents weight gain. Its use for purposes of weight control can neither be encouraged nor discouraged with great enthusiasm on the basis of the available evidence (see Chapter 42). The product was not a commercial success and it has been banned in several countries. Of note, Alli, the over-the-counter version of orlistat, blocks fat absorption (discussed earlier) and leads to modest weight loss (674).

Calcium

There is a suggestion, often employed in marketing by the Dairy Council of America, that calcium from dairy sources may facilitate weight loss and, in particular, the preferential loss of adipose tissue. The research literature on this topic is far from definitive, with conflicting results (675–681). In general, studies sponsored by the dairy industry more commonly demonstrate positive outcomes. There is insufficient evidence to justify reliance on calcium supplementation or dairy to facilitate weight loss, but the inclusion of low- or nonfat dairy in the diet and calcium supplementation are supported by other considerations (see Chapters 8 and 14).

Resveratrol

A phytoestrogen most notably found in grape skins, resveratrol has garnered recent interest as a potent antioxidant. While human studies are inconclusive, promising murine studies point to resveratrol's ability to reduce body weight and hyperglycemia in overweight and diabetic animals (682,683). One study (684) found that resveratrol supplementation in mice fed a high-fat, adipogenic diet actually induced downregulation of signaling cascades related to inflammation and adipogenesis.

Alcohol

Ethanol provides 7 kcal/g; therefore, it is more energy dense than either carbohydrate or protein and only slightly less so than fat. As a result of this energy density, ethanol consumption may contribute to obesity. There is some evidence that ethanol may increase REE while reducing fat oxidation (685). These effects may contribute preferentially to lipid storage. The role of alcohol in the diet is addressed more fully in Chapter 40.

Sugar-Sweetened Beverages and Soft Drinks

The beverage industry has long disavowed any causal link between soda consumption and obesity. The bias in industry-sponsored research on this topic has been highlighted (686), and systematic reviews show that calories from SSBs contribute meaningfully to the risk of weight gain, as well as diabetes and other adverse health outcomes (687–689). Globally, increasing soft drink consumption appears to correlate with increasing worldwide overweight and obesity (690). Reducing soft drink intake facilitates weight loss (691), especially in children and adolescents in whom sugar-sweetened beverages represent an increasing proportion of total calories consumed (692), and some studies show that small taxes on SSBs lead to decreased consumption and may contribute to fewer cases of diabetes and obesity

(693–695). Of note, although increased caloric intake from soft drinks may contribute to weight gain, decreasing caloric intake via diet soda remains controversial.

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Pregnancy

Women with normal weight generally should gain between 11.5 to 16 kg (25–35 lb) during pregnancy (696). The basis of a minimum weight gain recommendation in pregnancy is to reduce the risk of low birth weight in the neonate (696). There is agreement that, in overweight women, weight gain during pregnancy should be of a lesser magnitude. In 2009, the IOM released gestational weight gain guidelines for the first time in 20 years; the new recommendations suggest that women with a prepregnancy BMI in the overweight range, 25 to 29.9, should gain between 7 and 11.5 kg (15–25 lb) (697–700). While some have suggested that in women with a prepregnancy BMI of 30 and above no minimum weight gain is necessary (701), however the IOM guidelines recommend a total pregnancy weight gain of 5 to 9 kg (11–20 lb) (702). In the United States, each pregnancy is associated with the retention of as much as 5.5 lbs; therefore, pregnancies contribute to the development of lifelong obesity in women (703). There is evidence that women who are able to follow the IOM guidelines on gestational weight gain may not incur that risk of long-term weight retention (704). The prevention of excessive pregnancy-related weight gain and its retention in the postpartum period are therefore important to efforts at controlling the rising prevalence of overweight/obesity in women (705).

Pregnant women with obesity have an increased incidence of gestational diabetes (700,706,707), preeclampsia (700,706–710), fetal macrosomia (700,711–715), induction of labor (700,716), primary cesarean (709,707–719), postpartum infection (718721), and neural tube defects in offspring (722–724). Obesity in pregnancy may increase the risk of preeclampsia and pregnancy-induced hypertension (725,726). Available analyses suggest increased healthcare costs for women with obesity during pregnancy (727); in one small study comparing 89 overweight women with 54 normal-weight women, the cost at care during pregnancy was 3.2 times higher for women with severe obesity (706). Hood and Dewan (728) found that hospital stay was longer for heavier, compared with leaner, women at delivery. Based on data from the 1988 National Maternal and Infant Health Survey, Cogswell et al. (711) reported the incidence of obesity in pregnancy as 17%; slightly lower estimates have been reported by others. Further studies are warranted to explore the effect of lifestyle interventions in pregnant women (729). The topic is more fully addressed in Chapter 27.

Breastfeeding

In addition to its multiple nutritional benefits, protracted breastfeeding may confer weight-related benefits on both mother and baby. Because of its metabolic demands, breastfeeding can reduce postpartum weight retention (730). And, there is evidence from multiple observational trials that protracted breastfeeding may provide some protection against the later development of obesity in the child (635). Unfortunately, prospective clinical trials utilizing interventions to increase exclusive breastfeeding duration have thus far failed to cause significant reductions in childhood obesity prevalence (731,732). The importance of breastfeeding and establishing judicious dietary patterns early in life is discussed in Chapters 38 and 47.

Obesity Management in Children

Most weight-loss programs available for children are similar to adult treatment programs (128). Long-term weight loss is achieved more successfully in children than in adults (128,733,734). Analysis suggests that relatively small amounts of weight loss, or just slowed weight gain, may be all that is needed for children to return to normal weight-for-height growth curves over time (735). Evidence supports the

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inclusion of dietary change, behavior modification, parental involvement, and follow-up in a pediatric obesity program (736–738). Programs have emphasized both reduction in sedentary behaviors (739) and dietary modification (128). Childhood food preferences are greatly influenced by parents' food choices and eating habits (see Chapters 29 and 38); therefore, family-based approaches are encouraged (127). Recent evidence emphasizes the importance of parental role in childhood obesity; a randomized controlled trial of family-based or parent-only intervention found the parent-only intervention as effective as the family-based treatment of overweight children (740). Another study found a "halo effect" on the families of patients undergoing bariatric surgery; children who had obesity at baseline were found to have lower BMI at 12 months after their parent had undergone the surgery, emphasizing the characterization of obesity as a familial disease (741). More evidence is needed to determine best approaches to home-based prevention (127,742,743). One small study of snacking in school-age children found that offering a combination of vegetables and cheese compared to either alone or potato chips led to 72% fewer calories consumed during an ad-lib snacking session (744). A randomized controlled trial designed to reduce television, videotape, and videogame use among third- and fourth-grade children showed statistically significant decreases in BMI in the intervention group as compared with controls after the 6-month intervention (745). Novel school and camp residential experiences may offer comprehensive, multidisciplinary approaches that give children and adolescents structure and skills to support not only weight loss, but also increased fitness, emotional coping, and self-esteem (746). Experience with pharmacotherapy and surgery for obesity in children is rather limited, but may be appropriate in limited cases where comorbid medical conditions exist and benefits outweigh risks (747,748). Strategies for weight management in children are addressed in Chapter 47.

Summary of Recommended Management Strategies

Evidence that sustainable weight loss is enhanced by means other than caloric restriction is lacking. Whereas short-term weight loss is consistently achieved by any dietary approach to the restriction of choice and thereby calories, lasting weight control is not. Competing dietary claims imply that fundamental knowledge of dietary pattern and human health is lacking; an extensive literature belies this notion. The same dietary and lifestyle pattern conducive to health promotion is consistently associated with weight control. A bird's-eye view of the literature on diet and weight reveals a forest otherwise difficult to discern through the trees. Competing diet claims are diverting attention and resources from what is actually and urgently needed: a dedicated and concerted effort to make the basic dietary pattern known to support both health and weight control more accessible to all.

Against the backdrop of this increasingly acute need, the identification of practical and generalizable solutions to the obesity crisis has proved elusive. From research interventions, to commercial weight loss programs, to supplements, potions, and devices, innumerable approaches to weight loss have been devised. That none of these has yet met the need of the population is clearly reflected in the stubborn epidemiology of obesity.

Obesity is as relevant to prevailing views on beauty, fashion, and body image as it is to public health, and thus it engenders unique preoccupations (749–755). Individuals reluctant to take antihypertensive or lipid-lowering medication for fear of side effects may aggressively pursue pharmacotherapy, or even surgery, for weight control (756–758). The visibility of obesity, the stigma associated with it (758–761) (it is often said that antiobesity sentiment is the last bastion of socially acceptable prejudice), and the difficulty most people experience in their efforts to resist it contribute to its novel influences on attitude and behavior. This widespread state of volatile frustration renders the public susceptible to almost any persuasive sales pitch for a weight-loss lotion, potion, or program.

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The natural consequence of acute and substantially unmet need is frustration. This public frustration has created a seemingly limitless market for weight-loss approaches. This same frustration has engendered a prevailing gullibility so that virtually any weight-loss claim is accepted at face value. Dual aphorisms might be considered for characterizing the obesity epidemic. Until recently, organized responses to this degenerating crisis have been tepid at best, suggesting that among public health professionals, familiarity breeds complacency, if not outright contempt. Among members of the general public, desperation breeds gullibility.

It is thus a seller's market for weight-loss wares. The litany of competing claims for effective weight loss is producing increasing confusion among both the public at large and healthcare professionals (762). In the mix is everything from science to snake oil, with no assurances that science is the more popular choice.

The concept of the "ideal" body weight and efforts to reach it may be both unrealistic and harmful for most overweight patients. The benefits of moderate weight loss are sufficiently clear to justify efforts to induce a loss of 5% to 10% of total weight, which is apt to be much more readily achievable. Perhaps better still is an emphasis on the means of achieving weight loss—namely changes in diet and activity pattern rather than weight per se, as the patient has control over the former but can only indirectly influence the latter. Most adult patients concerned about weight regulation will have made multiple attempts at weight control, with at best transient success. Above all, clinicians must not submit to "blame the victim" temptations in this setting.

Temporary weight loss is no more a definitive resolution of the metabolic factors that promote obesity than transient euglycemia is a resolution of diabetes. Therefore, diets designed for short-term weight loss offer no convincing benefit either in terms of sustained weight loss or health outcomes. Because dietary and lifestyle management of weight must be permanent, it is essential that the dietary patterns applied be compatible with recommendations for health promotion in general. Fad diets promoted for purposes of rapid weight loss are unsubstantiated in the peer-reviewed literature. Even if conducive to weight management over time, such diets would be ill advised unless shown to promote health and prevent disease. There is overwhelming consensus that a diet rich in complex carbohydrates, particularly whole grains, fruits, and vegetables, along with healthful oils and lean protein sources, is conducive to optimal health outcomes (see Chapter 45). So that patients are not offered a choice between health promotion and weight control, a health-promoting diet should be recommended for purposes of weight control. Such a diet is nutrient dense, fiber dense, and relatively energy dilute—all properties supportive of weight loss and maintenance.

Several general modifications of the overall dietary pattern are likely to facilitate weight control. Some benefit may derive from frequent, small meals or snacks rather than the conventional three meals a day. One study examining snacking habits in overweight women enrolled in a weight-loss study found that mid-morning snackers lost more weight than afternoon or evening snackers (763). Physiologically, there is some evidence that distributing the same number of calories in small snacks ("nibbling") rather than larger meals ("gorging") may reduce 24-hour insulin production, at least in insulin-resistant individuals (764) (see Chapter 6). Speechly et al. (765) reported evidence that snacking attenuates appetite relative to larger meals spaced farther apart. A group of seven men were provided with an ad libitum lunch following a morning "preload" provided as a single meal or multiple snacks with the same total nutrient and energy composition. Subjects ate significantly (27%) less following multiple small meals than after a single larger one. Insulin peaked at higher levels following the single meal and was sustained above baseline for longer with the multiple small meals. Total area under the insulin curves was similar in both groups.

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Evidence in support of "snacking" as a means of controlling weight or improving insulin metabolism is preliminary and not undisputed (766,767). However, there is generally a profound psychological component to disturbances of weight regulation, and the distribution of meals and calories may be germane. Most patients trying to control their weight are both tempted by and afraid of preferred foods. Consequently, many such patients resist eating for protracted periods during the day, only to overindulge in a late-day or evening binge. This pattern perpetuates a dysfunctional and tense relationship between the patient and their diet.

Patients caught up in this pattern should be advised to bring healthful and calorically dilute foods with them every day (see Chapter 47) and systematically to resist foods made available by others. Patients should be encouraged to eat whenever they want, but only those foods chosen in advance. By having free access to low-calorie foods (e.g., fresh fruits, fresh vegetables, nonfat dairy, dried fruit, whole-grain breads or cereals), patients may overcome their fear of needing to "go hungry" for extended periods each day. In addition, frequent snacking during the day obviates the need and desire for a compulsive and binge-like meal at the end of the day. Finally, for many patients, the ideal time for exercise is after work. Overweight patients who have avoided food much of the day may simply be too hungry after work to exercise. A meal at such a time often is prepared impulsively and eaten not only to satisfy energy needs but also to assuage the pent-up frustrations of the day. On questioning, many overweight patients acknowledge that they often eat, and overeat, for reasons having nothing to do with hunger.

There are multiple benefits to physical activity after work and/or prior to the evening meal. Exercise is an effective means of moderating psychological stress (768) and may attenuate the need to resolve such stress with food. In addition, exercise may temporarily suppress appetite and generally enhances self-esteem, both of which are conducive to more thoughtful choices as the evening meal is prepared. Finally, and most evident, is the additional caloric expenditure resulting from the added activity. A meta-analysis of weight-loss studies published in 1997 reveals important limitations in the field of obesity management but suggests that best results to date have been achieved by combining energy-restricted diets with aerobic exercise (769).

In conjunction with redistribution of calories, several other specific recommendations may be made in the context of primary care encounters that may facilitate weight loss. Dietary fat restriction generally should be recommended, with sufficient detail provided to facilitate food choices (see Chapter 47). A recent systematic review of 33 randomized controlled trials and 10 cohort studies found consistent evidence that dietary fat restriction led to small but statistically significant and sustained weight loss (770). The best available evidence indicates that mean intake in the United States is approximately 34% of calories (NHANES). All other evidence aside, the caloric density of fat, not to mention the obvious link between calorie intake and weight control, justifies efforts to moderate dietary fat intake in all efforts at weight loss or maintenance.

Along with fat restriction, patients should be advised to liberalize or increase their intake of fruits and vegetables and whole-grain products. In addition to being calorically dilute, these foods tend to be rich in fiber, which is noncaloric yet satiating, at least in the short term (see Chapter 1). Foods such as dried fruits, which are relatively dense in calories, are nonetheless useful in weight loss efforts due to the high fiber content and their capacity to induce satiety with limited intake.

Among the most successful strategies for changing the overall dietary pattern is the substitution of ingredients in otherwise familiar dishes. Familiarity is among the principal factors governing dietary preference, and resistance to changing the diet can be formidable. Attempts at reducing dietary fat intake in the Women's Health Trial were most successfully sustained when they relied on substituting lower-fat ingredients in recipes that preserved the appearance and taste of familiar foods (771). Although this

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advice can be offered in the primary care setting, patients will need detailed information on ingredient substitutions to implement such recommendations successfully. Referral to a dietitian and referral to appropriate literature are often both necessary (see Section III). Difficulty in treating obesity has led to increased emphasis on the importance of prevention. However, effective and practical methods of prevention have yet to be demonstrated.

The likely reason for this is that no single approach to weight control will be effective at the population level. Weight gain and epidemic obesity are the consequences of a perfect storm of obesigenic influences of our own devising, from fast food to suburban sprawl. Long denizens of a world characterized by a relative scarcity of calories and unavoidably arduous physical exertions, we (and our patients) are victims of our own success. Quite simply, our species has no native defenses against caloric excess or the lure of the couch—because we never needed them before.

So while simple to explain, epidemic obesity will be anything but easy to fix. We must overcome the propensity of our genes, the propulsive force of culture, and some 6 million years of gathering momentum.

Obesity prevention will require a comprehensive system of reforms addressing prevailing knowledge, behavior, policies, and the environment. We need nutrition education and physical education in schools. We need schools that provide nutrition meeting high standards and regular bouts of physical activity. We need physical activity breaks to be a standard part of the work day. We need equitable approaches to health prioritized and baked into food systems to allow for better access and attainment of healthy and nutritious foods by our most marginalized households experiencing disparities. Every neighborhood needs to provide recreational facilities and sidewalks, and new neighborhoods should be designed so that it makes sense to get around them by foot rather than car. We need social engineering to give us back time to prepare food at home or ways to eat out that offer good nutrition at low cost.

We need to make use of stairs rather than elevators the social norm. We need to overhaul the food supply and eliminate the “junk” food category. We need to subsidize the sale of fresh fruits and vegetables. We need truth in advertising, marketing that emphasizes what matters for a healthy life, and controls on food marketing to children. We need to educate families about how to practice good nutrition and good physical activity together. It should once again be possible for children to walk and bike to school.

Clinicians will, in fact, not be *the* solution to the problem of epidemic obesity, as many components of a comprehensive weight-management campaign that would satisfy population needs fall outside the clinical purview. But clinicians have a vital role to play, as both educators and advocates. And given the magnitude and urgency of this crisis, to do otherwise is simply no longer acceptable. We have a choice of being part of the solution or, failing that, being part of a status quo that propagates the problem. As the IOM outlines in its recent report on obesity prevention, we need healthcare providers to adopt standards of practice for prevention, screening, diagnosis, and treatment of overweight and obesity; emphasize pre-pregnancy counseling on maintenance of a healthy weight before, during, and after pregnancy; and advocate publicly for healthy communities that support healthy eating and active living (772).

In the weight-loss literature, interventions achieve caloric restriction by various means, ranging from direct provision of food (773), systems of incentive/disincentive (774), cognitive behavioral therapy (775), fat restriction (776), and the color-coding of food choices based on nutrient density (777). In general, those interventions achieving the most extreme degrees of caloric restriction also produce the greatest initial weight loss. However, a rebound weight gain is typically observed; in general, the more rapid the initial weight loss, the greater and more rapid the subsequent weight gain (778,779). This observation appears to be of generalizable significance, likely due to the fact that the extreme caloric restriction necessary for very rapid weight loss is intrinsically unsustainable. When the means used to

achieve initial weight loss are unsustainable, weight regain is consistently observed.

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The recent preoccupation with carbohydrate restriction appears to be reactionary to the antecedent era during which fat restriction was prioritized. The popular press and media reports suggest that the public feels misled by promises that fat restriction would lead to weight loss. In particular, the widely known USDA food guide pyramid has come under attack as a contributor to worsening obesity rates (430). The adulteration of messages in the pyramid under the influence of special interest groups is the subject of a salient book (433). The CDC released data indicating that over the past several decades, weight has gone up as carbohydrate consumption has risen (387).

An impassive examination of these trends, and related scientific evidence, paints a rather different picture, however. Dietary guidelines have long emphasized consumption of specific low-fat foods, namely whole grains, vegetables, and fruits. In response to the public's interest in fat restriction, the food industry generated a vast array of low-fat but not necessarily low-calorie foods over the past two decades, prototypical of which is SnackWells cookies and other snacks. Upon close inspection, the CDC data reveal that total fat intake never meaningfully declined; rather, fat as a proportion of total calories was diluted somewhat by an increase in total calorie intake (386,780,781). The increase in calories was driven by increased consumption of calorie-dense, nutrient-dilute, fat-restricted foods, contemporaneous with a trend toward increasing portion sizes in general (350,388–391).

The competition between low-fat and low-carbohydrate diets for weight loss has in some ways polarized debate beyond the point of reason or utility. Lowering the fat content of processed foods while increasing consumption of simple sugars and starch is not consistent with the long-standing recommendations of nutrition authorities to moderate intake of dietary fat. Yet it is this distorted approach to dietary fat "restriction" that best characterizes secular trends in dietary intake at the population level and that subtends the contention that dietary fat is unrelated to obesity. An extensive literature belies this claim.

The theoretical basis for weight loss through dietary fat restriction is strong, given the widely acknowledged primacy of calories in weight governance and the energy density of fat (377).

Also, noteworthy are data from the National Weight Control Registry, which indicate that lasting weight loss is consistently attributable to relatively fat-restricted, balanced diets in conjunction with regular physical activity (288). The weight-loss benefit of advice to follow fat-restricted diets is, however, no more enduring than that of advice to restrict calories by any other means (782).

Despite the extensive literature supporting dietary fat restriction for weight loss and control, there are dissenting voices (385). For the most part, dissent is predicated on the failure of dietary fat restriction to achieve population-level weight control in the United States and on the good health of Mediterranean populations with fat intake as high as 40% of calories (783). In addition, the evidence is clear that when energy restriction can be achieved on a diet relatively high in fat content, weight loss is achieved (466), suggesting the primacy of energy intake over macronutrient intake in weight regulation. The principal basis for recommending fat restriction, per se, for weight control is as a healthful means of facilitating reduced energy consumption. To the extent that fast food and highly processed junk foods are also high in fat—especially saturated and trans fats—switching to less processed whole foods naturally lower in these fats is both health promoting and conducive to weight loss. Thus, given the increasing appreciation for the healthful properties of unsaturated oils, however (see Chapters 2, 7, and 45), advice to restrict certain fats (e.g., saturated, trans) in conjunction with other strategies for moderating the energy density of the diet and total caloric intake is more fully concordant with the current state of evidence.

Similarly, advice to limit carbohydrate intake is of some utility if the restrictions are directed preferentially to added sugar and refined grains. Restriction of total carbohydrate intake may facilitate

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short-term weight loss by limiting dietary variety and choice but is at odds with an abundance of evidence regarding sustainable weight control and overall health (see Chapter 45), and it epitomizes "throwing out the baby with the bathwater." Casting dietary guidance in terms of food choices, rather than macronutrient categories, is clearly warranted to avoid propagating such blunders (784).

Recent trends in the United States suggest that fat intake over recent decades has held constant, not been reduced, and that intake of total calories has risen to dilute the percentage of food energy derived from fat; increased consumption of highly processed, fat-reduced foods is the principal basis for these trends (386). Thus, the failure of dietary fat restriction to facilitate weight control is more a problem of adherence than effectiveness (385). The Mediterranean diet differs from the typical American diet not only in the quantity of fat but also in the type of fat and the quantity of unrefined grains, vegetables, fruit, and lean protein sources (456). Further, many of the Mediterranean populations enjoying good health have traditionally high rates of physical activity compared to Western societies; the effects of physical inactivity and high dietary fat intake may be synergistic with regard to weight gain (461).

There is some evidence to suggest that dietary protein may preserve REE following weight loss (785). This, together with protein's high satiety index, suggests a benefit of protein intake at the high end of the range advisable for overall health as an aid to weight loss and control efforts (407,786).

Although it is clear that a balance between energy intake and energy expenditure is the principal determinant of weight maintenance in an individual, the factors responsible for the wide variations in the set point for that equilibrium are only partly understood. Genetic factors apparently play both direct (i.e., by influencing levels of leptin) and indirect (i.e., by influencing levels of thyroid hormone, the degree of postprandial thermogenesis, the mass of brown fat) roles in establishing the propensity for weight gain or loss in an individual. Environmental influences, such as the prevailing food supply and accessibility of opportunities for physical activity, are comparably important. The rising prevalence of obesity throughout the industrialized world makes clear that far from being a problem of impaired self-restraint in an individual, obesity may be seen as a public health threat mediated by a "toxic" nutritional environment. An appreciation for the public health importance of obesity, its complex pathogenesis, and principles of management are supportive of optimal interventions by clinicians.

CLINICAL HIGHLIGHTS

The majority of patients with weight control problems seen in primary care either will be overweight or have nonsevere obesity (BMI between 25 and 35). Evidence is lacking that pharmacotherapy is beneficial in this group. Clinicians should be prepared to consider long-term use of pharmacologic agents, as is commonly done with other diet-sensitive conditions, such as hypertension and hyperlipidemia, as an adjunct to lifestyle in the management of obesity. Such decisions should be reached in consideration of the degree and duration of obesity, its refractoriness to lifestyle interventions, its physical and/or psychological sequelae, and the risk-to-benefit ratio of pharmacotherapy, to the extent it can be determined. The use of pharmacotherapy for minimal overweight without sequelae or for cosmetic reasons is generally not prudent.

There is no evidence that commercial weight-loss programs are successful in the long term, but such programs are modifying their methods over time and may yet prove to be of value. Although the results of dietary counseling are often disappointing, there is suggestive evidence that physician counseling and multidisciplinary behavioral intervention can be an important factor both in achieving weight loss and in encouraging patients to apply safe and appropriate methods. It is noteworthy that obesity may be the single most common condition encountered in primary care, yet it is often not addressed by primary care

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providers. There is convincing evidence that severe obesity can be managed effectively in the short term with low- and very-low-calorie liquid diets; evidence is little more than suggestive that such benefits can be sustained in the absence of intensive behavioral intervention. Evidence is decisive that surgery is beneficial in carefully selected patients with severe obesity—which is now approaching 8% prevalence among US adults—but intensive behavioral intervention is required to sustain the weight loss achieved, and novel residential programs may be effective as an alternative to surgery for children and adolescents.

The evidence favoring fat as well as total energy restriction to achieve and maintain weight loss is convincing, if not definitive. There is limited evidence that, within the context of a fat- and energy-restricted diet, relatively more protein and relatively less carbohydrate may result in lower fasting insulin levels. However, weight loss consistently lowers insulin as well. Further, studies have generally varied carbohydrate and protein content within close proximity to the recommended levels of intake. Thus, there is no meaningful evidence that extreme alterations of the basic mixed, balanced health-promoting diet (see Chapter 45) are indicated to achieve or maintain weight loss. On the contrary, weight loss is promoted by a diet consistent with recommendations for health promotion. Such recommendations include portion control to restrict energy intake; restriction of fat intake to reduce the energy density of the diet; abundant intake of vegetables, fruits, and whole grains; avoidance of sugar-sweetened beverages; and consistent physical activity (see Chapter 45). The advisable dietary pattern is rich in complex carbohydrates, but liberal intake of protein is reasonable and may be advantageous, provided that the protein is from mostly plant-based sources (e.g., beans, legumes, fish, poultry, egg white) and those low in saturated fat. The application of such a diet permits weight loss and the promotion of health to be addressed conjointly; alternative weight-loss diets, whether or not they facilitate short-term weight loss, are not consistent with the long-term dietary pattern advised for health maintenance and the prevention of disease. Physical activity is among the best predictors of long-term weight maintenance. Given the many impediments to long-term compliance with such guidelines (see Chapters 44 to 47), the ultimate control of epidemic obesity almost certainly will require environmental changes that facilitate consistent physical activity and consumption of a nutrient-dense but relatively energy-dilute diet. In the interim, the clinician can and should make a meaningful contribution to any given patient's capacity to resist and defy the obesigenic influences in their life. The clinical focus should consistently be placed on the family/household rather than just the individual; on health rather than just weight; and on long-term sustainability. Practical approaches to efficient counseling so these topics may routinely be addressed in the primary care setting are explored in Chapter 47.

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Chapter 6

Diet, Diabetes Mellitus, and Insulin Resistance

Saadia Alvi

INTRODUCTION

The role of dietary management of both type 1 and type 2 diabetes mellitus has been conclusively established. Although patients with type 1 diabetes require exogenous insulin, their glycemic control and the occurrence of diabetes-related complications are related to dietary factors. Most dietary recommendations for diabetes pertain to both types. It has been suggested that Alzheimer's disease represents "type 3 diabetes" (1) and may be due in part to chronic insulin resistance and insulin deficiency in the brain (see Chapter 35). Although type 2 diabetes is not sufficient to cause Alzheimer's disease, it may contribute to its pathogenesis or enhance progression, and diabetes medications may have a therapeutic role for dementia (1).

Of the approximately 34.2 million cases of diabetes in the United States, 90% of adult cases are type 2 (2), and 90% of those patients are overweight (see Chapter 5). The prevalence of type 2 diabetes has also been increasing among younger age groups. For those under 20, the annual relative increase in diabetes between 2002 and 2012 was 4.8% (3). The largest increases in youths in recent decades have been in minority racial and ethnic groups (4). Incidence of type 1 diabetes in youth has also increased during the last several years in most parts of the world, though the reasons for this trend are not known (5).

Weight control is a fundamental objective in the dietary management of all overweight diabetic patients (see Chapter 5). Whereas traditional approaches to diabetes have focused on exchange lists, and more recently on the glycemic index (GI) of individual foods, attention is now increasingly being focused on the effects of foods in combinations and on the overall dietary pattern. There is emerging consensus that the glycemic load (GL) of the diet is one useful gauge of dietary quality of particular relevance to diabetes management and prevention. The pathogenesis of the insulin-resistance syndrome continues to be investigated, as does debate over its defining characteristics and nomenclature. Nonetheless, there is widespread recognition that insulin resistance is increasingly prevalent, affecting up to 50% of overweight adults and 25% of overweight children and adolescents (see Chapter 5). There is at least suggestive evidence that obesity is necessary, if not sufficient, for the development of the insulin-resistance syndrome in most cases (6). Excess calorie intake can lead to weight gain, which in turn increases the risk for developing insulin resistance.

Insulin resistance and states of impaired glucose metabolism, including both impaired glucose tolerance (IGT) and impaired fasting glucose (IFG), constitute antecedents to type 2 diabetes. The Diabetes Prevention Program has provided definitive evidence that a lifestyle intervention predicated on healthful diet and regular physical activity can forestall the development of diabetes in the majority of such cases. Perhaps no condition offers better testimony than diabetes to the powerful role of lifestyle modifications.

OVERVIEW

Diagnostic Criteria for Diabetes Mellitus

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A fasting blood glucose level of 126 mg/dL or greater defines diabetes mellitus (7). When hyperglycemia occurs as a result of total or nearly total loss of insulin output, the condition is defined as type 1 diabetes. When hyperglycemia results from inadequate insulin action rather than primary β-cell failure, the condition is defined as type 2 diabetes. There is increasing appreciation for hybrid forms of diabetes that encompass features of both type 1 and type 2 as well (2,8).

Epidemiology of Diabetes Mellitus

In the United States, there are some 34.2 million people living with diabetes, of whom roughly 26.9 million are diagnosed and the remainder undiagnosed (9). The ratio of diagnosed to undiagnosed diabetes has declined slightly over recent years among the overweight, apparently in response to heightened awareness of diabetes risk in this group (10). More than 90% of the diagnosed cases and virtually all of the undiagnosed cases of diabetes are type 2. Prediabetes, encompassing both IGT (a blood sugar level of 140–199 mg/dL after a 2-h oral glucose tolerance test) and IFG (blood sugar level of 100–125 mg/dL after an overnight fast), affects some 88 million Americans.

The World Health Organization estimates that there were approximately 422 million people living with diabetes worldwide as of 2014. An estimated 1.6 million deaths were directly due to diabetes in 2016 and it projects that diabetes deaths will increase by two thirds between 2008 and 2030 (11,12). Projections in the United States suggests that adults diagnosed with diabetes would increase from 39.7 million (13.9%) in the year 2030 to 60.6 million (17.9%) in the year 2060 (13).

Pathogenesis of Diabetes Mellitus

Type 1 Diabetes Mellitus

Type 1, or insulin-dependent, diabetes mellitus is due to pancreatic *β*-cell dysfunction or destruction, generally considered the result of an autoimmune process (14). Although the inciting event or exposure is not known with certainty, there is some, albeit controversial, evidence that early exposure to bovine milk proteins in predisposed individuals may play a role (15–18). Wheat gluten has been proposed as an alternative precipitant, and vitamin D and early childhood immune stimulation by infectious agents have been suggested to be protective (19). In contrast to some early infectious exposures that may attenuate risk, there is an association between enterovirus infection and increased risk (15). There is general consensus that type 1 diabetes is the product of gene/environment interaction and that control of environmental triggers might prevent the disease. In general, however, there is little to suggest that dietary interventions can be used to prevent type 1 diabetes. While a protective role of breastfeeding is intuitive on the basis of prevailing theories of pathogenesis, the evidence to date is largely inconclusive (15,19–23). Discussed later in this chapter, disruptions in the microbiome may also be contributing factors.

Insulin Resistance and Type 2 Diabetes Mellitus

The fundamental distinction between type 1 and type 2 diabetes, at times blurred, is the preservation of endogenous insulin production in type 2. This distinction results in the susceptibility of type 1, but not type 2, diabetics to ketoacidosis. Severely uncontrolled hyperglycemia in type 2 diabetics generally leads instead to nonketotic, hyperosmolar coma, with ketone body production representing the effect of absent insulin-mediated glucose transport.

The development of type 2 diabetes results from the interplay of genetic susceptibility and

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environmental factors (24). The responsible genes have not been identified with certainty, although multiple alleles are almost certainly involved, and certain candidate mutations have been under study for some time (25). The clustering of type 2 diabetes in families is well established. Interest in genetic susceptibility to type 2 diabetes dates at least to the early 1960s, when James Neel (26), who went on to head the human genome project, speculated that expression of diabetes was due to the confrontation of a thrifty metabolism designed for dietary subsistence with a world of nutritional abundance. The theory of metabolic thriftiness essentially posits that a brisk insulin release in response to ingestion is advantageous in the utilization and storage of food energy when such energy is only sporadically available. The same brisk response in the context of abundantly available nutrient energy leads to hyperinsulinemia, obesity, insulin resistance, and, ultimately with the advent of β-cell failure, diabetes. The thrifty genotype theory is supported by certain lines of evidence but is far from universally accepted and continues to generate considerable interest and debate (27–32). Factors associated with expression of the disease include excessive nutrient energy intake with resultant obesity, physical inactivity, and advancing age. These factors contribute to the development of insulin resistance at the receptor, an often key element in the development of type 2 diabetes mellitus. Physical activity appears to protect against the advent of type 2 diabetes mellitus both independently and by preventing and mitigating weight gain and obesity (33). As with type 1 diabetes, the microbiome is currently the subject of much research for its potential role in the pathophysiology of both obesity and type 2 diabetes, and is discussed later in this chapter.

Insulin resistance generally precedes, by an uncertain and probably variable period of time, the development of diabetes, although type 2 diabetes can develop in the absence of insulin resistance (34–36). Diabetes generally occurs when receptor-mediated resistance is compounded by β-cell dysfunction and reduced insulin secretion. Basal insulin production in a healthy, lean adult is roughly 20 to 30 units/24-h period. In insulin resistance, that output may be as much as quadrupled to maintain euglycemia. Type 2 diabetes following insulin resistance indicates the failure of β-cells to sustain supraphysiologic output of insulin, a decline of insulin output to below normal levels, and the consequent advent of hyperglycemia (37,38). Whereas type 1 diabetes is associated with nearly absent insulin release (0–4 units daily), type 2 diabetes is generally thought to emerge in lean individuals when production falls to approximately 14 units/day.

An association between weight gain and the development of diabetes is supported by prospective cohort studies (39–41), although insulin resistance may contribute to the development of obesity as well, so that causality may be bidirectional (42). Data from such sources suggest that weight loss is protective against the development of diabetes. The currently worsening epidemic of obesity in the United States suggests that the prevalence of diabetes will likely rise and that efforts to combat obesity, if ultimately successful, will translate into reduced rates of diabetes as well (see Chapter 5).

The incidence of type 2 diabetes in the pediatric population parallels the increase in pediatric obesity (43). Less than a generation ago, type 2 diabetes was called “adult-onset” diabetes to distinguish it from “juvenile onset” diabetes. In the span of less than a generation, what was a chronic disease of midlife has become an increasingly routine pediatric diagnosis (44–46).

The Adult Treatment Panel of the National Cholesterol Education Program essentially equates diabetes with established coronary disease in its guidance for cardiac risk factor management (47). With adult-onset diabetes now seen in children younger than age 10, we may anticipate the emergence of cardiovascular disease (CVD) in ever younger individuals (48,49) (see Chapters 5 and 7).

The development and manifestations of insulin resistance relate to the principal actions of insulin. In the liver, insulin inhibits gluconeogenesis, inhibits glycogenolysis, and promotes glycogen production (50). In muscle and adipose tissue, insulin facilitates the uptake of glucose, as well as its use and storage.

Insulin exerts important influences on protein and lipid metabolism as well.
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The fundamental role of insulin is to coordinate the use and storage of food energy. This requires regulation of both carbohydrate and fat metabolism, as total body glycogen and glucose stores in a healthy adult approximate 300 g. At 4 kcal/g, this represents an energy reserve of 1,200 kcal, enough to support a fast of approximately 12 to 18 h. Energy stored as triglyceride in adipose tissue in a lean adult totals nearly 120,000 kcal, or 100 times the carbohydrate reserve. Thus, release of energy stores from adipose tissue can protect vital organs during a protracted fast.

In the fed state, the entry of amino acids and monosaccharides into the portal circulation stimulates release of proinsulin from pancreatic β-cells. Insulin is cleaved from the connecting ("C") protein to generate active insulin. Insulin transports both amino acids and glucose into the liver, where it stimulates glycogen synthesis, protein synthesis, and fatty acid synthesis, while suppressing glycogenolysis and gluconeogenesis, as well as proteolysis and lipolysis. Insulin carries both glucose and amino acids into skeletal muscle, and it carries glucose into adipose tissue. Insulin facilitates glycogen synthesis and glycolysis in muscle, and it facilitates fatty acid synthesis in adipose tissue. Insulin also stimulates the synthesis of lipoprotein lipase in capillaries, facilitating the extraction of fatty acids from circulation, and promotes hepatic very-low-density lipoprotein (VLDL) synthesis.

During a fast, insulin levels decline, as levels of glucagon, a product of the pancreatic α-cells, rise. Falling insulin levels promote glycogenolysis, followed by gluconeogenesis, in the liver. In adipose tissue, low insulin levels stimulate lipolysis, releasing fatty acids for use as fuel; ketones are generated in the process of hepatic fatty acid oxidation. High levels of circulating fatty acids inhibit insulin action. Reduced insulin action at skeletal muscle stimulates proteolysis.

In the insulin-resistant state, insulin levels are high, but receptors, particularly those on skeletal muscle, are relatively insensitive to insulin action (51,52). High levels of insulin presumably compensate for receptor-mediated resistance. High insulin levels promote fatty acid synthesis in the liver. The accumulation and circulation of free fatty acids and triglycerides packaged in VLDL aggravate insulin resistance, driving insulin levels higher. Thus, the metabolic derangements are self-perpetuating, generating in the process the manifestations of the insulin-resistance syndrome associated with cardiovascular risk, until the β-cells fail and diabetes develops. With β-cell failure, the resultant low levels of circulating insulin mimic conditions during a fast. The metabolic derangements that distinguish diabetes from fasting include pathologically low insulin levels and, of course, high levels of circulating glucose. Hepatic gluconeogenesis compounds the hyperglycemia, with excess glucose leading to tissue damage through glycosylation. Glycosylation of hemoglobin is routinely used as a measure of the extent of prevailing glycemia (i.e., HgbA1c). High ambient levels of glucose lead to the production of sugar alcohols (e.g., sorbitol, fructose) in many tissues, which in turn can cause cellular distention. The accumulation of such polyols in the lens is causally implicated in the blurred vision that often occurs with poorly controlled diabetes.

In studies of the Pima Indians, a tribe of Native Americans particularly subject to the development of obesity and diabetes mellitus (see Chapter 44), Lillioja et al. (6) showed that insulin resistance is an antecedent of diabetes. During the phase of insulin resistance, serum glucose is normal but insulin levels are abnormally elevated, both in the fasting and postprandial states. The development of obesity appears to be of particular importance in the development of IGT secondary to insulin resistance. A modest degree of hyperglycemia may occur during the period of insulin resistance, acting as a signal to the endocrine pancreas that insulin action is impaired and stimulating more insulin release. Ultimately, both protracted hypersecretion and hyperglycemia may contribute to β-cell dysfunction and overt diabetes.

In a longitudinal study of the Pima people, Lillioja et al. (53) characterized steps in the pathogenesis of

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type 2 diabetes. More than 200 nondiabetic subjects were followed for an average of over 5 years, undergoing body composition measures, glucose tolerance testing, and hyperinsulinemic–euglycemic clamp testing to assess insulin action and glucose disposal. The single, strongest predictor of the development of diabetes was impaired insulin action, with a relative risk of over 30; this remained significant after adjustment for body fat. Percentage of body fat and impaired suppression of hepatic gluconeogenesis were also significant predictors of diabetes. The authors concluded that impaired insulin action, or insulin resistance, was the strongest single predictor of impending diabetes, while impaired suppression of hepatic gluconeogenesis was likely to be a secondary event. The factors responsible for β-cell failure, possibly including glucose toxicity and/or "fatigue" secondary to hyperfunction over time, are uncertain. The possibility exists, however, that the pathogenesis of type 2 diabetes is variable in different populations; β-cell failure may occur independently of insulin resistance (54). Noteworthy with regard to the Pima Indians is evidence that restoration of their traditional diet, low in fat and simple sugar and high in fiber from various desert plants, particularly mesquite, ameliorates their tendency toward diabetes and obesity (55). That the habitual nutritional environment should have salutary effects is perhaps supportive of the "thrifty genotype" theory and certainly is supportive of the application of the evolutionary biology model to human nutrition.

Reaven et al. (55) reported that a substantial proportion of cases of hypertension may be related to insulin resistance. While noting that hypertension may occur independently of insulin resistance, and vice versa, the authors note that insulin resistance stimulates the sympathetic nervous system. Under normal fasting conditions, low serum glucose and insulin levels stimulate the activity of an inhibitory pathway from the ventromedial hypothalamus to sympathetic centers in the brainstem. With sustained elevations of both glucose and insulin, the inhibitory pathway remains suppressed, with resultant augmentation of sympathetic tone. Invoking this model, the authors suggest that amelioration of insulin resistance, with diet, weight loss, or pharmacotherapy, may be more important to the reduction of cardiovascular risk in certain hypertensive patients than blood pressure control per se (56).

Thus, the development of type 2 diabetes often is preceded by a protracted period of insulin resistance manifested as the "metabolic syndrome" of obesity, dyslipidemia, and hypertension. Abdominal obesity and hypertriglyceridemia may be particularly early markers of the syndrome and represent a readily detectable indicator of risk for diabetes (57). Of note, the defining features of the insulin-resistance syndrome, and the nomenclature applied, have of late been matters of contention. The American Heart Association supports diagnostic criteria for the metabolic syndrome (58) (see Table 6.1), while the American Diabetes Association has questioned the utility of defining a syndrome at all (59).

TABLE 6.1

American Heart Association Criteria for the Metabolic Syndrome

The American Heart Association and the National Heart, Lung, and Blood Institute recommend that the metabolic syndrome be identified as the presence of three or more of these components:

Elevated waist circumference	Men—equal to or greater than 40 inches Women—equal to or greater than 35 inches
Elevated triglycerides	Equal to or greater than 150 mg/dL
Reduced HDL ("good") cholesterol	Men—less than 40 mg/dL Women—less than 50 mg/dL
Elevated blood pressure	Equal to or greater than 130/85 mm Hg
Elevated fasting glucose	Equal to or greater than 100 mg/dL

Source: National Cholesterol Education Program. Adult treatment panel III guidelines. Available at http://www.americanheart.org/presenter.jhtml?identifier=4756; accessed 3/20/13
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Regardless of the terminology applied to the various manifestations of the insulin-resistant state, interventions to treat the condition, particularly supervised weight loss, may both mitigate associated cardiovascular risk and prevent the evolution of diabetes. The Diabetes Prevention Program has provided definitive evidence that although both are effective, lifestyle modification is superior to pharmacotherapy to prevent type 2 diabetes in a significant proportion of at-risk individuals (60). In individuals with diagnosed type 2 diabetes, the Look AHEAD trial has demonstrated that intensive lifestyle intervention can improve glucose control and reduce CVD risk factors and medication use (61,62).

There is now definitive evidence in type 1 diabetes (63,64) and strongly suggestive evidence in type 2 diabetes (65,66) that control of serum glucose levels to within the physiologic range delays the development of complications. There is consensus that nutritional management is an essential component in efforts to achieve and maintain good glycemic control. In certain cases, very aggressive glycemic control with pharmacotherapy may have adverse effects on mortality (67). Such findings are not entirely consistent across studies. However, the possibility of adverse effects of stringent glycemic control via pharmacotherapy, along with patient history and individual characteristics, should be considered when determining target values for blood glucose and HbA1c. Other goals of dietary therapy include regulation of serum lipids, weight control, and targeted management of incipient or advancing complications and concomitants of diabetes, such as hypertension, kidney disease, and coronary artery disease.

Nutritional interventions are essential for optimal management of diabetes. In contrast to prescribing lifestyle modification, when pharmacologic treatment is indicated, the potential contraindications and side effects will need to be considered. Sulfonylureas increase insulin production and similar to insulin can potentially increase weight as a side effect; α-glucosidase inhibitors such as acarbose delay glucose absorption and may cause GI symptoms as a side effect; biguanides such as metformin reduce hepatic gluconeogenesis and may cause GI symptoms as a side effect; thiazolidinediones such as troglitazone enhance peripheral insulin receptor sensitivity may cause weight gain as a side effect. Incretin mimetics, like GLP-1 agonists and DDP4 inhibitors, ameliorate glycemic control by multiple mechanisms of action, and although may have the side benefit of weight loss, may also cause GI side effects (68,69). Each class of medication, alone and in combination with others as well as insulin, offers distinct advantages and disadvantages. Excellent reviews of pharmacotherapy are available (70–72).

Dietary Management

Overview

The dietary management of diabetes has varied considerably over the course of the past century. The mainstay of treatment in the early decades of this century was carbohydrate restriction. Dietary fat intake was high to compensate for low caloric intake from carbohydrate. The role of carbohydrate restriction entered its modern era with the development of the GI by Jenkins et al. (73). The GI typically uses a slice of white bread as a reference standard, with a value of 100, and indicates the postprandial rise in serum glucose (and consequently insulin) for fixed portions of specified foods.

However, as shown in Table 6.2, the GI does not provide information that is readily translated into clinical advice. Common perceptions about the simple sugar content of foods do not allow one to predict the glycemic response evoked, as exemplified by the relatively low GI of ice cream and the high GI of certain fruits and vegetables. Similarly, variations in the glycemic responses to different polysaccharides

are minimal when these sugars are consumed in the context of a meal. Consequently, attention has turned increasingly to overall meal and diet composition.

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TABLE 6.2

Glycemic Index of Some Common Foods

Food Group	Food	Glycemic Index
Breads	White bread[a]	100
	Whole-wheat bread	99
	Pumpernickel	78
Cereal products	Cornflakes	119
	Shredded wheat	97
	Oatmeal	85
	White rice	83
	Spaghetti	66
	Bulgur wheat	65
	Barley	31
Fruit	Raisins	93
	Bananas	79
	Oranges	66
	Grapes	62
	Apples	53
	Cherries	32
Vegetables	Parsnips	141
	Baked potato	135
	Carrots	133
	Corn	87
	Boiled potato	81
	Yams	74
	Peas	74
Legumes	Lima beans	115
	Baked beans	60
	Chick peas	49
	Red lentils	43
	Peanuts	19
Dairy products	Yogurt	52
	Ice cream	52
	Milk	49
Sugar	Sucrose	86

[a]*Reference standard.*

Adapted from Jenkins DJA, Jenkins AL. The glycemic index, fiber, and the dietary treatment of hypertriglyceridemia and diabetes. J Am Coll Nutr. 1987;6:11–17.

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Foods with a high GI, such as pasta and bread, need not elicit a postprandial spike in glucose and insulin if such an effect is blunted by other foods consumed concurrently. Foods rich in soluble fiber (see Chapter 1 and Appendix E) are particularly effective at attenuating such a response. There is some evidence that the distribution of foods may be as important as their GI in the glucose and insulin responses they evoke. Comparing identical diets distributed as either three daily meals or multiple daily snacks, Jenkins et al. (74) reported that frequent snacking, or "nibbling," resulted in significant reductions in insulin release, although there is limited corroborating study of this contention.

As noted in Chapter 5, the GL is increasingly supplanting the GI in both research and clinical practice applications. The GL accounts for both the presence of sugar in foods and its concentration (see Table 6.3). The GL may be applied to meals and even to the overall diet. The initial studies of low-GL diets have shown promise for management of insulin resistance, diabetes, obesity, and cardiometabolic risk (75–82). In regards to decreasing cardiovascular disease risk, subsequent data has shown that it may be optimized by a higher carbohydrate (55%), lower-GI dietary pattern (83,84).

TABLE 6.3

Glycemic Index and Glycemic Load of a Few Foods that Demonstrate How the Values May Diverge[a]

Food	GI	Serving Size	Carbohydrate Dose (g)	GL
Chickpeas	51	150 g	30	11
Vanilla ice cream	54	50 g	9	3
Strawberries	57	120 g	3	1
Orange	69	120 g	11	5
Whole-wheat bread	73	30 g	13	7
Orange juice	81	250 mL	26	15
Coca-Cola	90	250 mL	26	16
Plain bagel	103	70 g	35	25
Doughnut	108	47 g	23	17
Carrots	131	80 g	6	5

[a]*The foods are listed from lowest to highest GI.*

Data from Foster-Powell K, Holt SH, Brand-Miller JC. International table of glycemic index and glycemic load values. Am J Clin Nutr. 2002;76:5–56.

The principal goals of nutritional management of diabetes are to maintain a normal or near-normal serum glucose level, to prevent or reverse lipid abnormalities, and to thereby mitigate the potential complications of diabetes. Nutritional management of insulin resistance, or prediabetes, if identified as such before the advent of diabetes, is aimed at the prevention of progression to diabetes. Insulin resistance is apt to be detected in the context of the insulin-resistance syndrome, as discussed previously (see also Chapter 5). The combination of elevated serum triglycerides and obesity may be an early

indication of insulin resistance (85); postprandial hypertriglyceridemia may be an even earlier indicator.
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The utility of a prudent, balanced, health-promoting dietary pattern, in conjunction with moderate physical activity and resultant weight loss, in the prevention of diabetes has been clearly established by the Diabetes Prevention Program (60). In this trial, more than 3,000 adults with prediabetes were randomly assigned to usual care, treatment with 850 mg/day of metformin, or a lifestyle intervention comprising guidance toward a healthful dietary pattern and 150 min of physical activity per week. The trial was concluded early, at 4 years, due to significant treatment effects. Pharmacotherapy reduced the incidence of diabetes by 30%, while the lifestyle intervention was nearly twice as effective, reducing the incidence of diabetes by 58%. Ten years after randomization, diabetes incidence rates were similar between groups, but cumulative incidence of diabetes remained lowest in the lifestyle group (86). The potency of the lifestyle intervention in the Diabetes Prevention Program corresponds very closely to the 60% reduction in the incidence of diabetes reported with use of rosiglitazone in the DREAM trial (87). Evaluation of the Diabetes Prevention Program suggests the lifestyle intervention is a cost-effective strategy for diabetes prevention in high-risk individuals (88–90).

According to the American Academy of Clinical Endocrinology (AACE) and the American College of Endocrinology (91), the principal goals of nutritional management of type 2 diabetes fall within the idea that lifestyle therapies should be included in first-line treatment. Lifestyle intervention should emphasize the key components of a healthy eating pattern, physical activity, sleep, behavioral support, and avoidance of tobacco. For those who are overweight or obese, the initial goal should be a weight loss reduction of 5% to 10% of total body weight through caloric restriction. In a more detailed version of these guidelines dating back to 2013, patients are encouraged to avoid variations in carbohydrate intake (recommended intake between 45% and 65% of carbohydrates), the consumption of sucrose- and fructose-containing processed foods, and other high GI foods. For foods consumed, the guidelines recommend the consumption of high fiber, whole-grain products, fruits (especially berries), and vegetables (especially raw) to facilitate fiber consumption, a high phytonutrient intake, and calorie control. In terms of protein, the guidelines recommend 15% to 35% of animal or plant protein intake to replace saturated fat and/or refined carbohydrates that may have been previously consumed in a prior diet. Both reduced-fat animal protein and dairy are recommended in these guidelines but are limited to 6 oz and 3 servings, respectively. However, plant protein is recommended without limitation due to additional benefits in regard to cholesterol and blood pressure. In 2020, more recent guidelines from the AACE have recommended that all patients (91) (with and without diabetes) “should strive to attain and maintain an optimal weight through a primarily plant-based meal plan high in polyunsaturated and monounsaturated fatty acids, with limited intake of saturated fatty acids and avoidance of trans fats.” Recommendations for specific macronutrient intake have been removed with a stronger emphasis on the source of food being consumed.

Similarly, the ADA guidelines currently state that there is no ideal percentage of macronutrient ratio for type 2 diabetes and recommends that macronutrient distribution “should be based on an individual assessment of current eating patterns, preferences, and metabolic goals (92).” Instead, the emphasis should rather be on a healthful eating pattern, examples of which include “Mediterranean style, low-carbohydrate, and vegetarian or plant-based eating patterns.” Although the current ADA nutrition guidelines do not include specific targets for percentage of calories from carbohydrates, protein, total fat, polyunsaturated fatty acids (PUFAs), or MUFAs (93), they do recommend that saturated fat be limited to less than 10% of total calories and to minimize the intake of trans fat. Saturated fats should be replaced with monounsaturated and/or polyunsaturated fats.

It should also be noted that the ADA now endorses low-carbohydrate and very low-carbohydrate diets

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as options for eating patterns. They are the most studied diets among all for type 2 diabetes. The definition of a low-carbohydrate diet is not consistent and can vary from 26% to 45% of total calories, while a very low carbohydrate is less than 26% of total calories. These eating patterns have been associated with A1c reductions when compared to other diets (26,27). There is a short-term evidence of a carbohydrate-restricting diet to be beneficial for lowering the A1c; however, there is no clear data on long-term safety or benefits (94). Although long-term data is lacking for this dietary pattern, observational data has shown an association of lower-carbohydrate diets with increased mortality (20–28,95–99). A large prospective meta-analysis of observational studies demonstrated that low-carbohydrate dietary patterns favoring animal-based proteins were associated with higher mortality, while those that favored plant-based proteins were associated with lower mortality (30). Despite these issues, a low-carbohydrate diet may be useful for some who are able to maintain a benefit or unable to adhere with other dietary options.

Macronutrient Distribution

Protein

In general, the protein intake recommended for healthy adults, approximately 0.8 g/kg/day, is appropriate in both insulin-resistant states and diabetes. Protein restriction may be indicated if kidney disease develops (see Chapter 16). Excessive protein intake may accelerate the development of kidney disease, however. Because the long-term effects of diets with more than 20% of energy from protein are not yet clear, the ADA does not recommend high-protein diets for individuals with diabetes, and advises against protein intakes greater than 0.8 g/kg/day in patients with chronic kidney disease (93). Some large population studies have shown that high intake of protein was actually associated with an increased prevalence and risk of developing both prediabetes and diabetes (100). Replacing (101) red meat with an alternative protein source was also associated with a lower risk of developing diabetes. Popular books advocating high-protein diets for weight loss and control of insulin release (102–105) are of dubious merit for healthy individuals and are to be avoided in the management of diabetes. The source of protein has been an overlooked yet important factor when it comes to diabetes management and overall mortality. There is evidence to show that replacing animal protein with plant protein can be beneficial in the management of diabetes. One large systemic review showed a significant decrease in hemoglobin A1c, fasting glucose, and fasting insulin levels in those who had replaced animal protein with plant protein (106). As noted earlier, the quality of any dietary pattern is best measured in terms of the specific foods of which it is consisted rather than merely its macronutrient distribution.

Carbohydrates and fats

comparisons of low-fat and low-carbohydrate diets in diabetic patients have yielded somewhat mixed results, perhaps owing to other differences in the prescribed diets within and among studies. Evidence is pointing toward the specific type of fat or carbohydrate playing a bigger role in insulin resistance and diabetes, rather than the macronutrient as a whole. Supporting evidence comes from the DIETFITS trial, which randomized participants who were overweight or obese with insulin resistance to a healthy low-carb or low-fat diet for 12 months and found no difference in weight change between the two groups (107).

The type of fat likely also has clinical relevance. Fat types include trans fats, saturated fats,

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polyunsaturated, and monounsaturated fats. Research has shown that the saturated and trans fats increase the risk of diabetes (108). A study that looked at cohorts from the large European Prospective Investigation into Cancer and Nutrition (EPIC) trial found that in patients with diabetes, substitution of carbohydrates with saturated fats was associated with a higher mortality rate (109). The substitution of monounsaturated fatty acids (MUFAs) for carbohydrate in the diet has been found to improve glycemic control, while lowering triglycerides, raising HDL, and preserving low-density lipoprotein (LDL) levels (110,111).

With regards to nutritional guidance for carbohydrates, the evidence is pointing toward taking a closer look at quality rather than quantity. Similar to the concept of unhealthy fats, unhealthy carbohydrates take the shape of refined carbohydrates. Higher-quality, unrefined carbohydrates include foods such as whole grains, fruits, and legumes. Evidence from meta-analyses demonstrate that an increased intake of carbohydrates of a higher quality as measured by markers such as fiber is associated with a decrease in intermediate cardiovascular risk factors (112–114). This was also associated with weight loss, decreased incidence of diabetes, cardiovascular disease, and cardiovascular mortality, further emphasizing the importance of focusing on dietary patterns rather a specific macronutrient profile.

Guldbrand and colleagues reported improvements in HbA1c and HDL concentrations in patients following a low-carbohydrate diet, but no significant change in patients following a low-fat diet (115). Insulin dose also decreased in the low-carbohydrate group relative to the low-fat group. The favorable effects of the low-carbohydrate diet occurred despite similar weight loss in both groups. On the other hand, Davis and colleagues reported similar weight loss in type 2 diabetics following either a low-fat or low-carbohydrate diet after 1 year, but no significant change in hemoglobin A1c or blood pressure in either group (116). Notably, a meta-analysis of overweight and obese participants with and without type 2 diabetes mellitus following either a low-carbohydrate diet or a balanced weight-loss diet found no difference in weight loss or cardiovascular risk factors after 2 years of follow-up (117).

The lipid perturbations seen with high carbohydrate intake may be due, in part or in whole, to ingestion of processed carbohydrate with relatively low-fiber content and a high GL. Therefore, the most appropriate comparisons of diets varying in fat content should include a low-fat diet that is also high in fiber.

Several such studies have been completed in recent years, with somewhat mixed results. Some studies have found low-fat diets that are high fiber and/or low GI to be comparable or even superior to diets lower in carbohydrates and higher in MUFAs (118–120), whereas others have found a diet moderate in fat to be more beneficial (121,122). For example, in a comparison of low-fat and high-MUFA diets where mean fiber intake was significantly higher in the low-fat group (36.1 g vs. 24.6 g, $p < 0.05$), Gerhard et al. observed greater weight loss in the low-fat group and no differences in blood lipids or glycemic control between groups (120). In a randomized trial, Milne et al. (118) found both glycemic and lipid control to be comparably, favorably influenced by either a high-carbohydrate, high-fiber diet or a diet in which monounsaturated fat was substituted for carbohydrate. Similarly, Luscombe et al. (119) found both a high-monounsaturated-fat diet and a high-carbohydrate diet with low glycemic properties to be superior to a high-glycemic, high-carbohydrate diet with regard to HDL levels; with regard to other outcomes, all three diets were comparable. Of note, subjects in this study all consumed at least 30 g/day of fiber.

Barnard et al. found that a low-fat, high-carbohydrate plant-based diet improved glycemia and lipid concentrations significantly more than a diet based on the 2003 recommendations of the ADA (123). Although carbohydrate intake was higher in the vegan diet group, intakes of fiber, fruits, and vegetables were also higher. The results of this study highlight the importance of food choices over macronutrient distribution. Similarly, a large systemic review concluded that in type 2 diabetes, the consumption of a

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vegetarian diet was associated with improved glycemic control (124). Focusing on a whole-food, plant-based eating pattern has also been shown to decrease the risk of developing diabetes in prospective studies (125,126).

Shai and colleagues reported differential effects of low-fat, low-carbohydrate, and Mediterranean diets in 322 moderately obese adults (121). In this study, weight loss over a 24-month period was greater in the low-carbohydrate and Mediterranean diet groups than in the low-fat group, and lipid profile improvements were greater in the low-carbohydrate group than in the low-fat group. In subgroup analysis of 36 participants with type 2 diabetes, the Mediterranean diet significantly reduced fasting glucose and insulin relative to the low-fat group. Of note, the Mediterranean diet group also consumed the most fiber. In a 2010 study, Elhayany et al. also found that a traditional Mediterranean diet (TM) improved glycemic control, measured by HbA1c, compared with an ADA diet (122). However, a low-carbohydrate Mediterranean diet (LCM) improved glycemic control more than both the TM and ADA diets. It was also the only diet to increase HDL concentrations over time. The ADA and TM diets had the same macronutrient distribution: 50% to 55% carbohydrates, 30% fat, and 15% to 20% protein. The LCM diet was 35% carbohydrates, 45% fat (50% MUFA), and 20% protein.

Some lines of evidence (see Chapters 7 and 45) suggest that maximal metabolic and cardiovascular benefit may be achieved with restriction of saturated and trans fat in combination to below 10% of energy and preferably below 5%; allocation of between 10% and 15% of calories to polyunsaturated fat, but with a 1:4 or higher ratio of n-3 to n-6 fatty acids; and allocation of approximately 15% of calories to monounsaturated fat. Such a pattern is enhanced further by ensuring that the 50% or more of calories from carbohydrate are derived predominantly from complex carbohydrates with an abundance of fiber, especially soluble fiber. Diets with as much as 50 g/day of fiber have been well tolerated. Whereas high-carbohydrate, low-fiber diets may elevate triglycerides, high-fiber diets generally lower both fasting and postprandial triglycerides.

To date, there have been few if any direct comparisons of the several variations on the theme of healthful eating—notably, a Mediterranean diet rich in unsaturated fat, a diet relatively rich in protein from lean sources, and a low-GL diet rich in complex carbohydrate—that might reasonably compete as best suited for the management and prevention of diabetes.

The Carbohydrate Insulin Model and The Ketogenic Diet

Some have proposed that significant carbohydrate consumption is obesogenic, leading to the theory known as the “carbohydrate-insulin model” of obesity (127,128). Under this model, the consumption of large amounts of refined carbohydrates (and some starchy, unrefined carbohydrates) is thought to result in postprandial hyperinsulinemia, which then promotes the deposition of calories into fat cells rather than for oxidation in lean tissues. According to the theory, this promotes “cellular internal starvation” with resultant increases in energy intake and decrease in energy expenditure, all of which contribute to weight gain and adiposity (129). However, rigorous experimentation in the form of randomized, controlled trials have not produced the predicted increase in total energy expenditure or body fat loss with low-carbohydrate (or very-low-carbohydrate) diets when compared to higher-carbohydrate diets (130,131). To date, one randomized trial showed findings supportive of the carbohydrate-insulin model of obesity, but its methodology and findings have been questioned publicly with a reanalysis of (129,132,133) the results using a prespecified analysis plan showing no benefit of lower-carbohydrate diets, leading some to describe this study as evidence of “experimental falsification.”

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Nonetheless, popular conceptions of the unhealthfulness of carbohydrates, including both refined and unrefined carbohydrates, have fueled the ongoing popularity of low-carbohydrate diets, including the ketogenic diet, which is considered to be a "very-low carbohydrate diet (134)" for the treatment of type 2 diabetes and obesity. The ketogenic diet promotes a restriction of all or nearly all carbohydrates regardless of the quality of the carbohydrate. The majority (>70%) of calories are obtained from consuming fats, while limiting excess protein.

In regards to type 2 diabetes, a nonrandomized study in patients with type 2 diabetes showed a 1.3% reduction in glycosylated hemoglobin at 1 year in the group following a ketogenic diet; however, this group did receive more support when compared to the control group (135). Short-term randomized studies have also shown a benefit—but waning with increasing duration of the study (136–138). A meta-analysis of long-term randomized studies (studies lasting > 1 year) comparing low-fat diets to ketogenic diets did not demonstrate a difference in glycemic control for those with type 2 diabetes (139). In randomized controlled trials, the benefit of ketogenic diets tends to decrease with duration of the study such that by 1 year no difference is discernible. A possible explanation for this is the lack of adherence to the diet given its extremely restrictive nature.

The diet has also been used for the treatment of obesity, but evidence is lacking to support its use over other dietary approaches. A 2013 meta-analysis demonstrated less than a kilogram of additional weight loss after 12 months for those on a ketogenic diet compared to those on a high-carbohydrate, low-fat diet (139). Some have also claimed that the ketogenic diet raises metabolic rate and increases fat loss more than that seen with low-fat diets. In support of this, one study has shown a minimal increase in energy expenditure with isocaloric ketogenic diets (140). However, a meta-analysis of 32 controlled feeding studies with isocaloric substitution of carbohydrate for fat found that both energy expenditure and fat loss were greater with diets lower in fats (141).

Finally, the ketogenic diet has been observed to have side effects, including nephrolithiasis, hyperlipidemia, and vitamin and mineral deficiencies (134). Although the ketogenic diet may be useful for some with type 2 diabetes and obesity, the risks of the diet should be considered. Robust long-term data regarding the diet's safety and effectiveness over other diets in adults is currently lacking.

Exchange Lists to Dietary Patterns

Historically, exchange lists have been a useful, if potentially tedious, tool in dietary management of diabetes. The lists, published at intervals by the American Dietetic Association, generally represent collaborations between the Academy of Nutrition and Dietetics, formerly the American Dietetic Association, and the ADA. Foods are grouped by category, with serving sizes that provide comparable amounts of energy and each class of macronutrient indicated. Thus, foods within a category may be substituted, or "exchanged," for one another with preservation of a particular nutritional composition for that meal or day. More recently, Ziemer et al. (142) showed that an emphasis on healthful dietary pattern might serve as an alternative to use of exchange lists, with potential advantages in low-literacy populations.

Special Considerations

The management of diabetes varies to some degree with the circumstances of care for a particular patient. Diabetes management in children must incorporate attention to the maintenance of appropriate growth and invariably should be a collaboration between one or more clinicians (pediatrician or family practitioner and endocrinologist) and a dietitian. Pregnancy induces a sharp decline in insulin requirements during the first trimester, due to glucose uptake by the embryo and placenta. Insulin requirements rise markedly in the

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third trimester, due to high counterregulatory hormone levels. The management of diabetes during pregnancy should best involve obstetrician, endocrinologist, and dietitian (see Chapter 27). The maintenance of strict glycemic control during pregnancy, both in established and gestational diabetes, is crucial to a good pregnancy outcome and requires intensive and multidisciplinary care. The principles of nutritional management of diabetes during pregnancy are essentially the same as those applied under other conditions. The benefits of strict glycemic control have been conclusively demonstrated for both type 1 (143) and type 2 (144–147) diabetes.

Hypoglycemia is a potential complication of tight glycemic control in diabetes. Some evidence suggests that a combination of foods with varying glycemic indices can mitigate the risk of hypoglycemia (148). Eating a nutrition bar containing sucrose, protein, and cornstarch results in a "triphasic" glucose release and may be helpful to hypoglycemia-prone diabetics (149). Strict glycemic control in a type 1 diabetic inevitably increases the risk of hypoglycemic episodes. Some studies have suggested that a snack bar at night containing uncooked corn starch may help forestall such episodes, but others have suggested that only pharmacotherapy is a reliable defense (150–152).

Weight Loss and Energy Balance

A mainstay of dietary management of both type 2 diabetes mellitus in the overweight patient and of insulin resistance is weight loss (see Chapters 5 and 47). Clear clinical benefit of even fairly modest weight loss has been demonstrated (153–157). Significant amelioration of cardiometabolic risk is generally seen with loss of 7% to 10% of body weight in the obese (156). The amount of weight loss required to induce favorable metabolic effects likely varies with anthropometry, however. Individuals with a predilection for not only central but also visceral fat deposition are most subject to the adverse metabolic effects of weight gain, and they also appear to be most responsive to the beneficial effects of even very modest weight loss (157–162). The adverse effects of intra-abdominal fat accumulation explain why some ethnic groups, notably various populations in Southeast Asia, are subject to adverse metabolic effects of obesity at lower BMI values than are generally deemed harmful in the United States (163–165).

Independent of its impact on weight, negative energy balance could possibly play a role in mitigating insulin resistance. In bariatric surgery patients, hepatic insulin sensitivity is normalized within days of surgery, before any considerable weight loss can be achieved (166). In their study, Jazet and colleagues found that just 2 days of a very low-calorie diet significantly reduced basal endogenous glucose production in a small sample of obese type 2 diabetic patients (167). However, during hyperinsulinemia, endogenous glucose production was unchanged. Whole-body glucose disposal and lipolysis were not affected in the basal or hyperinsulinemic conditions.

Bariatric surgery can have dramatic effects on weight and glycemic control, reversing diabetes in many cases. In one study, diabetes remission was achieved in 75% of bariatric surgery patients over 2 years (168). In contrast, conventional medical therapy resulted in no remissions and only small improvements in glycemic control. Medical therapy was associated with an 8% reduction in HbA1c, whereas gastric bypass and biliopancreatic diversion led to reductions of 25% and 43%, respectively. BMI also decreased by approximately 33 kg/m^2 in both bariatric groups, compared with a decrease of 4.7 kg/m^2 in the medical therapy group. Although studies like this one would appear to clearly demonstrate the effectiveness of bariatric surgery in the treatment of type 2 diabetes in severely obese patients, some have suggested that study designs that do not include a truly intensive lifestyle intervention as a comparison treatment are biased toward the surgical intervention (169). The modest weight loss that occurred in the medical therapy group in the Mingrone et al. study is an indication that the diet and lifestyle intervention was not sufficiently intensive. It has been suggested that an appropriate lifestyle intervention would

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involve residential treatment over several weeks and in-home treatment for several months afterward (169). Provision of prepared meals is recommended initially and regular visits with nutritionists and exercise specialists thereafter.

Glycemic Index and Glycemic Load

The GI, developed by Jenkins et al. (73,170), characterizes the postprandial glucose response to various foods relative to a reference standard, typically white bread; sucrose is an alternative referent. The area under the postprandial glucose curve for a test food is divided by the area under the curve for white bread with an equal amount of carbohydrate (50 g) and multiplied by 100 to establish the GI for the test food.

Complex carbohydrate containing starch initially was thought to induce less of a rise in postprandial glucose than simple carbohydrate, but this has been refuted. The GI of foods is somewhat unpredictable on the basis of the apparent complexity of the carbohydrate content (see Chapter 1), as shown in Table 6.2 (171), as it is influenced by fiber content, processing, and the ratio of amylose to amylopectin (171).

Jenkins and Jenkins (171) suggested that dietary fiber may serve as a surrogate measure of the GI of foods, with high fiber content, particularly the amount of soluble fiber, lowering the glycemic response. Noteworthy is that sucrose has a lower GI than white bread, carrots, baked potato, and lima beans. Bantle et al. (172) studied healthy individuals, as well as type 1 and type 2 diabetics, and found virtually no differences in glycemic or insulin responses to test meals containing fixed amounts of total carbohydrate as glucose, fructose, sucrose, potato starch, or wheat starch. The authors interpreted their data to indicate that sucrose consumption in the context of balanced meals need not be restricted in diabetes other than under specific circumstances, such as during intentional weight loss. In general, the weight of evidence indicates that the sucrose content of the diet is not a reliable indicator of glycemic control, and sucrose restriction in diabetes is not specifically indicated to control the serum glucose (173).

A study by Liljeberg et al. (174) provides one potential explanation for the limited utility of focusing on the glycemic indices of individual foods for the overall control of glucose metabolism. The investigators found that varying the fiber content of breakfast altered the glucose response to foods with a high GI at lunch in a group of healthy subjects (173).

Taking into account both GI and standard serving sizes, the GL is the weighted average GI of a food multiplied by the percentage of energy from carbohydrate (175,176) and is believed to better predict the glycemic impact of foods under real-world conditions (177). The relationship between weight and BMI is roughly analogous to the relationship between GI and GL. Weight may be high, but a person may still be lean if tall. Similarly, the GI may be high, but the glycemic effect of that food may be modest if the carbohydrate content is relatively dilute. An expansive table of GI and GL values of common foods was published in 2002 (178). A few foods representing the range of potential divergence between GI and GL are shown in Table 6.3.

To date, no randomized trials have directly compared the effects of low-GL diets to those of low-GI diets. Therefore, little is known about the relative utility of these measures. The two measures are sometimes grouped together in systematic reviews and meta-analyses. However, there appears to be benefit for both low-GI and low-GL dietary patterns. In a 2008 meta-analysis of 37 prospective cohort studies, Barclay and colleagues reported significant positive associations between diets with higher GI or GL and risks of type 2 diabetes, coronary heart disease (CHD), gallbladder disease, breast cancer, and all diseases combined (179). The effect was strongest for type 2 diabetes; diets in the highest quintile for GI or GL were associated with a 40% increased risk, compared with diets in the lowest quintile. Although both GI and GL were associated with greater risk of chronic disease, the GI had a stronger effect than the GL. In another cross-sectional study, a low-GI diet was associated with improved insulin sensitivity and

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blood lipid levels, and lower levels of high-sensitivity C-reactive protein (180). GL was not significantly associated with these measures.

Several recent trials have investigated the effects of a low-GI or low-GL diet on weight loss, insulin sensitivity, and cardiovascular risk factors (181,182). In 2007, a Cochrane review summarized the results of six randomized controlled trials of low-GI or low-GL diets (183). The results of the included studies suggest that a low-GI/GL diet may enhance weight loss and decrease total cholesterol and LDL. No differences in HDL, fasting glucose or insulin, or blood pressure were observed. A number of trials have been completed since this review. In the CALERIE study (184), there were no differences between groups randomized to a high-GL or low-GL diet in body composition, metabolic rate, or diet adherence throughout a 12-month intervention period. It is worth noting that the low-GL diet was also lower in carbohydrates (40% of total energy vs. 60% in the high-GL group) and higher in protein (30% vs. 20%) and fat (30% vs. 20%), so the effect of GL per se was not isolated. Philippou and colleagues conducted a series of trials to compare the effects of a low-GI diet to a high-GI diet of comparable macronutrient distribution in overweight men and women, with somewhat mixed results. In a 12-week study, only the low-GI group experienced significant weight loss (182). This group also had significantly lower 24-h area under the curve (AUC) values for glucose compared with the high-GI group. There were no differences in serum lipid concentrations. In a separate study in middle-aged men with at least one CHD risk factor, a low-GI diet significantly reduced fasting insulin and HOMA-IR, and resulted in significantly greater reductions in total cholesterol and 24-h ambulatory blood pressure compared with a high-GI diet (184). The low-GI diet was also associated with significant reductions in carotid–femoral pulse wave velocity, LDL, and triglycerides. These effects occurred independently of weight loss, which was not significantly different between groups. In contrast to the findings of this study, Philippou et al. found no effect of dietary GI on anthropometric measures, blood lipids, or measures of insulin sensitivity in men and women during a 4-month weight maintenance period following weight loss (185).

An important issue often overlooked is that a low GL may be achieved in various ways. The importance of this was beautifully demonstrated by McMillan-Price et al. (84) in a randomized trial of roughly 130 overweight adults. Two diets relatively high in carbohydrate and two diets relatively high in protein (and thus lower in carbohydrate) were compared on the basis of differing GLs. The study showed, as most do, that restricting calorie intake by any means led to roughly comparable weight loss in the short term, although trends hinted at a benefit of low GL. The percentage of subjects achieving an at least 5% weight reduction was significantly greater on the low-glycemic-load diets whether they were high carbohydrate or high protein than on their higher-GL counterparts. Similarly, body fat loss was enhanced, at least among women, by the low-GL diets. Whereas LDL cholesterol decreased significantly on the high-carbohydrate, low-GL diet, it actually increased on the high-protein, low-GL diet.

The findings support the importance of food choices rather than choices among macronutrient categories, as a major arbiter of cardiac risk. High-carbohydrate foods such as most whole grains, beans, legumes, vegetables, and even fruits can contribute to a low-GL dietary pattern. Such foods also provide a diversity of micronutrients of potential importance to overall health, and cardiovascular health specifically, antioxidants flavonoids and carotenoids noteworthy among them. By demonstrating that a high-carbohydrate, low-GL diet may offer particular cardiac benefit, this study points toward a diet in which choice within macronutrient categories is given at least as much consideration as choice among those categories. This perspective is concordant with a large volume of research suggesting that cardiac risk may be mitigated by reducing dietary fat, as well as by shifting fat intake from saturated and trans fatty acids to monounsaturates and polyunsaturates. Cardiac health at the population level will likely be well served when dietary guidance is consistently cast in terms of healthful, wholesome foods rather than

competition among the three macronutrient classes from which a diet is composed (see Chapter 45).

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NUTRIENTS, NUTRICEUTICALS, AND FUNCTIONAL FOODS

Nuts and Peanuts

Nut consumption has been consistently associated with reduced risk of CVD and cardiovascular risk factors, particularly serum lipids, but the effect of nuts on diabetes risk and management is less clear (186). Although nuts vary in their nutritional composition, as a whole, they have a favorable nutrient profile; they are rich in monounsaturated and PUFAs, fiber, protein, micronutrients, and polyphenols while containing relatively small amounts of saturated fatty acids and carbohydrates (187). Because of their high fat and fiber content and low carbohydrate content, the inclusion of nuts in the diet may help to improve glycemic control in type 2 diabetes and metabolic syndrome or prevent these conditions from developing.

In the Nurses' Health Study (NHS) cohort, women who consumed nuts at least five times per week had a 27% reduced risk of developing type 2 diabetes compared with those who rarely or never consumed nuts (188). A small but significant reduced risk was also observed for women who consumed peanut butter five or more times per week. However, these findings were not replicated in the Iowa Women's Health Study (189). A more recent analysis of the NHS and NHS II cohorts confirmed the results of the first analysis, also finding that consumption of total nuts (including peanuts, walnuts, and other nuts) or tree nuts five or more times per week was associated with an approximately 15% reduced risk of type 2 diabetes; though these associations were explained by BMI (190). Interestingly, women who ate just two or more servings per week of walnuts had a 24% reduced risk of diabetes compared with those who never or rarely ate walnuts, even after controlling for BMI and other relevant confounders ($p = 0.002$).

Clinical trials have generally not found that the addition of nuts to the diets of individuals with type 2 diabetes or metabolic syndrome improves glycemic control (187). One trial reported reduced fasting insulin and HOMA among participants with metabolic syndrome assigned to an intervention of 30 g/day mixed nuts and healthy diet advice compared to healthy diet advice alone (191). Another study reported greater reduction in fasting insulin in type 2 diabetes patients assigned to a walnut-enriched (30 g/day) low-fat diet compared to an isocaloric low-fat diet without walnuts (192). However, two trials reported increased fasting glucose with the addition of walnuts or cashews to the diet (193,194). The remaining four studies did not find any significant differences in glycemia-related outcomes between intervention and control groups. However, one study published since this review found that the inclusion of 2 oz of mixed nuts daily for 3 months was associated with significant reductions in HbA1c in type 2 diabetics, compared with an isocaloric portion of muffins, or a half dose each of nuts and muffins (195). The results of this study suggest that both the dose of nuts and the foods they replace in the diet may be important determinants of their effects on glycemic control. Additional studies assessing the dose-response effect of nut consumption are needed.

In addition to the evidence supporting the benefits of nut consumption in metabolic syndrome, insulin resistance, and diabetes management, the documented improvements in cardiovascular risk associated with nut consumption are highly relevant to the diabetic population. A study from the author's own lab found that a walnut-enriched ad libitum diet led to significant improvements in endothelial function, serum total cholesterol, and serum LDL concentrations compared with an ad libitum diet without walnuts in type 2 diabetic individuals (193). Despite the high energy density of nuts, high intake of nuts does not appear to be associated with weight gain or obesity in observational studies or experimental trials (187). Given the

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strong likelihood of cardiovascular benefits and the low likelihood of adverse effects, the inclusion of nuts in the diet can be recommended to individuals with type 2 diabetes and those at risk.

Sugar, Fructose, and High-Fructose Corn Syrup

White sugar, usually in the form of granulated sugar, is purified sucrose, the crystals of which are naturally white. Brown sugar is less refined and so still contains some molasses from sugar cane. Alternatively, manufacturers may add back molasses to purified sucrose in order to control the ratio and the color. Nutritionally, the differences between white and brown sugar are fairly trivial. When matched on the basis of volume, brown sugar has more calories because it tends to pack more densely; one cup of brown sugar provides 829 cal, while a cup of white granulated sugar provides 774 cal. However, when matched by weight, brown sugar has slightly fewer calories due to the presence of water in the molasses; 100 g of brown sugar contains 373 cal, as opposed to 396 cal in white sugar (196). Sugar crystals provide no nutrients other than sucrose, but molasses adds enough calcium, iron, and potassium to distinguish brown sugar from white sugar, although not enough to make it an important source of any of these nutrients.

Fructose (see Chapter 1), referred to as fruit sugar, is a monosaccharide that does not require insulin for its metabolism. Fructose in the diet comes from honey and fruit; from sucrose, which is made up of fructose and glucose; and from the use of high-fructose corn syrup as a sweetener in soft drinks and processed foods (197–200). Fructose intake reduces postprandial glucose relative to other sugars and starches (201), but it has been conditionally associated with increased triglycerides in type 2 diabetics (202). Fructose restriction in diabetes is not indicated, but substitution of fructose for sucrose does not appear to confer benefit and is not recommended. Ingested fructose is largely cleared by the liver, where it is a substrate for triglyceride production; ingestion of fructose is associated with postprandial hypertriglyceridemia. It is worth noting that high intake of fruit, a concentrated source of fructose, is not associated with adverse effects; this may be attributable to the slow digestion rate of whole fruit (203). An emphasis on limiting ingestion of fructose, per se, is not warranted. Rather, the evidence-based approach is to focus on reducing consumption of refined carbohydrates, including starches and all added sugars.

High-fructose corn syrup (HFCS), produced industrially through a series of enzymatic reactions on corn syrup, is widely used as a sweetener in the US food supply (198,199,204). There is unresolved debate about the relative contributions of HFCS, as compared to sucrose, to weight gain and diabetes risk. The inconclusive nature of this literature, reviewed previously in the *New York Times* (205), suggests that HFCS is, at present, best considered roughly comparable to other forms of added sugar in terms of adverse metabolic effect. In a recent review, White contends that, at levels typically consumed in the United States, fructose is unlikely to elicit the metabolic consequences observed in feeding trials (206). A study by Stanhope and Havel supports White's view; in this trial, postprandial triglyceride concentrations increased similarly after consumption of beverages sweetened with fructose, HFCS, or sucrose (207). However, corn subsidies in the United States make HFCS a particularly inexpensive sweetener, leading to its use in a startling variety of foods and often in surprisingly copious amounts. (The author has identified, for example, popular commercial brands of marinara sauce with more added sugar in the form of HFCS than chocolate fudge ice cream topping, matched for calories.) The ubiquity and abundance of HFCS likely makes it a particular and noteworthy dietary hazard, a contention supported by recent reviews linking soft drink consumption to obesity (208–211). The importance of sugar in any form in the etiology of type 2 diabetes is the subject of ongoing research and much debate. A well-publicized ecologic study of 175 countries by Basu and colleagues (212) has drawn renewed attention to the

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potential contribution of sugar consumption to the rising worldwide prevalence of type 2 diabetes. The study concluded that for every 150 kcal/person/day increase in sugar availability, there was a 1.1% increase in type 2 diabetes prevalence; an association that was not accounted for by obesity. The findings of this study prompted some to declare sugar “toxic” and the primary villain in the diabetes epidemic, relegating obesity to at least the runner-up position (213). This proclamation is misguided. Although added sugars may contribute to diabetes risk, an ecological study cannot provide evidence of a causative relationship.

Other Sweeteners

Nutritive sweeteners, including corn syrup, honey, molasses, and fruit juice concentrates, appear to offer no advantage to sucrose in the management or prevention of diabetes. Nonnutritive sweeteners (see Chapter 42 for a more detailed discussion), such as aspartame, sucralose, and saccharin, confer sweetness without calories and do not raise serum glucose. Such sweeteners may be of some benefit in efforts to control serum glucose and facilitate or maintain weight loss, but evidence is lacking of sustainable benefit in either case. Although fructose does not induce an insulin release, this may actually be disadvantageous with regard to effects on satiety (214).

Aspartame, marketed as Equal and Nutrasweet, is made by linking two amino acids together. While it contains no sugar, it is roughly 200 times as sweet as sugar. Aspartame does contain some calories, but it is used in small amounts due to its intense sweetness, so the calories it adds to the diet are negligible. There is ongoing controversy about health effects of aspartame, but claims that it can cause brain tumors or neurological disease are not considered credible by the FDA. Because aspartame lacks bulk and is not heat stable, it cannot be used in baked goods.

Sucralose, marketed as Splenda, is made by modifying the structure of sugar molecules through the addition of chlorine atoms. It is marketed in the United States as a no-calorie sweetener, but it actually contains 96 cal/cup, about one eighth the calories of sugar. Splenda contains roughly 2 cal/teaspoon, but FDA regulations allow a product to be labeled as free of calories if it contains fewer than 5 cal/standard serving. Sucralose is up to 1,000 times as sweet as sugar, so Splenda contains relatively small amounts of sucralose combined with fluffed dextrose or maltodextrin to give it bulk for use in baking.

Stevia is a sweetener made by purifying extracts from a group of herbs by the same name that grow in Central and South America. Due to some early controversy about the safety of the extracts, called stevioside and rebaudioside, stevia was available only as a dietary supplement in the United States for some time. The FDA now considers the use of highly refined stevia extracts to be Generally Recognized as Safe (GRAS) when used in nonnutritive sweeteners, foods, and beverages (215). Stevia has been widely used in foods in Japan for the past several decades, without any apparent adverse effects. Stevia provides 30 to 300 times the sweetness of sugar, but it can produce a slightly bitter aftertaste.

While there is much made of the potential toxicity of artificial sweeteners in the blogosphere, the evidence that these compounds directly cause disease is not strong. However, the evidence that they serve to reduce calories or weight or offer other benefits is not conclusive. Research on artificial sweeteners does not show convincingly that they take calories out of the diet over time; they may simply cause calories to be displaced. Given that these sweeteners are as much as 1,000 times as sweet as sugar, it is possible that they could raise the preference threshold for sweet and contribute to the consumption of processed foods with significant, and arguably superfluous, additions of sugar, typically in the form of HFCS.

Several animal studies have reported weight gain in rats exposed to saccharin or aspartame relative to glucose or sucrose, with (216,217) or without (218) accompanying increases in caloric intake.

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Prospective cohort studies in humans somewhat corroborate the findings of animal trials; many have reported associations between intake of artificial sweeteners, often in diet sodas, and weight gain or obesity-related chronic disease (219). However, reverse causality and residual confounding are important potential sources of bias. Observational studies that are less prone to reverse causality have reported small, nonsignificant associations (220). Studies in animal models, though essential to clinical research, are not always directly translatable to humans. In particular, the doses of artificial sweeteners typically provided to study rats are not comparable to levels that humans are commonly exposed to. As an example, the amount of aspartame fed to rats in a recent study was approximately 0.27 to 0.4 g/kg body weight per day (218). To consume this much aspartame, a 150-lb person would need to drink more than 100 12-oz cans of diet soda every day (221).

The majority of short-term experimental human trials have found that artificial sweeteners do not increase appetite or energy intake relative to sucrose (222). Of five trials with longer intervention duration (3–19 weeks) included in a 2007 review, four noted a beneficial effect of aspartame-sweetened foods or beverages on body weight relative to sucrose-sweetened products. The fifth study reported no differences between groups (223). Because long-term randomized controlled trials are still sparse, the safety and efficacy of artificial sweeteners remains a controversial topic, and more research is needed before their effects can be fully understood. In the meantime, the positions of the American Heart Association, the ADA, and the Academy of Nutrition and Dietetics all support the use of artificial sweeteners in place of sugar as a means to reduce intake of calories and refined carbohydrates in the context of an otherwise healthful, calorically restricted diet (224,225). Given that there is little evidence that the use of nonnutritive sweeteners is helpful for weight loss, reducing all sweeteners in the diet may be the optimal strategy for individuals with type 2 diabetes and others.

Fiber

A daily intake of approximately 30 g of dietary fiber from a variety of food sources is recommended to the general public for health promotion and in the management of diabetes (see Chapters 1 and 45). There is evidence that soluble fiber in particular may be of benefit in controlling both glucose and lipid levels in diabetes (226,227). A large prospective study demonstrated consumption of fiber is inversely related to the development of type 2 diabetes (228). In a study of men with type 2 diabetes, Anderson et al. (229) reported significant improvements in both serum lipids and glucose with twice daily psyllium totaling 10 g, for a period of 8 weeks. Of note, our Paleolithic ancestors were thought to have consumed nearly 100 g of fiber daily, and this pattern persists among rural peoples in the developing world (230). Fruits, oats, barley, and legumes are particularly good sources of soluble fiber (see Appendix E). Fiber intake of up to 40 g/day is advocated by the ADA; average fiber intake by US adults ranges between 12 and 18 g/day.

Ethanol

Ethanol consumption independent of other food intake can result in hypoglycemia by transiently interfering with hepatic gluconeogenesis. Therefore, diabetics, particularly those treated with insulin or sulfonylureas, should be advised to consume alcohol only with food. Excessive alcohol intake may contribute to hypertriglyceridemia and deterioration of glucose control. Moderate alcohol intake in diabetes is generally without known adverse effects. The potential cardiovascular benefits of moderate alcohol consumption are discussed in Chapters 7 and 40.

Caffeine

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Whether caffeine has beneficial or adverse effects on the cardiometabolic health of individuals with diabetes remains uncertain. In cohort studies, regular coffee consumption has been associated with significantly reduced risk of type 2 diabetes (231). However, there appears to be a similar relationship between consumption of both tea and decaffeinated coffee and diabetes risk (232), so caffeine may not be the primary component of coffee that contributes to a protective effect. Furthermore, caffeine may actually have adverse effects on glucose metabolism in individuals who already have diabetes. A recent review of randomized controlled trials found that caffeine increased plasma glucose and insulin levels and decreased insulin sensitivity in individuals with type 2 diabetics (233). However, the trials included in this review generally tested single doses of caffeine that were relatively large (200–500 mg) and assessed only acute effects on glycemic control when consumed with an oral glucose load. Therefore, the generalizability of these findings to typical caffeine consumption patterns is limited. Of note, one uncontrolled pilot study in 12 coffee drinkers with type 2 diabetes found that abstinence from caffeine was associated with significant reductions in HbA1c after 3 months (234). Long-term trials of caffeine consumption in diabetics, at doses and frequencies that represent typical consumption, are needed before conclusions can be made. The health effects of coffee are discussed in more detail in Chapter 41.

Chromium

Chromium is established as an essential nutrient, with roles in lipid and carbohydrate metabolism (see Chapter 4). Known to function as an insulin cofactor, chromium may bind to a carrier molecule and thereby activate the insulin receptor kinase (235). Chromium may stimulate expression of insulin receptors in skeletal muscle as well (236). Evidence of improved glycemic control with chromium supplementation has been reported (237), but there are conflicting reports in the literature (238–242). Discordant findings to date may relate to varied utility of chromium among the various populations studied; efforts to identify specific populations in which chromium may prove of certain therapeutic benefit are ongoing. Daily supplementation with as much as 8 µg/kg/day is apparently safe and potentially beneficial. A National Institutes of Health-funded trial of chromium picolinate in insulin resistance at doses of 500 µg and 1,000 µg/day, completed in the author's lab, did not find a benefit of either dose on measures of glucose tolerance, insulin resistance, or endothelial function in insulin-resistant individuals (243). However, some studies suggest that individuals with diagnosed type 2 diabetes may benefit from chromium supplementation (240,244), and particularly those with poorer glycemic control (245).

Vanadium

Vanadium is an ultratrace element. A review of vanadium suggests potential benefit as a cofactor in insulin metabolism in both type 1 and type 2 diabetes (246). The therapeutic window for inorganic vanadium is very narrow. Efforts to improve the safety of vanadium are proceeding concurrently with research into its mechanisms of action (247). Research on vanadium is severely limited. A 2008 review identified only five very small studies of poor methodological quality (248). All studies reported a high incidence of gastrointestinal side effects. Until further progress is made in each of these endeavors, therapeutic applications of vanadium cannot be encouraged.

n-3 Fatty Acids (Fish Oil)

Fish oil is used in the treatment of refractory hypertriglyceridemia, typically when treatment with fibric acid derivatives is incompletely effective. A meta-analysis by Hartweg et al. indicates that n-3 fatty acid supplementation consistently lowers triglycerides by a mean of 25%, with no untoward effects on glucose control in diabetes (249). The same analysis revealed a modest elevation of LDL in response to fish oil

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therapy. The authors concluded that fish oil may be an appropriate means of managing the dyslipidemia commonly seen in diabetes. There is some evidence to suggest that n-3 fatty acids stimulate hepatic gluconeogenesis and thereby can degrade glycemic control. A large meta-analysis concluded that supplementation with long-chain fatty acids should not be encouraged for either the prevention or treatment of DM2 (250). An AHA science advisory group reviewed 17 clinical trials and concluded that there was a lack of scientific data supporting the use of omega-3 fatty acid supplementation to prevent heart disease in the general population. Elevated triglycerides are an indication for the use of prescription omega-3 fatty acids (251).

MUFAs

Improvements in glycemic control and insulin metabolism have been seen in numerous trials that increased the proportion of calories from monounsaturated fats (252–261). A relatively generous intake of monounsaturated fat is now widely recognized among the salient features of a healthful dietary pattern and is addressed further in Chapters 2, 7, and 45. Beneficial effects of MUFA intake on metabolic and cardiovascular risk factors may be responsible for some of the favorable outcomes associated with a Mediterranean diet pattern, discussed elsewhere in this chapter.

Cocoa/Flavonoids

A quickly burgeoning literature suggests beneficial effects of dark chocolate on glycemic control and insulin sensitivity (262–266); the dense concentration of bioflavonoid antioxidants in cacao is the purported “active” ingredient. There are as yet no clear guidelines for the dosing of dark chocolate as a functional food, although efforts to generate such guidance are under way. The topic is further addressed in Chapter 39.

Other Dietary Supplements

Interest in the use of complementary and alternative medicine (CAM) supplements is high among diabetic patients. Approximately one third of type 1 and type 2 diabetics reported current use of CAM supplements in a 2011 study (267). It is important for clinicians to be able to provide guidance to patients on the evidence regarding the safety and efficacy of dietary supplements.

α-lipoic acid (ALA) is an endogenously produced antioxidant that may ameliorate symptoms of diabetic neuropathy (268). According to a 2012 meta-analysis, intravenous administration of *ALA* at 600 mg/day is effective in reducing peripheral neuropathy in diabetic patients; however, the effectiveness of oral supplementation has not been demonstrated (269).

Cinnamon has also been evaluated for its potential glucose-lowering effects. Some, but not all, supplementation trials have reported modest glucose-lowering effects in patients with type 2 diabetes or insulin resistance (270). In a 2012 pooled analysis, there were no statistically significant differences in measures of glycemic control between intervention groups receiving oral cinnamon preparations with a mean dose of 2 g daily and control groups (271). This review included studies in patients with type 1 or type 2 diabetes (272). More recently, a randomized controlled trial evaluated cinnamon supplements in those with prediabetes. It demonstrated improved fasting glucose levels in the participates given the cinnamon supplements.

New Considerations: Genomics and the Microbiome

Interactions between nutrition and the human genome and microbiome are emerging areas of research in diabetes. Genome-wide association studies (GWAS) have identified at least 44 gene variants associated

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with type 2 diabetes (273). However, approximately 90% of genetic heritability remains unaccounted for, suggesting that many additional genes with small effect sizes contribute to risk. As a result, incorporating genetic variants into risk prediction models does not significantly improve predictive value. Although the continued identification of additional genes may improve the power to predict diabetes risk, the value of this approach is uncertain; placing added emphasis on the genetic basis of type 2 diabetes may adversely affect patients' attitudes toward prevention and treatment (274). On the other hand, genetic testing might increase motivation to adopt lifestyle changes and adhere to medication regimens among individuals identified as "high risk" (275). A randomized controlled trial testing the effects of genetic testing on BMI, insulin resistance, and health behaviors in primary care patients is currently underway (276).

While effective, widespread use of genetic testing to predict type 2 diabetes may be several decades away; the identification of factors in the environment that influence the expression of diabetes-promoting genes is immediately applicable to practice. In diabetic rats, energy restriction prevents hyperglycemia and alters the expression of hundreds of genes related to glucose or lipid metabolism and signaling pathways in insulin-sensitive tissues (i.e., pancreatic islets, skeletal muscle, and liver) (277). In human subjects with IGT, the Pro12Ala polymorphism of the peroxisome proliferator-activated receptor-gamma 2 (PPAR-γ 2) isoform gene has been associated with increased diabetes risk, particularly among less obese individuals (278). However, this effect was only observed in individuals randomized to a control condition and not in individuals assigned to an intensive diet and exercise intervention. The results of this study provide an example of the potential modulating effect of diet and physical activity on the association between a genotype and diabetes. The microorganisms inhabiting the human gut, or the microbiome, may represent an important link between genes, the environment, and risk of type 1 and type 2 diabetes. Although the mechanisms by which intestinal microbiota influence the pathophysiology of type 1 diabetes have not been fully elucidated, it appears likely that different species of bacteria have varying effects on the integrity of the intestinal epithelium and immunity (279). For example, in vitro studies suggest that species of *Bifidobacteria* may protect intestinal epithelial cells from gliadin, a glycoprotein found in gluten that is known to cause intestinal inflammation and permeability (280,281). On the other hand, *Escherichia coli* or *Shigella* may exacerbate gliadin's effects (282). It is not known whether alteration of intestinal microbiota by probiotic supplementation can influence diabetes risk, but a study is currently underway in Finland to determine the effects of probiotic supplements on type 1 diabetes-associated autoantibodies in genetically susceptible children (283).

A 2010 review by Musso et al. summarized the current evidence on the relationship between the microbiome and obesity and diabetes (284). There is now evidence from animal studies to suggest that the composition of the microbiome may mediate obesity through effects on energy absorption from food and energy expenditure via fatty acid oxidation (285). However, the development of obesity in mice also appears to change gut microbiota, favoring the Firmicutes phylum at the expense of Bacteroidetes; this alteration increases the efficiency of energy extraction from food. The same effect is observed when mice are fed a Western (high-fat, high-sugar) diet, and is reversed when a standard (low-fat, high-polysaccharide) diet is resumed. Transplanting gut microbiota from obese mice to lean mice leads to increased energy extraction from food and increased body fat mass. Several small studies in humans have had similar results: obese subjects have a higher proportion of Firmicutes in the gut compared with lean subjects and reduced bacterial diversity, and weight loss increases the proportion of Bacteroidetes. However, these findings have not been consistently replicated in humans. Significant differences have been observed between the gut microbiota compositions of diabetic and nondiabetic individuals, and one study found that probiotic supplementation in pregnant women reduced the risk of gestational diabetes. However, this area of research is still in its infancy; more long-term studies are necessary to determine

the safety and efficacy of supplementation with prebiotics or probiotics (284). In the meantime, a healthy diet and weight loss when necessary may promote a favorable composition of gut microbiota.

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CLINICAL HIGHLIGHTS

The literature guiding the management and prevention of diabetes is voluminous, complex, and evolving. Pharmacotherapy is, of course, a mainstay in the management of all varieties of diabetes mellitus, the details of which are beyond the scope of this chapter. There are excellent recent reviews covering type 1 and type 2 diabetes, as well as gestational diabetes and diabetes prevention (285–291).

Nutritional and lifestyle therapy is, however, comparably important in effective diabetes management, and it offers far greater promise for diabetes prevention at the population level. Placed in the context of nutritional principles pertinent to the management of related conditions, including obesity, CVD, hypertension, and kidney disease, a cohesive approach to the dietary management of both insulin resistance and diabetes emerges.

For the majority of patients with diabetes, weight loss and maintenance are mainstays of clinical management. Complex topics in their own right (see Chapters 5, 44, and 47), weight loss and maintenance, are best achieved by restriction of nutrient energy in combination with consistent exercise; the Diabetes Prevention Program has clearly demonstrated the value of this approach in the prevention of diabetes in high-risk individuals. Both weight loss and exercise have demonstrated independent benefit in the control of diabetes and its sequelae. Lifestyle changes resulting in weight loss have also been demonstrated to delay the progression of chronic kidney disease in the Look Ahead Trial.

In conjunction with efforts at weight control, diabetes warrants attention to all three classes of macronutrients. Protein intake generally should be maintained at or near 0.8 g/kg/day, with restrictions below this level as required only with the diagnosis of kidney disease (see Chapter 16); slightly higher protein intake, up to 25% of calories, is among the strategies highlighted for reducing the dietary GL.

Focusing on dietary patterns is the mainstay of nutritional recommendations rather than the macronutrient profiles since the ideal macronutrient profile continues be controversial in the literature. The dietary pattern included in AACE lifestyle guidelines emphasizes plant foods, high in PUFA and MUFA, and avoiding trans and saturated fats. Other dietary patters may be allowed, but careful consideration of their risks and benefits is warranted with each patient case. A comprehensive review has highlighted the role of plant-based diets in the prevention and treatment of type 2 diabetes.

Although controversies persist regarding optimal levels of carbohydrate and fat, the literature on this and other topics generally supports a carbohydrate intake of approximately 55% of calories, with fat comprising 25% to 30%. Carbohydrate should be complex and, perhaps even more importantly, should provide at least 30 g/day of fiber, preferably more. Sources of soluble fiber of particular metabolic benefit include fruits, grains, and legumes. The combination of saturated and trans fat ideally should be restricted to below 5%, and certainly below 10%. The n-3 fatty acids calories to polyunsaturated fat should approximately have a 1:4 ratio of n-3 to n-6 PUFAs. This pattern is achieved by using unsaturated vegetable oils, eating nuts and seeds, and including fish routinely in the diet. The remaining, approximately 15%, of calories should be allocated to monounsaturated fat. Monounsaturated fat is derived from olive oil, canola oil, olives, avocado, nuts, and seeds in particular.

Given the benefits attached to soluble fiber, a particular effort should be made to increase its intake. Oatmeal, apples, and berries are concentrated sources, readily worked into any health-promoting dietary pattern. Beans and lentils are excellent sources as well, and, if used as alternative protein sources to meat, offer the additional potential advantage of reducing saturated fat intake. The economy of beans and

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lentils is also noteworthy in light of the often-heard, inaccurate lament that healthful eating is prohibitively expensive.

The recommendation to eat a dietary pattern favoring the consumption of predominantly plants foods, unrefined carbohydrates, and unprocessed foods for diabetes is consistent with other data supportive of these foods for long-term health promotion and planetary health, which is an increasingly important issue in the third decade of the 21st century (292,293). Alternative dietary patterns, like low-carbohydrate diets, may provide health benefits in the short-term but may be at odds with personal and planetary-health in the long run, particularly if they rely on animal-based fats and proteins. However, more sustainable variations of low-carbohydrate diets, like the Eco-Atkins diet described by Jenkins et al., may mitigate some of the long-term health and planetary issues that (294,295) limit popular low-carbohydrate diets.

In conclusion, weight control, physical activity, and emphasizing a healthier dietary pattern as described earlier should be judiciously combined with carefully selected pharmacotherapy to optimize the control and clinical outcomes of diabetes and to achieve optimal rates of diabetes prevention. In overweight patients with insulin resistance or diabetes, marked benefit may be expected with a 7% to 10% weight loss. The weight loss required for appreciable metabolic benefit likely varies markedly with anthropometry and ethnicity, but population-specific guidelines are as yet unavailable. Finally, consultation of a dietitian should be routine in diabetes care and should facilitate the development of meal plans to accommodate clinical recommendations.

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Chapter 7

Diet, Atherosclerosis, and Ischemic Heart Disease

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INTRODUCTION

Atherosclerosis starts early in life and clinically manifests as coronary artery disease, cerebrovascular disease, or peripheral vascular disease. It is a leading cause of morbidity and mortality for both men and women. The evidence for associations between both macronutrients and micronutrients and the pathogenesis of coronary artery disease is decisive, deriving from multiple, large observational studies, randomized trials, and in vitro studies.

The American College of Cardiology (ACC) and American Heart Association (AHA) emphasize adherence to a healthy lifestyle, including dietary interventions for primary atherosclerotic cardiovascular disease (ASCVD) prevention and management of its risk factors (1). Risk factors for atherosclerosis include diabetes mellitus, hyperlipidemia, hypercholesterolemia, hypertension, poor lifestyle habits (i.e., smoking and obesity), and physical inactivity. It is critical to address dietary patterns with all patients, as they influence many of the risk factors, including blood pressure (see Chapter 8), hemostatic tendencies and platelet aggregability (see Chapter 9), adiposity (see Chapter 5), insulin sensitivity and glucose metabolism (see Chapter 6), inflammation (see Chapter 11), and oxidation and endothelial function (see Chapter 11). Given the high impact of diet on cardiovascular disease (CVD), the AHA recommends dietary screening for all patients by all members of the healthcare team, with the help of electronic health record platforms (2). When tailored specifically for the purpose, diet offers lipid lowering similar to the power of statin drugs (3), albeit by means not easily adopted or maintained by some patients. As addressed in Chapter 8, the blood pressure–lowering potency of diet can also approximate or exceed that of pharmacotherapy (4). Further, lifestyle intervention has been shown to lead to lower cumulative rates of diabetes over time compared to treatment with metformin (5).

The aggregate effect of dietary pattern on cardiovascular risk is formidable (6). Plant-based and Mediterranean diets, which include increased consumption of fruits, nuts, vegetables, legumes, fiber, and lean protein consumption, have been associated with lower risk and all-cause mortality than control or standard diets in select studies. It is important to note that the Primary Prevention of Cardiovascular Disease with a Mediterranean Diet Supplemented with Extra-Virgin Olive Oil or Nuts (PREDIMED) study, which evaluated the effects of the Mediterranean diet, noted no change in cardiovascular or all-cause mortality and that the overall composite results were driven largely by a reduction in stroke (7). Additionally, a provegetarian diet, in comparison to a nonvegetarian diet, has shown a more significant mortality reduction in post hoc analysis of the PREDIMED cohort (8). Dietary practices, in conjunction with other judicious lifestyle practices, such as tobacco avoidance and regular physical activity, contribute to a reduction in ASCVD risk, cardiovascular events, and mortality (1). Conversely, adverse dietary patterns, such as the Western diet, which has an increased intake of fat, red meat, and carbohydrates with minimal fruit and vegetable intake, have much to do with the hyperendemicity of CVD in the United States, other industrialized nations, and developing countries as they undergo cultural

transitions (9).

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Evidence for the role of nutrition in primary, secondary, and tertiary prevention of acute coronary events is definitive. Dietary counseling (see Chapter 47) is thus an essential component in the primary prevention of heart disease and in the clinical management of all patients with established coronary disease, as well as in the mitigation of known cardiac risk factors. A team-based clinician support that incorporates shared decision-making and accounts for social determinants of health is important for people to achieve their dietary goals (1). Emerging methods, including web- and mobile-based nutrition tools, can be used to increase dietary compliance (10).

The National Cholesterol Education Program Adult Treatment Panel (NCEP ATP-III) refers to the use of diet and lifestyle as a targeted strategy for cardiac risk reduction as "therapeutic lifestyle changes (TLC)" (11). Table 7.1 shows the low-density lipoprotein (LDL) values on which decisions to initiate TLC or pharmacotherapy are based. Table 7.2 provides an overview of the nutrient distribution that the NCEP recommends. Table 7.3 provides an overview of foods to prioritize in order to achieve the nutrient distribution characterized in Table 7.2.

TABLE 7.1

Low-Density Lipoprotein Cholesterol Goals and Cutpoints for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories

Risk Category	LDL Goal	LDL Level at Which to Initiate TLC	LDL Level at Which to Consider Drug Therapy
CHD or CHD Risk Equivalents			
(10-year risk > 20%)	<100 mg/dL	≥100 mg/dL	≥130 mg/dL (100–129 mg/dL: drug optional)[a]
2+ Risk Factors			
(10-year risk ≤ 20%)	<130 mg/dL	≥130 mg/dL	10-year risk, 10% to 20%: ≥130 mg/dL 10-year risk <10%: ≥160 mg/dL
0 or 1 risk factor[b]	<160 mg/dL	≥160 mg/dL	≥190 mg/dL (160–189 mg/dL: LDL-lowering drug optional)

[a]Some authorities recommend use of LDL-lowering drugs in this category if an LDL cholesterol <100 mg/dL cannot be achieved with TLC. Others prefer use of drugs that primarily modify triglycerides and HDL, for example, nicotinic acid or fibrate. Clinical judgment also may call for deferring drug therapy in this category.

[b]Almost all people with 0 or 1 risk factor have a 10-year risk <10%, thus 10-year risk assessment in people with 0 or 1 risk factor is not necessary.

CHD, coronary heart disease; LDL, low-density lipoprotein; TLC, therapeutic lifestyle changes.

Reproduced with permission from National Institutes of Health. Detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). Bethesda, MD: National Institutes of Health, 2001. Available at http://www.nhlbi.nih.gov/guidelines/cholesterol/atp3xsum.pdf.

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TABLE 7.2

Nutrient Composition of the Therapeutic Lifestyle Changes Diet

Nutrient	Recommended Intake
Saturated fat[a]	Less than 7% of total calories
Trans-fat	0% of total calories
Polyunsaturated fat	Up to 10% of total calories
Monounsaturated fat	Up to 20% of total calories
Total fat	25%–35% of total calories
Unrefined Carbohydrates[b]	50%–60% of total calories
Fiber	20–30 g/day
Protein	Approximately 15% of total calories
Cholesterol	Less than 200 mg/day
Total calories (energy)[c]	Balance energy intake and expenditure to maintain desirable body weight/prevent weight gain

[a]*Trans-fatty acids are another LDL-raising fat that should be kept at a low intake.*

[b]*Carbohydrate should be derived predominantly from foods rich in complex carbohydrates, including grains, especially whole grains, fruits, and vegetables.*

[c]*Daily energy expenditure should include at least moderate physical activity (contributing approximately 200 kcal/day).*

LDL, low-density lipoprotein.

Modified with permission from National Institutes of Health. Detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). Bethesda, MD: National Institutes of Health, 2001. Available at http://www.nhlbi.nih.gov/guidelines/cholesterol/atp3xsum.pdf.

TABLE 7.3

Recommended Foods and Overall Dietary Pattern to Meet Nutritional Recommendations of the National Cholesterol Education Program Adult Treatment Panel

Food Group	Foods to Choose[a]
Whole grains	Choose 6 oz/day of whole grain breads, cereals, and grains having 3 g or more of fiber per serving. Include oatmeal, oat bran, brown and wild rice varieties, semolina and whole wheat pasta, couscous, barley, and bulgur wheat.
Fruits	Choose 2 cups per day from a rainbow of colors, especially deep yellow, orange, and red: all

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	berries, apples, oranges, apricots, melons, mangos, etc. Select from fresh, frozen, canned packed in juice, and dried varieties. Buy locally grown in season whenever possible.
Vegetables	Choose 2½ cups/day from a rainbow of colors, especially deep yellow, orange, red, and leafy greens, such as yellow, red, and green bell peppers; squash; carrots; tomatoes; spinach; sweet potatoes; broccoli; kale; Swiss chard; Brussels sprouts; eggplant; and so on. Select from fresh, frozen, and canned varieties but be mindful of the higher sodium content of canned. Buy locally grown in season whenever possible.
Beans and legumes	Include 3–4 times per week. These can be eaten instead of meat. Include all varieties of beans: black, red, kidney, white, cannellini, garbanzo (chickpea), navy, pinto, lentils, split peas, black-eyed peas, soy, and tofu.
Fish*b*	Include 3–4 times per week, especially the good sources of omega-3 fatty acids: tuna, salmon, mackerel, and cod.
Chicken and turkey*b*	Include up to 1 or 2 times per week. Skinless breast meat is preferred.
Lean beef, pork, and lamb*b*	If desired, include no more than 3–4 times per month. The loin and round cuts are the leanest.
Milk and cheese*b*	Choose at least 2 cups per day from fat-free, skim, or low-fat versions.
Vegetable oils and other added fats	Choose monounsaturated sources daily but use in small amounts: olive oil, canola oil, olives, avocados, almond butter, and peanut butter.
Nuts and seeds	Include 4–5 times per week in *small amounts* of unsalted raw or dry-roasted types: almonds, walnuts, pistachios, peanuts, pecans, cashews, soy nuts, sunflower seeds, pumpkin seeds, and sesame seeds. Mix 1 tablespoon of ground flaxseed daily into other cooked foods.
Eggs*b*	Two egg yolks per week. Choose an omega-3 fatty acid–enriched brand.
Sweets	In moderation. Choose low or nonfat varieties whenever reasonable.

[a]*Optional items. Well-balanced vegetarian and vegan diets are wholly compatible with the dietary recommendations of the National Cholesterol Education Program. Note that fish is recommended for particular health benefits; flaxseeds and/or an omega-3 fatty acid supplement is especially recommended for those who don't eat fish.*

[b]*See* https://health.gov/sites/default/files/2019-09/2015-2020_Dietary_Guidelines.pdf *for guidance on age- and calorie intake-specific guidelines for food group targets linked to the 2015–2020 Dietary Guidelines for Americans.*

Adapted from Katz DL, Gonzalez MH. The way to eat. Naperville, IL: Sourcebooks, 2002, and based in part on US Department of Health and Human Services. Dietary guidelines for Americans, 2010. Available at www.cnpp.usda.gov/dietaryguidelines.htm

OVERVIEW

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CVD remains the leading cause of death in the United States among both men and women. This is largely due to rising obesity and type 2 diabetes, despite a combination of prevention and treatment, a decreased incidence of cigarette smoking, improvements in managing risk factors such as hypertension and hyperlipidemia, and a decline in cardiovascular deaths related to advanced technologies and pharmacotherapy (12). Thus, it is important to address the role of diet in primary and secondary prevention of ASCVD to minimize its prevalence and deleterious consequences.

Throughout history, "natural experiments" have shown a strong association between decreased dietary fat intake and decreased incidence of coronary artery disease. The link between diet and heart disease has been apparent since at least the 1930s, when food shortages in the United States due to the Great Depression were observed to be associated with a reduction in the incidence of cardiovascular events. Similar observations were made in Western Europe during World War II. Since the 1950s, an ever-expanding pool of data derived from a wide variety of study types has overwhelmingly linked dietary patterns to atherosclerotic disease of the coronary arteries, and the risk of cardiovascular morbidity and mortality. The seminal work of Ancel Keys (13) in the 1960s revealed a linear relationship between the total mean per capita fat intake of a country and the incidence of cardiovascular events.

Transcultural studies, such as the Seven Countries Study (14–16), and migration studies, such as Ni-Ho-San (17–19), established the powerful role of environmental, cultural, and lifestyle factors in the epidemiology of heart disease. Even within the United Kingdom, diet variations between Wales, Scotland, Northern Ireland, and England are associated with differences in chronic disease mortality rates (20). The increasing capacity to identify genetic susceptibility to heart disease (21) does not diminish the primacy of lifestyle influences. Migration studies reveal a marked variation in the epidemiology of heart disease associated with environmental variation, against a backdrop of genetic constancy.

Diet influences the pathogenesis of coronary artery disease in a variety of ways. The initial development of fatty streaks in coronary arteries is associated with high-serum lipid levels and oxidative, both of which are modifiable by nutrients (22). Progression of coronary lesions is affected by serum lipids, hypertension (see Chapter 8), hyperinsulinemia (see Chapter 6), adiposity (see Chapter 5), and oxidation and inflammation (see Chapter 11), all of which are mediated by both macronutrient and micronutrient intake. Once coronary artery atherosclerosis is established, diet continues to play a role in determining progression of plaque deposition and the reactivity of the endothelium, both of which may be predictive of cardiac events (23–25). Interestingly, salt intake is associated with left ventricular hypertrophy and heart failure, independent of blood pressure; thus, dietary salt alterations may be just as protective in addition to weight loss and blood pressure-lowering medications. Dietary manipulations have been shown to modify all the known, modifiable coronary risk factors (26–28) and, when extreme, to induce regression of established lesions (29,30). The role of diet in the management of coronary artery disease and risk factors is determined by the efficacy of dietary interventions and their complementarity with pharmacologic interventions of proven benefit.

The association between total dietary fat intake and hyperlipidemia and coronary disease is well established. Not all dietary fat, however, have the same impact on health. Work over recent years has been focused increasingly on the contribution of specific dietary fats to the atherogenic process. The relative cardiovascular benefits of total fat restriction versus modifying diet to promote monounsaturated fatty acid (MUFA) and polyunsaturated fatty acid (PUFA) intake relative to saturated (and trans) fat intake is an area of particular interest (31–35). Intake of MUFA and PUFA—specifically n-3 PUFA (see Chapter 2)—should perhaps be liberalized, as the intake of unsaturated fat may not be as bad as once believed.

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While debate over the relative merits of restricting versus revising dietary fat intake is protracted and intense (36–39), the practical utility of the discord is suspect: the means by which either pattern is achieved and the cultural context housing the dietary pattern may have far greater practical importance than their relative benefits. The Mediterranean dietary pattern, which is characterized by fairly generous portions of MUFA and PUFA, is noteworthy for its cardioprotective and cerebroprotective influences. It is important to note, however, that in Mediterranean countries, a so-called Mediterranean diet abundant in unsaturated oils is coupled with a traditional lifestyle that includes plenty of walking and many energy-dilute, nutrient-rich foods. In this context, the energy density of healthful oils does not contribute to obesity. Enthusiasm for liberalizing total dietary fat intake in the United States must cautiously consider any potential contributions an energy-dense diet might make to obesity risk (see Chapters 2, 5, and 38), especially in the context of the characteristics of a Western diet (40–44). Based on prevailing dietary patterns in the United States and other Western countries, both dietary fat restriction and the substitution of unsaturated for saturated fats may be advantageous; there is evidence of cardiac risk reduction with either approach (32–35). Even putatively labeled “healthful oils” may confer net harm rather than benefit if they contribute to weight gain and obesity. By reducing the energy density of foods, restricting dietary fat intake may facilitate energy balance and lead to weight loss (46).

Similar caveats pertain to dietary fat restriction. The advent of the “low-carb” diet era (see Chapter 5) owes much to the failings of dietary fat restriction as a strategy for health promotion and especially weight control. These failings, however, reside more in the application of the guidance than in the guidance itself. Traditional Asian societies and vegetarian groups such as Seventh-Day Adventists (see Chapter 43) with very low-fat dietary patterns predicated on natural, unprocessed foods have excellent health profiles and very low rates of either obesity or CVD (47–49). Uptake of the “low-fat” dietary guidance in the cultural context of the United States, however, resulted in high intake of fat-reduced processed foods. This adulteration of advice to restrict dietary fat, in which the food industry and the public colluded, may have obscured genuine merit in the advice. There is little, if any, health benefit in substituting refined starches and simple sugars in highly processed foods for atherogenic fats; the metabolic pathways for harmful effects may differ, but the effects themselves may be much the same (see Chapter 6).

Comparable trends have been seen with “low-carb” dieting, as energy-dense, highly processed foods that claimed to be low in carbohydrates with otherwise few benefits rapidly proliferated. Indeed, ketogenic diets, which are lower in carbohydrates but high in protein and fat, may portend worse peripheral artery endothelial function and promote atherosclerosis (50,51). A diet with high intake of animal fat and a low intake of carbohydrates has been associated with an increased total mortality (52,53), particularly when pursued after myocardial infarction (MI) (54). On a molecular level, studies of carbohydrate-restricted, high-fat diets have generally resulted in modest decreases in LDL and increases in high-density lipoprotein (HDL) cholesterol, with a beneficial effect on the LDL:HDL ratio (55–59). The type of protein and fat intake may play a role, as low-carb diets favoring animal-derived protein and fat sources were associated with higher mortality, whereas those that used plant sources were associated with lower mortality (53). Additionally, diets rich in both saturated and MUFAs may raise HDL, but the former may compound, and the latter ameliorate, other cardiac risk factors, including insulin resistance, inflammation, and platelet aggregation (60).

At present, there is evidence to support dietary fat restriction and fat substitution. There is also data to substantiate the restriction of refined starches and added sugars in processed foods and for their replacement with natural carbohydrate sources, such as vegetables, fruits, whole grains, and legumes. For the most part, a direct comparison of dietary patterns low in total fat and abundant in unsaturated fats,

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with both based on an optimal array of pertinent foods, is very limited; available data suggest comparable benefits of reducing total dietary fat and improving the distribution of dietary fat, provided that both approaches emphasize wholesome food choices (61). Even more deficient are data regarding the reliability with which these alternative patterns may be adopted and maintained, in true accord with the guidance for food choices on which they are based, in real-world settings subject to diverse cultural influences. Such translational research is much needed and eagerly awaited. Thus far, advice to restrict dietary fat or carbohydrate has translated, at the population level, into very questionable dietary practices.

The role of total caloric intake in CVD is somewhat less clear than the role of obesity (see Chapter 5). When caloric expenditure is high, caloric intake is not thought to represent a cardiac risk factor. However, total calorie intake may have implications for senescence (see Chapter 31), and degradation of cardiovascular health is typically an age-dependent phenomenon. Caloric intake in excess of caloric expenditure results in weight gain, and obesity is associated with heart disease risk (see Chapters 5 and 10). A calorie-restricted diet has been consistently associated with longevity in laboratory animals, including primates (see Chapter 31). Reduced oxidative stress in the arterial wall with calorie restriction may contribute to antithrombogenicity (62). The benefits of calorie restriction, if relevant to humans, apply to a wide variety of diseases, as well as aging, rather than to cardiovascular risk in particular. In contrast, an “empty calorie” diet does not appear to offer any advantages. Recent data have also highlighted the benefits of an intermittent fasting diet, where an 18-hour fasting period if followed by a 6-hour eating period triggers a metabolic switch between glucose-based metabolism and ketose-based metabolism and cellular resistance. Intermittent fasting has shown to have increased longevity, increased stress resistance, decreased inflammation, and decreased incidence of diseases (63).

Weight loss is of clear and potentially profound cardiac benefit to overweight and obese patients, namely by reducing the incidence of hypertension (HTN), diabetes mellitus (DM), and other sequelae of metabolic syndrome. The subject matter is addressed extensively in Chapter 5. The National Heart, Lung, and Blood Institute (NHLBI) recommends a loss of roughly 5%–10% body weight over 6 months to achieve meaningful improvement in patients’ cardiac risk profile (61,64). However, this advice presupposes that all obesity is equal with regard to cardiac risk, which is not the case. As addressed in Chapter 5, body fat distribution has important implications for health effects. Central, visceral adiposity is of special concern for cardiac health. Of note, an average 7% weight loss produced a 58% reduction in the incidence of diabetes in the Diabetes Prevention Program (see Chapter 6) (65). Interestingly, this association may be stronger in women (66). Further, weight loss leads to reduced systolic and diastolic blood pressures (67). Unfortunately, sustained weight loss proves more challenging. Many longitudinal studies demonstrate significant decreases in adherence over time or even weight loss recidivism depending on the diet regimen (68,69).

Intake of fruits, vegetables, and cereal grains is inversely correlated with cardiovascular risk, as is total fiber intake (70). The intake of soluble fiber in particular appears to have cardiovascular benefits attributable at least to a hypolipidemic effect (71); hypotensive effects have also been described (see Chapter 8) as having potentially important influences on glycemic and insulinemic responses (see Chapter 6). On a population basis, separating the effects of soluble and insoluble fiber, fruit, vegetable, cereal, and fat intake is complicated by the tendency of dietary behaviors to cluster (72,73). Diets low in atherogenic fat tend to be relatively high in fiber of both types, and vice versa. Nonetheless, convincing epidemiologic associations exist between both low-fat, predominantly vegetarian diets and the MUFA-rich Mediterranean diet and a low incidence of cardiovascular events. The several mechanisms of cardiac risk mitigation attributable to soluble fiber make a strong case for specific benefit; concentrated food sources include oats, beans, lentils, apples, and berries (see Chapter 1 and Appendix E). In addition,

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protein source has been shown to influence cardiovascular mortality with plant-based protein having a positive effect as compared to animal-based protein (74).

Among the important characteristics apparently common to heart-healthy dietary patterns is a relatively low glycemic load (see Chapters 5 and 6) (75–77). There is evidence for health benefits from both low-fat and Mediterranean dietary patterns, derived from both observational and intervention studies. In both cases, cardiovascular benefit is clearly dependent on dietary details. For example, a low-fat diet might be based predominantly on highly processed snack foods or on natural foods, such as vegetables, fruits, beans, grains, and so on; the implications for cardiovascular and overall health differ markedly. McMillan-Price et al. (76) have demonstrated the importance of the specific means by which any given nutritional objective is met; both high- and low-carbohydrate dietary patterns may be adopted to achieve a low glycemic load, and the former may offer cardiovascular advantages. In addition, dietary fat composition may have variable effects on the glycemic index, as compared to the overall proportion of vegetable matter intake (78).

For now, an emphasis on cardioprotective foods may be more helpful than undue preoccupation with macronutrient distribution. Both the NCEP guidelines (see Table 7.2) and the Institute of Medicine (IOM) reference ranges recommend (79) a diet rich in fruits, vegetables, whole grains, nuts, seeds, fish, beans, and lentils, which are abundant with fiber, antioxidants, unsaturated oils, and lean protein, and a relative paucity of refined carbohydrate, added sugar, and atherogenic fats (see Table 7.3). The Optimal Macronutrient Intake (OMNI) Trial for Heart Health study looked at the cardioprotective benefits of heart-healthy food choices (80). This clinical trial assessed the influence of macronutrient intake on adiponectin levels, which is a hormone specific to fat cells and has been linked to high levels of HDL cholesterol and lower rates of insulin resistance. The study found that a diet rich in MUFAs, even without weight loss, was associated with higher levels of adiponectin compared with carbohydrate or protein-rich diets. This suggested that incorporation of MUFAs may be helpful for those with high cholesterol and diabetes (81).

Diet is critical in mitigating overall risk of CVD and its risk factors. Dietary prevention and management of hypertension can contribute to the prevention of CVD; this topic is discussed in Chapter 8. Chapter 9 covers diet and hemostasis. The effects of diet on peripheral vascular disease and cerebrovascular disease are discussed in Chapter 10. Other topics pertinent to the link between nutrition and CVD risk include obesity (see Chapter 5) and diabetes (see Chapter 6).

Dietary Fat

Total Fat

Excess intake of certain dietary fats produces predictable elevations in serum cholesterol and lipoproteins (Hegsted and Keys equations; see Appendix A), which translate into fairly predictable increases in the risk of cardiac events (82). The Institute of Medicine, therefore, recommends that “saturated fatty acid, trans fatty acid, and cholesterol consumption be as low as possible while consuming a nutritionally adequate diet” (83). Dietary guidelines in the United States (84) have been based, in large measure, on evidence linking diet to heart disease. The current guideline for total fat intake is 20% to 35% of total calories for adults ages 19 and older, and excess fat intake has been defined relative to this reference. The US Department of Agriculture recommends consuming less than 10% of calories from saturated fatty acids and replacing them with polyunsaturated and MUFA, as it is associated with lower risk of CVD and blood cholesterol (9).

Dietary fat contributes to atherogenesis primarily by inducing a rise in serum lipid levels, and in this

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regard, as noted earlier, not all fat is created equal. The principal mechanism by which fat and cholesterol ingestion translate into increased cardiovascular risk is the induced elevation of serum lipoproteins, especially LDL. Intake of saturated fatty acids is associated with increased cholesterol levels. Elevations of LDL result in saturation of the receptor-mediated uptake by hepatocytes (85,86) and the consequent uptake of LDL by tissue-fixed macrophages. This process of so-called foam cell formation is accelerated by the oxidation of LDL. The ingestion of certain PUFAs, notably of the n-6 class, although not associated with elevations of serum lipids, has been implicated in the promotion of lipoprotein oxidation; n-3 PUFAs are apparently protective. The deposition of foam cells in the coronary intima and media induces smooth muscle cell hyperplasia and the growth of obstructing lesions (87,88).

In addition to the chronic effects of fat intake on atherogenesis, there is some evidence that the acute ingestion of a meal high in saturated fat content may represent a cardiac stressor (89). An interest in postprandial atherogenesis dates to at least the 1970s (90). Although the postprandial rise in triglycerides may contribute to the progression of coronary atherosclerosis, the magnitude of lipid changes seems insufficient to explain the observed increase in events; there are a variety of concomitant metabolic responses (91). The acute ingestion of saturated or fat may destabilize coronary plaque and impair endothelial function (89,92). Evidence is now considerable that endothelial function is a fundamental index of cardiac risk, and it is modified in response to a variety of nutritional influences (93–97).

Currently, there is little evidence directly implicating total dietary fat in CVD risk. Rather, the association between increased dietary fat intake and increased cardiovascular risk observed in industrialized countries highlights a link between heart disease and specific categories of fat. Imbalance in PUFA intake, with a relative excess of proinflammatory omega-6 fats (98) and a relative deficiency of antiinflammatory omega-3 fats, may contribute as well (see Chapters 2 and 11). In societies prone to excess caloric intake and obesity via energy-dense processed foods, total dietary fat may contribute indirectly to heart disease risk.

The optimal dose of dietary fat has been a matter of debate for some time (99,100). The beneficial effects of MUFAs, and certain PUFAs, specifically n-3 fatty acids, on cardiovascular health justifies a recommended intake of total fat consisting of 30% of calories (101). The recommended reduction in total fat intake or the consumption of predominantly MUFA and n-3 PUFA both represent significant dietary changes for most patients seen in the United States (102,103).

Saturated Fat

Saturated fatty acids, those with no carbon–carbon double bonds (see Chapter 2), in particular, raise total cholesterol and LDL. An increasing understanding of lipoprotein subtypes has suggested that saturated fats may only raise levels of large buoyant LDL particles—thought to be antiatherogenic—as opposed to the small, dense, atherogenesis-promoting variants (105). Foods rich in saturated fatty acids include the flesh of most domestic mammals raised for human consumption, dairy products, and several vegetable oils such as coconut, palm, and palm kernel.

The 2019 ACC and AHA guidelines on primary prevention of CVD recommend replacement of saturated fat with dietary MUFA and PUFAs to reduce cardiovascular risk, as trans and saturated fats have been associated with a higher risk of total and cause-specific death (1). It is important to note that evidence linking diets high in saturated fats to cardiovascular events is limited by difficulties in conducting long-term studies requiring assignment of subjects to dietary interventions. A recent 10-year study in over 5,000 people looked at the influence of different saturated fats on CVD (106). After adjusting for demographics, lifestyle, and dietary confounders, a higher intake of dairy-saturated fats was associated with lower CVD risk, while a higher intake of meat-derived saturated fatty acids was

associated with greater risk.
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Current recommendations call for reducing the intake of saturated fat to 7% or less of calories (11) in those with cardiac risk factors; 90% of Americans, however, are at or above the recommended intake of fat (84). Prehistoric adaptations may be informative; paleolithic intake of saturated fat was approximately 5% to 12% of calories (104,107). There is nothing to suggest a disadvantage in advocating this lower level of saturated fat intake, unless saturated fats are replaced with proinflammatory n-6 PUFAs (108). Nonetheless, a recent review of randomized controlled trials showed that replacing saturated fatty acids with PUFAs (n-3 and n-6 and presumably in a favorable ratio) actually reduced the risk of coronary heart disease (CHD) (109).

The evidence that excessive intake of saturated fat, specifically C14 myristic and C16 palmitic acids, raises serum lipids and promotes atherogenesis is decisive (see Chapter 2). Apparently unique among the highly saturated fatty acids, stearic acid, C18, is neutral with regard to serum lipids and, apparently, cardiac risk—this may just be because stearic acid is absorbed by the body less efficiently (110). This fat is relatively abundant in beef, and particularly so in dark chocolate. Notably, the 2015–2020 Dietary for Americans recommended restricting saturated fat intake, not including stearic acid (84). For further discussion of stearic acid, see Chapters 2 and 39.

In counseling patients to modify intake of saturated fat, a consideration of all sources of such fat in the diet is essential. The prevailing notion that dietary fat, and saturated fat in particular, derives predominantly from red meat is only partly true. The primary source of dietary fat and saturated fat in the diets of American menis red meat; in the diets of American children, it is milk; and in the diets of American women, it is a combination of dairy products, including cheese, and processed foods (111,112). Studies demonstrate that even subjects educated to be fat averse, in attempting to reduce dietary fat intake in general and saturated fat intake in particular, tend to substitute fat from one source (e.g., meat) with comparable fat from another source (e.g., dairy) (112); however, a recent long-term study found that people who substituted meat-saturated fats with dairy-saturated fats significantly lowered their risk of heart disease (106). A recent meta-analysis suggests that the danger may actually lie within processed meat rather than red meat, which has been shown to have no association with CHD in some studies (113,114).

Of note, even the societal trend toward “low-fat” dieting did not actually reduce total fat intake; data from the National Health and Nutrition Examination Survey (NHANES) suggest that total fat consumption remained fairly constant, while total calorie intake was driven up by more consumption of processed carbohydrate foods. Fat intake thus declined as a percentage of total calories, but only because total calories increased (115). This is important to note, as studies examining saturated fat content can be misleading. For example, a meta-analysis by Chowdhury et al. did not clearly support a diet low in total saturated fat, which may lead some to liberalize saturated fat intake (116). A closer look at the study, however, reflects that the applied metric was as a percentage of calories; a decrease in fat percentage, therefore, corresponded with an increased percentage in sugars, which also has known adverse cardiovascular effects. Similarly, Astrup et al. suggested that a limitation on saturated fat intake would not prevent CVD or reduce mortality, as saturated fatty acids are found in a variety of foods, such as dark chocolate, whole-fat dairy, and unprocessed meat, which are not associated with increased cardiovascular mortality (117). Again, the alternative choice of nutrient (and food) to saturated fatty acids must be carefully considered. Additionally, it is important to evaluate the studies used to come to this conclusion. For example, the Prospective Urban Rural Epidemiology (PURE) study (118) derived data largely from poor, developing countries, where any fat and protein intake is beneficial, and may have resulted in the application of misleading conclusions regarding the deleterious effects of saturated fats,

especially when applied to modern, industrialized countries.

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When counseling patients in an effort to reduce saturated (or total) fat intake, a reasonably detailed dietary history is essential (see Chapter 47). The contribution to total fat intake of often-overlooked and unreported constituents of diet can be substantial (112). Assertions by patients that they are eating a diet low in saturated fat because they have reduced or eliminated red meat is generally unreliable.

Cholesterol

The relative contribution of dietary cholesterol to serum lipids is confounded to some extent by the highly correlated distribution of saturated fat and cholesterol in the diet. The meat of domestic mammals, dairy products, and organ meats are all rich in nutrients and associated with elevated serum lipids. Cholesterol is a constituent of cell membranes and is found only in animal products.

Eggs are a concentrated source of cholesterol, but not fat, and there has been conflicting evidence that egg consumption is unrelated to cardiovascular risk (119–122). Shellfish, also relatively high in cholesterol content but low in total and saturated fat, are not convincingly linked to an increase in cardiovascular risk. Conversely, coconut, palm, and palm kernel oils are highly saturated but are derived from vegetable sources free of cholesterol. These oils have been linked to increased cardiac risk, although the evidence for coconut oil in particular is inconclusive in this regard (123,124) (see Chapter 2).

The varying effect of food type intake on cholesterol levels in different patients may be in part due to the role of Niemann-Pick C1 Like-1 (NPC1L1) proteins in serum cholesterol levels. NPC1L1 is responsible for dietary cholesterol and biliary cholesterol absorption, and is targeted by ezetimibe, a hypocholesterolemic drug. A low NPC1L1 expression is associated with a significantly lower cholesterol absorption and plasma cholesterol levels, and therefore a reduction in the development of atherosclerosis (125). At lower levels, the relationship between ingested cholesterol and the subsequent increase in serum cholesterol is essentially linear ($y = 0.0974x$) (126), and large increases in serum cholesterol are seen in “hyperresponders,” particularly in those who have a lower baseline degree of cholesterol consumption (127).

The Keys and Hegsted equations (see Section Appendix A) indicate that cholesterol contributes relatively less to serum lipids than does saturated fat intake, in part because while fat intake is measured in grams, cholesterol intake is measured in milligrams. Even so, these equations were devised when support for a role of dietary cholesterol in hyperlipidemia was far stronger than it is now.

Overall, in the United States, a diet containing reduced amounts of cholesterol is recommended to decrease ASCVD risk (1). The recommended intake of cholesterol is up to 300 mg/day in general, with the NCEP advising restrictions below 200 mg in patients with hyperlipidemia (LDL > 100 mg/dL) or established coronary disease (11). A large egg contains about 71% of the recommended 300 mg of cholesterol intake per day, and for most American adults, consuming one egg per day accounts for <1% of their CHD risk (128). To comply with this recommendation, patients must eliminate or minimize their intake of egg yolks and restrict their intake of red meat, deli meats, cheese, and whole milk and its products. To further support the benefits of a plant-based diet, a meta-analysis of 30 observational studies and 19 clinical trials showed that a vegetarian diet, compared with omnivorous diet, was associated with lower mean total cholesterol levels, LDL cholesterol, and HDL (129).

Trans-Fatty Acids

Intake of trans-unsaturated fats, or trans-fatty acids, fat has been shown to be harmful and increase the risk of ASCVD and should be avoided (1). Trans fat exists naturally in small quantities as “natural” or

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"ruminant" trans-fatty acids in milk and in the gut of some animals. Modern food preparation techniques have greatly increased human exposure to trans-fatty acids. It is important to remember that trans fats are not essential. The atherogenicity of artificial trans-fatty acids appears to be much greater than that of their naturally occurring counterparts, attributed in part to their LDL-raising effects (130). Some trans fats are produced commercially by bombarding partially unsaturated fatty acids (i.e., fatty acids with some preserved carbon–carbon double bonds; see Chapter 2) with hydrogen. The hydrogenation process saturates most of the double bonds in PUFAs in order to make the fats solid at room temperature. The trans isomeric configuration around the remaining double bond results in molecules that pack tightly together, limiting the fluidity of the fat and producing a higher melting point. The stability of these fats at room temperature results in products that retain their shape (e.g., margarine in stick form as opposed to liquid vegetable oil) and increases product shelf life. Although they are advantageous to the food industry, trans fats have deleterious health effects, including on lipid and lipoproteins, and promote endothelial dysfunction, insulin resistance, inflammation, and arrhythmias (131).

Recent evidence has made a compelling case for uniquely harmful effects of trans fats, suggesting that they contribute far more on a per-gram basis to heart disease risks than the saturated fats they were designed to replace. The intake of trans fats is strongly associated with CVD and all-cause mortality rate (132). Regulations to curb trans fat use in the food industry have been associated with decreased cardiovascular events, including stroke and MI (133).

To replace trans fats, the food production industry has either reverted to natural saturated fats without cholesterol (e.g., palm oil) or produced newer interesterified (IE) oils. IE oils are unsaturated oils modified in labs in a process that links them to saturated oils, to give them longer shelf life and more heat tolerance. Like trans fat, IE fats are the product of an industrial process, which involves moving around the fatty acids within or among the fat molecules to alter the way the compound responds to changes in temperature. IE fats have been used in shortenings and margarine, as well as in parenteral, enteral, and infant feeding to improve the stability of fats. Evidence is lacking regarding the influence of IE fats on digestibility or energy balance in adult humans, though benefits have been seen in animals and human infants (134). There are few definitive comparison studies, but it appears that IE fats may offer a slightly reduced atherogenic risk compared with hydrogenated fats (135). In two randomized crossover trials, Berry et al. concluded that interesterification of palm oil does not result in adverse postprandial changes in lipids or insulin (136). Other studies have revealed negative impacts on cholesterol (reduced HDL and increased LDL) with both IE and trans-fat diets (137,138). Compared with natural palm oil, chemically and enzymatically IE palm oil has been found to increase fat deposition and triglycerides levels in animals. Most research has been conducted on IE fats that are not widely used commercially. There is a need for further investigation into the average intake and health effects of commercial IE fats (139).

Another altered fat, conjugated linoleic acid, has been suggested as preventative of CVD, but definitive evidence is lacking. Conjugated linoleic acid refers to a mixture of positional and geometric isomers of linoleic acid, which occur naturally in vegetable oils, nuts, and seeds. The beneficial effects of conjugated linoleic acid consumption are often associated with reductions in cardiac risk factors (i.e., decreased cholesterol and triglyceride levels) (140) however, other studies suggest that conjugated linoleic acid may have negative effects. For example, one study found that conjugated linoleic acid consumption in mice had no effect on atherosclerosis and actually caused adverse changes in lipoprotein and liver lipid metabolism (141). Clinical trials in humans have yielded ambiguous results with both positive and negative effects on cardiac biomarkers found, as well as no effects. Some evidence suggests a proinflammatory effect via upregulation of eicosanoids via an arachidonic acid intermediary. This mechanism is controversial in its actual clinical effect (142). These discrepancies are due to the lack of

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standardization in the studies, similar to other clinical nutritional studies in humans (143). In patients with a cardiac history, a recent large clinical trial found that substituting dietary omega-6 linoleic acid in place of saturated fats may even increase mortality. At this point, it does not appear that supplementation with dietary conjugated linoleic acid should be recommended.

Polyunsaturated Fat

The two essential fatty acids in the human diet, linoleic (18:2, n-6) and 2-linolenic (18:3, n-3) fatty acids (see Chapter 2), are both polyunsaturated. Humans and other mammals share the capacity to synthesize saturated fatty acids, as well as unsaturated fatty acids of the n-9 and n-7 series, but lack the requisite enzymes to manufacture n-6 and n-3 polyunsaturates. The metabolism of these fats is discussed in greater detail in Chapter 2. Linoleic acid serves as a precursor to arachidonic acid, whereas alpha-linolenic acid (ALA) serves as a precursor for eicosapentaenoic acid [EPA (20:6, n-3)] and docosahexaenoic acid [DHA (22:5, n-3)].

Collectively, the products of essential fatty acid metabolism are known as eicosanoids, and they include prostaglandins, thromboxanes, and leukotrienes. The optimal intake of n-3 fatty acids is a topic of considerable interest across a wide array of health issues. The n-3, or “omega-3,” fatty acids are PUFAs with the first double bond after the third carbon molecule (see Chapter 2). An extensive literature has developed linking high intakes of n-3 polyunsaturates, particularly from marine sources, to low rates of heart disease and blood pressure (144–148).

Whereas n-6 polyunsaturates are readily available in commonly consumed vegetable oils, including soybean, safflower, sunflower, and corn, n-3 fatty acids are less widely distributed. Oils rich in n-3 fatty acids include flaxseed, linseed, marine oils, and, to a lesser degree, canola oil (146). Whereas fish and seafood provide EPA and DHA, the plant sources of n-3 PUFAs generally contain ALA. The distinctive benefits of n-3s are associated with EPA and DHA, and thus the substitution of ALA is of less convincing benefit. The manufacture of EPA and DHA apparently occurs with variable efficiency (see Chapter 2).

Fat-restricted diets may result in relative, if not overt, deficiency of n-3 intake, as well as less-than-optimal intake of MUFA (99, 149–151). A diet rich in n-3 fatty acids has been linked to reduced levels of serum triglycerides, reduced platelet aggregation, and lower blood pressure; the evidence to date for a protective role of n-3 fatty acids against sudden cardiac death is decisive (152), and a general cardioprotective role is strongly suggested (6).

The Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto miocardico (GISSI)Prevenzione Trial lends strong support to the practice of n-3 fatty acid supplementation. In a factorial design trial of more than 11,000 patients post-MI, nearly 3,000 patients received fish oil capsules containing approximately 850 mg EPA and approximately twice the dose of DHA, and another nearly 3,000 patients received matching placebo. At 42-month follow-up, n-3 PUFA supplementation had significantly reduced the cardiovascular event and mortality rates and all-cause mortality (149–151). Data from the GISSI trial demonstrate a clear benefit of fish oil for the prevention of sudden cardiac death in individuals post-MI, with benefit apparently greatest among those with impaired left ventricular function (153–156). A recent randomized clinical trial on n-3 PUFA supplementation in older men at high cardiovascular risk showed a nonsignificant reduction in all-cause mortality, but the results were limited by a small sample size (157). An observational study conducted in China found that serum levels of n-3 PUFA were inversely associated with a diagnosis of hypertension, indicating that these fatty acids may be protective against high blood pressure (148). Even when foods traditionally lacking n-3 PUFA (i.e., tomato juice) are enriched with the molecules, consumption can ameliorate cardiovascular risk factors (158).

On the other hand, the Alpha Omega Trial investigated the effects of 400 mg of EPA + DHA and 2 g of

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ALA on the secondary prevention of CVD in 4,837 people with a history of an MI. Low-dose supplementation did not significantly reduce the rate of major CVD but in women, ALA as compared with placebo and eicosapentaenoic acid-docosahexaenoic acid (EPA-DHA) alone, was associated with a lower risk. In a post hoc analysis, there was a significant rate reduction in major cardiovascular events in the EPA+DHA group, as compared with ALA alone and placebo, most of which were arrhythmia-related events (159). Though this further supports the notion that the beneficial effects of n-3 PUFA may be antiarrhythmic in nature, a recent meta-analysis showed that n-3 PUFAs do not prevent postoperative or recurrent atrial fibrillation (160) (see broader cardiovascular effects).

Further, the benefits of n-3 PUFA may be related to restoring a balance with n-6 PUFA to achieve our native dietary state. While our native diet consisted of n-3 and n-6 fats in a ratio between 1:1 and 1:4 (with a slight excess of n-6 PUFAs), our modern diet provides us with these fats in a ratio of 1:20 (with an excess of n-6s). Evidently, prospective randomized trials have yielded inconsistent results with regards to the association of PUFA with CVD. According to recent meta-analyses, PUFAs do not appear to confer any protection in regard to all-cause or cardiovascular mortality, stroke, or MI (161,162). PUFAs may, however, improve left ventricular remodeling and reduce the risk of heart failure, especially in those with preexisting cardiac disease (163,164). Overall, it is sensible to conclude that we should increase our intake of n-3 PUFA or take supplementation (165).

Monounsaturated Fat

The cardioprotective effects of MUFAs have come to light largely through cross-cultural epidemiologic studies. Rates of heart disease are low in populations with high consumption of MUFA, even when total fat intake is high, leading to interest in the Mediterranean diet (166–170). There is convincing evidence that monounsaturates' apparent neutral effects on serum cholesterol are due to reductions in LDL and concomitant elevations of HDL, both of which reduce cardiovascular risk (171–174). A meta-analysis in 1995 suggested that the effects of monounsaturates and polyunsaturates on HDL are comparable (175), but a subsequent study has generally refuted this contention, suggesting particularly beneficial effects on the LDL:HDL ratio in association with MUFA intake (171). Along with having favorable effects on the LDL:HDL ratio, MUFAs may attenuate atherogenesis by inhibiting LDL oxidation (177–182). Olive oil, a predominant source of MUFA, also contains phenolic compounds with antioxidant properties.

Monounsaturates are abundant in traditional diets of the countries bordering the Mediterranean Sea. There is abundant research on the Mediterranean diet, which consists of fresh fruit and vegetables, olives, olive oil, wine, fish, and grains, has received increasing attention as a means of lowering cardiovascular risk (183–189). In a 2-year randomized trial, Shai and colleagues compared the effects of a low-carbohydrate, low-fat, and Mediterranean-style diet on body mass index, glycemic control, and serum lipids in 322 moderately obese adults (190). They demonstrated that although all diets were safe and effective for weight loss, the Mediterranean and low-carbohydrate diets had more favorable effects on glycemic control and lipids than the low-fat diet. The Mediterranean diet was particularly effective in reducing fasting blood glucose and insulin in diabetic subjects. These findings suggest that the optimal diet for any individual may be dependent on his or her risk factors and personal preferences. Results of the OMNI-Heart trial provide some support for a Mediterranean-type diet, though this trial had a shorter 6-week intervention period. The randomized crossover study assessed the effects of three diets: rich in carbohydrates, MUFA, or protein. The diet rich in MUFA was associated with higher levels of adiponectin compared to the other two diets. Several meta-analyses of prospective cohort studies and/or clinical trials have been carried out in recent years (191–193). In these studies, adherence to the Mediterranean diet was associated with reduced overall mortality, cardiovascular mortality, cancer

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incidence and mortality, and neurodegenerative diseases (193) and was inversely associated with components of the metabolic syndrome (191). Just one meta-analysis included randomized trials comparing the Mediterranean diet to a low-fat diet (192). That meta-analysis concluded that the Mediterranean diet produced modestly more favorable effects on body weight, blood lipids, blood pressure, fasting plasma glucose, and C-reactive protein, compared with a low-fat diet. However, in two of the trials, the low-fat diet group also had significantly lower intakes of fiber, protein, and fruits and vegetables; and higher intakes of energy and saturated fat (194). More recently, the PREDIMED study showed that the Mediterranean diet supplemented by either extra-virgin olive oil or nuts showed reduced combined endpoint of MI, stroke, and cardiovascular mortality, with the improved outcome driven only by reduction in stroke, with no reported reduction in LDL cholesterol, MI, CV mortality, or all-cause mortality (7). However, in a subanalysis, a more significant mortality reduction was seen with a more provegetarian food pattern (8).

Various aspects of the Mediterranean diet may contribute to its stroke-protective properties. As discussed earlier, n-3 PUFA in fish may favorably affect serum lipids and inhibit platelet aggregation. Alcohol, discussed later (and in Chapter 40), favorably influences serum lipids and raises endogenous tissue plasminogen activator (195). Fruit and vegetable consumption, discussed later, is likely to be cardioprotective by a variety of mechanisms, as is consumption of grains, seeds, and certain nuts (196). Finally, the effects of polyphenols in olive oil (197) and nuts (198) cannot be disentangled from those of MUFAs. Therefore, the studies completed to date are inadequate to provide decisive evidence of the isolated benefits of monounsaturates but clearly convey the cardioprotective influence of the traditional Mediterranean dietary pattern.

Further evidence supporting a role for monounsaturates in modifying cardiovascular risk derives from intervention studies. Garg et al. (199,200) showed that the Mediterranean diet results in greater improvements in glycemic control than does a diet rich in carbohydrates. One small study identified a positive, linear relationship between proportion of MUFAs relative to saturated fatty acids in a meal and postprandial insulin sensitivity and beta-cell function (201). It showed that decreased levels of insulin in patients with manifestations of the insulin-resistance syndrome (truncal obesity, hypertension, hypertriglyceridemia) may result in reduced cardiovascular risk by several mechanisms, including modification of the lipid profile and declines in norepinephrine levels (202–204). The Lyon Diet Heart Study, a controlled trial in patients following a first MI, showed convincing evidence of event reduction with a Mediterranean diet (205,206). A Mediterranean diet is rich in a variety of nuts and seeds, olives, and avocados, which are excellent sources of MUFAs.

Dietary Fats: Summary

The optimal level of dietary fat intake for primary prevention of heart disease, or for the management of established heart disease, remains somewhat controversial. The ACC AHA Guideline on Primary Prevention of Cardiovascular Disease recommends the use of monounsaturated and polyunsaturated fat over the use of saturated fat (1). Opinion is divided between total fat restriction and more liberal intake of n-3 PUFAs and MUFAs (208,209). The weight of evidence appears to be accumulating in support of the latter (210–212), although they need not be fully mutually exclusive.

Prehistoric human diets may have provided anywhere from 20% to 39% of calories from fat, with about 7.5%–12% from saturated and naturally occurring trans fat, and the remainder a combination of MUFA and PUFA (107,213). Whereas estimates of the contribution of total and saturated fat to the paleolithic diet vary substantially, and likely varied with geographical location, there is more agreement about the contribution of MUFAs and PUFAs, which was significantly higher than in typical modern diet.

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The ratio of n-6 to n-3 PUFA, which is approximately 11:1 in the United States and Western European diets, was between 2:1 and 8:1 for our ancestors (107,213). Until or unless intervention studies such as OMNI-Heart (214,215) further elucidate the optimally cardioprotective diet (an eventuality potentially obviated, as noted earlier, by excessive focus on macronutrient distribution and insufficient attention to the foods contributing to each macronutrient category), recommendations consistent with both current evidence and evolutionary theory are appropriate. Saturated fat should be restricted to below 7% of total calories in all cardiac patients; this guideline is appropriate for primary prevention in willing patients as well (216). Trans fats should be minimized in the diets of all individuals. Intake of fish, nuts, soy, olives, avocados, seeds, olive oil, canola oil, and linseed oil should be encouraged to raise n-3 PUFA and MUFA intake. However, these items should substitute in the diet for other sources of fat to avoid raising total fat and/or calorie intake. Dietary fat and cholesterol reduction is best achieved by restricting intake of red meats; processed meats; whole-fat dairy products, especially cheese; cheese- and cream-based sauces and dressings; fatty spreads; and processed foods. Particular attention to detail is necessary to prevent substitution of lipid-raising fats from one source for fats from other sources. Foods rich in cholesterol but low in fat, notably eggs, may not impose any cardiac risk, although opinion in this area is still under controversy.

Optimal management of dietary fat intake appears capable of lowering LDL by as much as 20% and total cholesterol by as much as 30%, although lesser reductions are usually seen. Even greater reductions are possible when extreme dietary adjustments specifically tailored to lipid lowering are made (3). Although dietary manipulation produces benefits other than lipid lowering, more aggressive lipid lowering than can be readily achieved by diet alone is indicated for virtually all hyperlipidemic patients with coronary disease. Statin drugs can lower LDL by up to 60%; the effects of these agents are enhanced by dietary therapy.

Finally, the means by which dietary fat is titrated matter as much as the intake levels achieved. The substitution of processed carbohydrate foods for fatty foods substitutes one adverse cardiac influence for another. Objectives related to dietary fat intake should be met within the context of a dietary pattern that places an emphasis on whole foods, providing good nutrition within each of the three macronutrient classes.

Carbohydrate

Initial interest in the effects of carbohydrates on cardiovascular health was propagated when studying the effects of a carbohydrate-restricted diet on weight loss (see Chapter 5). Concerns about the potential cardiac hazards of low-carbohydrate, high-fat diets led to numerous studies that examined the diet's effects on lipids as well as weight. Trials have shown that a focus on low intake of carbohydrates and a high intake of animal fat and protein are associated with increased cardiac and noncardiac mortality rate (52,53,222). Indeed, the ketogenic diet, which is lower in carbohydrates but high in protein and fat, may portend worse peripheral artery endothelial function and promote atherosclerosis (50,51). Moreover, these diets are associated with increased total mortality if pursued for extended periods (54), particularly if used in post MI (53). Not so surprisingly, the Atherosclerosis Risk in Communities (ARIC) study database showed that favoring animal-derived protein and fat sources, such as lamb, beef, pork, and chicken, were associated with higher mortality than using plant-based sources such as vegetables, nuts, and whole-grain breads (53). Of note, the ARIC investigators also noted a 23% increased mortality rate with high carbohydrate diets and observed the optimal carbohydrate intake to be 50% to 55% (53). The Institute of Medicine advocates for a moderate optimal carbohydrate intake, as 45%–65% of calories.

In addition, a liability in thinking in terms of "carbohydrate restriction" is that carbohydrate

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encompasses a large and very diverse array of foods, including fruits, vegetables, and whole grains. The distinctions among food choices within the carbohydrate category may be of far greater importance to health than alterations in total carbohydrate intake. Health benefits, including cardiovascular benefits, of diets rich in vegetables, fruits, beans, and legumes, and, whole grains, are well established. Conversely, diets high in processed foods, refined starches, and added sugars are disadvantageous for overall health. In fact, refined carbohydrates, added sugars, and refined grains intake ought to be restricted to reduce ASCVD risk (1,84). Sugar-sweetened and artificially sweetened beverages have been associated with ASCVD risk and the development of diabetes mellitus (218), and cohort studies have shown that the consumption of added sugar at >10% of daily calories is associated with increased mortality rate (219). Moreover, a diet with sweetened beverages, refined grains, simple carbohydrates, and sweets has been shown to result in a greater increase in coronary events than the increase seen with the consumption of animal products (220,221).

Many trials have simply emphasized the relative quantity of one macronutrient class versus another rather than the quality of choices within each class (214). It is important to make prudent food choices within each macronutrient class beyond dietary patterns advantageous for cardiac health.

Fruit and Vegetable Intake

Whereas the nutrients responsible for the health-promoting properties of fruits and vegetables are a source of ongoing investigation and controversy, the cardioprotective influence of fruit and vegetable intake is compelling. Population-based studies consistently demonstrate health benefits of high fruit and vegetable intake (65) (see Chapter 43). This dietary pattern is strongly associated with a reduced cancer risk as well (see Chapter 12). The cardioprotective benefits of produce may be multifold: from their vitamins, minerals, antioxidants, soluble and insoluble fibers; the combined effects of several of these components acting in concert and with other components of the diet; and the effect of displacing less-healthy foods (e.g., refined grains, simple sugars, processed meats) that might otherwise be consumed.

The extreme expression of fruit and vegetable intake is a strict vegetarian or vegan diet. Whereas some vegetarians exclude only meat (i.e., lacto-ovo vegetarians), vegans exclude all animal products, including dairy and eggs. The latter group may be at risk for certain micronutrient deficiencies, especially some B vitamins. The association between deficiency of vitamin B12, which occurs naturally only in animal foods, and elevated levels of homocysteine raises concern that this dietary pattern might be associated with increased cardiovascular risk, although the significance of homocysteine levels to cardiac risk remains in question. According to a recent Cochrane review, interventions to lower homocysteine levels have not been shown to prevent cardiovascular events (222). It is interesting to note that in a study by Song et al., dairy consumption was associated with an 11% increase in cardiovascular mortality rate as compared with vegetable protein (74), which may advocate for minimal animal fat and protein intake.

Overall, population-based studies suggest that vegetarianism is associated with decreased cardiovascular risk in developed countries (8,74,229). For a variety of reasons, vegetarians should become knowledgeable about dietary sources of both macronutrients and micronutrients of importance to ensure proper balance. Taking a daily multivitamin may be a prudent practice for some vegetarians. Vegetarianism is discussed in greater detail in Chapter 43.

Protein Intake

Protein source may play an important nutritional role in atherosclerosis development. Plant-based diets have been associated with lower risk of all-cause mortality than control or standard diets. As noted earlier, the post hoc analysis of the PREDIMED study, the provegetarian food pattern, with more

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vegetable consumption versus animal, egg, fish, dairy, or meat product consumption, was associated with a 41% mortality rate reduction (8). An Adventist Health Study-2 cohort showed that using meat for protein was associated with a 61% increase in mortality rate (223). Moreover, Song et al. showed that a lower mortality rate was associated with plant protein ingestion in comparison to animal protein intake: poultry and fish were associated with a 6% higher mortality rate, dairy with an 8% higher mortality rate, unprocessed red meat with a 12% higher mortality rate, eggs with a 19% higher mortality rate, and processed red meat with a 34% higher mortality rate. The overall reduction in mortality rate was 10% for every 3% incremental replacement of animal protein with plant protein (74). The ARIC database also showed that favoring animal-derived protein and fat sources, such as lamb, beef, pork, and chicken, were associated with higher mortality than using plant-based sources such as vegetables, nuts, and whole-grain breads (53). Given their benefits, plant-based diets are therefore recommended to decrease ASCVD risk factors (1). This was confirmed in the US National Institutes of Health–American Association of Retired Persons (AARP) Diet and Health Study (224).

Meat is a large source of protein and dietary phosphatidylcholine and L-carnitine. Phosphatidylcholine and L-carnitine are found in a variety of meat, including red meat, poultry, fish, and eggs. It is digested by intestinal microbiota into trimethylamine, which is then oxidized in the liver into trimethylamine N-oxide (TMAO), which has been linked with increased risk of CVD, stroke, and death through atherogenic, prothrombotic, and inflammatory mechanisms (225). TMAO has also been correlated with increased mortality in congestive heart failure (226). Red meat has been found to have the strongest correlation with L-carnitine and TMAO levels, with increased red meat intake also correlating with a shift in gut microbiome for increased digestive abilities. Alternatively, cessation of red meat intake has shown to decrease TMAO levels. Other animal products, such as white meat, eggs, or dairy, do not appear to influence TMAO levels to the same levels as red meat or deep-sea fish (227). The clinical application of monitoring and addressing TMAO levels is still under development.

The type of meat ingested may play a role in risk of atherosclerosis. A meta-analysis suggests that the danger may actually lie within processed meat rather than red meat, which has been shown to have no association with CHD in some studies (113,114). Additionally, the Mediterranean diet, which utilizes seafood as a key source of protein, has been shown to have mortality benefits, as discussed earlier. Overall, prudent food choices within each macronutrient class is important for optimal cardiac health.

NUTRIENTS, NUTRACEUTICALS, AND FUNCTIONAL FOODS

Antioxidants (Vitamins E and C, Carotenoids, and Flavonoids)

Evidence linking antioxidation to a reduced risk of CVD is convincing, but evidence in support of specific antioxidant nutrients or compounds is lacking (228). This may be because antioxidants are most effective in as-yet-unidentified combinations or because other nutrient-mediated reactions are equally important. The principal mechanism by which antioxidants confer cardiovascular benefit is thought to be inhibition of LDL oxidation (229,230), although protection of nitric oxide is of nearly comparable interest (231). A diet rich in fruits and vegetables typically provides abundant antioxidants, including carotenoids, tocopherols, flavonoids, and ascorbate, and has been decisively linked to reduced cardiac risk. Statins act as effective antioxidants via interfering with nitric oxide synthase (NOS) and LDL cholesterol oxidation (232).

A variety of antioxidants have been studied for cardioprotective effects (233). The overall weight of evidence does not support a protective role for beta-carotene, although observational studies suggest that

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foods rich in beta-carotene are almost certainly protective (234,235). The literature to date is supportive of protective effects of bioflavonoids, found particularly in dark chocolate/cocoa, tea, red wine, and grape juice, as well as the skins of many fruits and vegetables (236,237). There currently is no convincing evidence of a cardioprotective effect of vitamin C, although diets naturally high in ascorbate appear to be protective (239,240). One potential explanation for the inability to elucidate an independent benefit of vitamin C is that its mechanism of action may require interaction with fat-soluble antioxidants (241). Timimi et al. (242) reported a beneficial effect of acute vitamin C infusion on endothelial function in diabetic subjects. Plotnick et al. (89) reported prevention of dietary fat–induced endothelial dysfunction with concomitant vitamin C and E supplementation in healthy subjects. Such findings tend to perpetuate interest in the potential cardioprotective role of vitamin C despite the paucity of clear evidence to date.

Data from the Cambridge Heart Antioxidant Study suggested a benefit of supplemental vitamin E in the prevention of second MI, although evidence of a mortality benefit was not found (243,244). Beneficial effects of acute vitamin E supplementation on endothelial function have been reported (89). However, in the GISSI–Prevenzione Trial, patients with recent MI (n = 11,324) randomly assigned to vitamin E supplementation (300 mg) did no better than those assigned to placebo with regard to MI or death (245). Similarly, the HOPE trial demonstrated a significant benefit of angiotensin-converting enzyme inhibition with regard to both MI and death in high-risk coronary patients, whereas vitamin E (400 IU) failed to reveal such benefit (246,247). Sesso and colleagues also found no benefit of long-term supplementation (mean follow-up of 8 years) with vitamin E (400 IU every other day) or vitamin C (500 mg daily) on the risk of major cardiovascular events among middle-aged men (248). Thus, the most definitive trials to date fail to support a cardioprotective role of supplemental vitamin E, at least as an isolated intervention. The HOPE and GISSI trials further suggest that excessive intake of vitamin E may lead to slight increase in risk of mortality (249,250). Vitamin E actually constitutes a family of compounds, encompassing tocopherols and tocotrienols (see Chapter 4), but studies have generally used alpha-tocopherol exclusively. Whether lack of benefit is a reliable finding or the result of using the wrong formulation and/or wrong dose of vitamin E is as yet unknown. A recent meta-analysis of antioxidant supplements reached the same conclusion (251). Isolated antioxidant supplementation cannot be recommended as a cardioprotective strategy at present; consumption of a diet naturally rich in antioxidants certainly can be.

B Vitamins

Accumulating evidence has pointed to the importance of elevations of serum homocysteine in up to one-third of all patients with coronary artery disease (252). Hyperhomocysteinemia is particularly likely to be seen in patients with coronary disease and normal serum lipids (253). A meta-analysis of observational studies has linked the lowering of plasma homocysteine levels to reduced rates of CHD and stroke (254). Vitamins B_6 and B_{12} and folate participate in the metabolism of methionine. Specific metabolic steps beyond the production of homocysteine are dependent on several B-complex vitamins. Folate levels are apparently most likely to contribute to elevated homocysteine (255). There is some evidence that intake of B vitamins above levels currently recommended may offer protection against CVD (252). However, despite clear evidence that B vitamin supplementation can lower homocysteine levels, cardiac benefits are uncertain (256–259). It is possible that the effects of supplementation depend on baseline homocysteine levels, and on individual genotype. In addition, common grain fortification practices have influenced homocysteine levels and the subsequent effect of folate supplementation (260). A meta-analysis of six trials found that folic acid supplementation decreased CVD risk in participants with lower baseline homocysteine levels but slightly increased risk in participants with higher homocysteine levels (261). The interaction between the effect of supplementation and baseline homocysteine levels above

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versus below the overall mean was significant (p = 0.03). Common polymorphisms in the gene for methyltetrahydrofolate reductase (MTHFR) are associated with hyperhomocysteinemia and stroke risk, but these associations appear to be stronger in populations with low folate intakes (262).

B-complex supplementation at or near RDA levels may be beneficial and is unlikely to be harmful (B vitamins are water soluble and excesses are renally cleared). However, recommendations for multivitamin supplementation to all patients attempting to reduce their risk of heart disease are not strongly supported by scientific evidence (263), and there is a suggestion of cardiovascular harm with folate supplementation in those with greater homocysteine levels at baseline (261). Reliance on specific B vitamins for cardioprotective effects is unsubstantiated at present, and supplementation cannot be recommended.

Coenzyme Q_{10}

Coenzyme Q_{10} (CoQ_{10}) is a benzoquinone, also known as ubiquinone because of its remarkably widespread distribution in nature. Minute quantities are found in virtually all plant-based foods. CoQ_{10} functions within the mitochondrion, where it facilitates electron transport and oxidative phosphorylation (264,265). Given the fundamental role of this coenzyme in energy metabolism, it is perhaps not surprising that its putative health effects are protean.

With regard to CVD, evidence is strongest for a beneficial role of CoQ_{10} in heart failure and cardiomyopathy, where supplementation has been associated with improvement in left ventricular function, quality of life, and functional status (266,267). There is evidence of reduced complications post MI (268), improved hemodynamics post bypass grafting (269), and improved functional status and symptom relief in patients with angina (270). CoQ_{10} has been shown to have antihypertensive effects as well (271–274). Some trials have tested the effects of CoQ_{10} in combination with other antioxidants, making it difficult to determine whether each compound individually is effective (274,275). Supplementation with CoQ_{10} and selenium has been associated with reduced cardiovascular mortality (275). Antioxidant effects of CoQ_{10} apparently preserve levels of both ascorbate and alpha-tocopherol, enhancing both extracellular and intracellular antioxidant function (275–278). Finally, supplementation with CoQ_{10} appears to reduce levels of lipoprotein (a) (279) and preserve serum levels depleted by statin therapy (280), leading to alleviation of statin-associated muscle symptoms (SAMS). Despite these findings, larger prospective trials are needed to support the routine use of CoQ_{10}.

Until recently, there was an absence of adequately powered trials in the literature, possibly due to the nonproprietary nature of the compound and the inability of an industry sponsor of such trials to generate correspondingly large profits as a result. New evidence supports the effectiveness of CoQ_{10} in preventing cardiovascular events and increasing survival among patients with heart failure. In their meta-analysis of 13 randomized controlled trials in patients with congestive heart failure, Fotino and colleagues reported a pooled mean net change of 3.67% in the ejection fraction associated with CoQ_{10} supplementation (281). The individual trials included in the meta-analysis had sample sizes ranging from 6 to 69. In contrast, the Q10-SYMptoms, BIomarker status (Brain-Natriuretic Peptide), and long-term Outcome (hospitalizations/mortality) (Q-SYMBIO) trial, presented by Mortensen et al. at the Heart Failure 2013 meeting (282) enrolled 420 patients from nine different countries. Participants were assigned to CoQ_{10} (100 mg 3 times daily) or placebo. After 2 years of follow-up, the CoQ_{10} group had significantly lower rates of major adverse cardiac event (14% vs. 25% in placebo group, p = 0.03),

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cardiovascular mortality (p = 0.02), hospitalizations (p = 0.05), and all-cause mortality (9% vs. 17% in placebo group, p = 0.01). The CoQ_{10} group also experienced greater improvements in functional New York Heart Association class (p = 0.047). The results of this trial represent some of the strongest evidence regarding CoQ_{10} supplementation to date.

In the aggregate, the evidence supporting a role for CoQ_{10} in the amelioration of CVD and the modification of risk factors has not been conclusive (282–284). Improvements in blood pressure, dyslipidemia, and glycemic control have been less apparent than the benefits to heart failure metrics (285). Larger prospective trials are needed to support the routine use of CoQ_{10}.

Alcohol

Low to moderate alcohol consumption has been linked to a reduced risk of CVD through mitigating mechanisms that affect atherosclerosis and inflammation, and pathophysiologic processes integral to most CVD (286). A meta-analysis of longitudinal cohort studies conducted in the United States and internationally reported that alcohol consumption, compared with no alcohol consumption, was associated with reductions in relative risks of 25% for CVD mortality, 25% for CHD mortality, and 29% for incident CHD (287). Consumption of ≤1 drink per day was most consistently associated with reduced cardiovascular risk. Long-term observational studies in the United States have also observed light to moderate drinking to be associated with reduced risk of MI in men and women (288) and reduced cardiovascular and all-cause mortality among males who had survived a first MI (289).

Proposed mechanisms by which alcohol may attenuate cardiovascular risk include elevation of HDL (although this is unlikely after Cardiovascular Health in Ambulatory Care Research Team (CANHEART) (290) and Copenhagen studies (291) showed increasing HDL's association with increased mortality), elevation of tissue plasminogen activator, and inhibition of platelet aggregation. At doses above 30–45 g/day, alcohol raises blood pressure and is associated with increased cardiac risk, as well as increased risk of other morbidity and mortality. Consumption of one to at most two drinks per day (preferably red wine) is reasonable for cardiovascular risk reduction.

Ethanol may only be partly responsible for the cardioprotective effects of alcoholic beverages; red wine may confer additional benefits due to the polyphenolic compounds in the skin of the grape, in particular, resveratrol (292) (see Chapter 31). This is shown by studies that show benefits of dealcoholized red wine. A small study demonstrated enhanced endothelial function following consumption of dealcoholized red wine, with no improvement following consumption of an equivalent amount of red wine with alcohol (293). In another trial, reductions in systolic and diastolic blood pressures and increases in plasma nitric oxide were observed among men with cardiovascular risk factors after consumption of dealcoholized red wine (294). Neither consumption of red wine with alcohol nor gin was associated with improvements in these measures. Still, most studies suggest beneficial effects of ethanol in moderate doses (see Chapter 40).

Other factors should be considered when advising patients on alcohol consumption. The adverse effects of heavier drinking generally mitigate enthusiasm for recommending alcohol consumption for health promotion (295–297). Alcohol can also have deleterious effects, including on mitochondrial dysfunction and changes in circulation, inflammatory response, oxidative stress, and programmed cell death, as well as damage to the CV system itself (286). Even small amounts of alcohol measurably increase the risk of several cancers (particularly of the respiratory tract, digestive tract, and breast), thus limiting or avoiding alcohol may be advisable for those at risk (298–300). It is also important to consider genetic, socioeconomic, racial, and ethnic factors, and alcohol-medication interactions when counseling

patients on alcohol use.

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Iron

There is controversy regarding the role of iron and the risk of CVD. Observational studies have shown a higher CVD risk with higher iron exposure, but epidemiologic studies have found a significant association between the two (301). Heme-iron that is not reduced iron from vegetable sources may act as a pro-oxidant, generating speculation that it may contribute to the risk of cardiac disease in men and postmenopausal women. Iron has been proposed to act in "ferroptosis," or iron-dependent cell death, and has been reported in ischemia-reperfusion injury as a significant form of cell death in cardiomyocytes and may play a role in adverse left ventricular remodeling after MI (302).

It is important to note that there is some concern that our measures of body iron stores are inadequate to gauge the potential pro-oxidant effects of iron. A meta-analysis of prospective cohort studies evaluated the association between dietary iron intake and body iron stores with CVD risk. It found that total iron intake and serum iron concentrations were inversely associated with CVD incidence, whereas heme iron intake was positively associated. Serum transferrin saturation was inversely associated with CVD incidence and mortality (303). In another study, high ferritin levels have been directly associated with mortality in patients with peripheral artery disease (PAD) (304), but a randomized controlled trial found that reduction of iron stores with phlebotomy in PAD patients was ineffective in reducing all-cause mortality, MI, or stroke (305). Overall, the potential association between iron and heart disease risk remains speculative, and somewhat controversial (306,307), current knowledge would suggest that supplements be avoided barring a clear indication for their use.

Magnesium

Serum magnesium (Mg) concentrations have been found to be inversely associated with CVD risk, where a higher Mg intake has shown beneficial effects on cardiac risk factors by improving glucose metabolism, enhancing endothelium-dependent vasodilation, ameliorating lipid profile, and having hypertensive and antiinflammatory effects (7). Mg is also known to have antiarrhythmic properties and has corresponding potential therapeutic applications in acute cardiac care beyond the scope of this discussion. Although the clinical trial data on the role of supplemental Mg in cardiac risk reduction are by and large equivocal, the data on antihypertensive effects are conclusive (311–321).

Serum Mg levels may be a reflection of overall dietary pattern, including intake of fruits and vegetables. For most patients, a generous intake of Mg from dietary sources is to be encouraged, whereas supplementation as a matter of routine, other than at doses incorporated into multivitamin/mineral preparations, need not be. Mg is discussed further in Appendix E.

Calcium and Potassium

Cardiovascular benefit of calcium and potassium is associated with blood pressure–lowering effects in particular, as discussed in Chapter 8 (see also Chapter 4).

Cocoa/Dark Chocolate

The cardiovascular effects of dark chocolate consumption are convincingly favorable across a wide array of measures. The topic is addressed in Chapter 39.

Plant Stanols/Sterols

The hypolipidemic effects of plant stanols and sterols are well established (322,323). These naturally

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occurring compounds are found in small quantities in a large range of plant foods. Stanols and sterols interfere with cholesterol absorption in the gut, both from food and from enterohepatic circulation. A dose of roughly 2 g/day has been shown to induce meaningful reductions in LDL. The inclusion of higher doses of plant stanols as part of a dietary portfolio designed for optimal lipid lowering resulted in effects rivaling those of statins (3). Furthermore, adding plant sterols or stanols to a statin regimen is associated with greater reductions in total cholesterol and LDL compared with statin therapy alone (324). There does not appear to be a significant difference between plant sterols and stanols in their effects on serum lipid levels (325).

Garlic

There has long been interest in potential lipid-lowering and blood pressure–lowering effects of garlic and its putative active ingredient. The healthful effects of garlic are, however, unclear. A 2007 clinical trial refutes a lipid-lowering effect, and the blood pressure lowering effect is uncertain (326). A more recent Cochrane review concluded that garlic did lower blood pressure in two trials in hypertensive patients, but there was insufficient evidence of a beneficial effect on cardiovascular morbidity and mortality (327). While the inclusion of whole garlic in the diet is healthful, its use in pill form to achieve targeted cardiovascular benefit cannot be recommended on the basis of available evidence.

Walnuts, Almonds, and Other Nuts

Nut intake is convincingly and consistently associated with beneficial effects on cardiac risk factors in intervention studies and with reduced event rates in observational studies (328–333). Despite their energy density, nuts are not clearly associated with risk of weight gain (334–336). Honey-roasted or sugar-coated nuts are likely another story. In one large prospective study in a Mediterranean population, men and women who ate nuts at least twice per week had a 40% reduced risk of weight gain during the 28-month follow-up period, compared with those who did not eat nuts (337). Other studies have also showed benefits, without weight gain (338), including a reduced risk of mortality (339).

Overall, the evidence for benefits of nuts is greatest for walnuts, which offer a particularly favorable fatty acid profile. Almonds have also been associated with cardiac benefit (340,341). In contrast with the findings of an earlier review (333), a 2009 meta-analysis concluded that almond intake appears to lower total cholesterol but does not improve LDL, HDL, or triglycerides (342). There is some evidence that a lipid-lowering effect of almonds may be limited to hypercholesterolemic individuals (343).

Red Yeast Rice Extract

Red yeast rice can improve serum cholesterol levels, as it contains a multitude of beneficial components, including monacolins that exhibit 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase activity, sterols, isoflavones, and monosaturated fatty acids (344,345). Given its impact on cholesterol levels, and overall cardiovascular health, it can be considered in patients who are resistant to statin therapy. It is important to note, however, that the variable potency and possible adulteration of the commercially available products make red yeast rice a suboptimal treatment option for lowering LDL and total cholesterol in comparison to statin therapy.

Other

Interest is intense in the development of nutraceutical agents with cardioprotective effect. Among compounds of current interest are bioflavonoids, the herb, hawthorn, and resveratrol, a compound extracted from grape skins, to name a few. Many other compounds and nutrients have received attention in

the popular press. Evidence is insufficient to recommend clinical applications of most such compounds at present. The pace of developments in this area is so rapid that no print text can be fully current.

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CLINICAL HIGHLIGHTS

Data and opinions pertaining to the nutritional mitigation of cardiovascular risk are scattered throughout a staggeringly vast literature. Within this body of work is room for diverging opinions, both on the basis of data and the current absence thereof. Nonetheless, diverse lines of research and observation have long converged on a discrete set of dietary recommendations.

The typical American diet suffers from both excesses and deficiencies relative to the ideal diet for cardiovascular health. A total fat intake below 35% of calories is recommended, (346) although maldistribution of fat calories is likely more important. Trans fat should be avoided altogether and replaced with dietary MUFA and PUFAs to reduce CVD risk. Polyunsaturated and MUFA in a ratio of between 1:1 and 1:2 may be ideal. PUFA should be divided between n-6 and n-3 fatty acids in a ratio between 4:1 and 1:1 rather than the prevailing ratio of 11:1 (n-6:n-3). In patients consuming relatively little wild game or fish, fish oil supplementation, or consistent use of flaxseed oil may be recommended to supplement n-3 fat (alpha-linolenic acid). Some controversy persists as to the relative health benefits of short-chain versus long-chain n-3 fatty acid consumption (see Chapters 2 and 4). The importance of supplementing n-3 fatty acids may be even greater in patients with established coronary disease.

Benefits of dietary fiber are well established, and prevailing intake is deficient. A daily intake of at least 30 g of fiber is appropriate and is readily achievable if whole grains, vegetables, and fruits are the principal sources of food energy. This dietary pattern will similarly serve to raise intake of diverse micronutrients, including antioxidants, while allowing for a low glycemic load despite generous intake of total carbohydrates. The benefits of specific micronutrients are suggested, while the health advantages and specific cardiovascular benefits of generous intake of whole foods are conclusively established. The most recent, and most definitive, trial data argue against a benefit of high-dose (i.e., >400 IU/day) vitamin E supplementation, at least in established heart disease. The potential preventive effects of combinations of antioxidant supplements before coronary disease are overt remain uncertain, but there is reason for concern with many individual agents. Arguments for a variety of other micronutrients and nutraceuticals can be made with available evidence.

Barring alcohol-related health problems or contraindications such as liver disease or personal or family history of specific cancers, mild to moderate alcohol consumption (15–30 g/day) appears to confer overall benefit; the lower end of this range is more appropriate for women. Restriction of dietary cholesterol may be unjustified, and patients may have varied effects on cholesterol levels based on food type ingested due to their NPC1L1 protein levels. Eggs and shellfish may not need to be banished from a heart-healthy diet.

In general, most dietary recommendations for the primary prevention of CVD in adults appear to be safe and appropriate for children over the age of 2 years (347,1) (see Chapter 29). Application of a heart-healthy dietary pattern is appropriate for primary, secondary, and tertiary prevention of heart disease. This pattern is consistent with prevailing and emerging recommendations for health promotion in general (see Chapter 45) and can be expected to confer non-cardiovascular health benefits as well. Given the high impact of diet on cardiovascular and non-cardiovascular diseases, dietary screening should be completed for all patients by the healthcare team, with the help of electronic health record platforms (2). In conjunction with other health-promoting lifestyle practices, the adoption of a heart-healthy diet reliably ameliorates cardiac risk across a broad array of measures (4).

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Dietary guidance to patients should be cast in terms of foods rather than nutrient classes. The wide array of foods that comprise our diets span just three macronutrient classes: carbohydrate, fat, and protein. Thus, the actual composition of diets high or low in any given macronutrient can and does vary markedly. Diets high in carbohydrate, for example, may be based on nutrient-poor, energy-dense processed foods, or on fruits, vegetables, and whole grains. Diets relatively high in fat may be based on fast food, or on the Mediterranean dietary pattern, which is rich in nuts, seeds, olives, avocado, and fish.

The food-based theme of heart-healthy eating is consistent and clear across a wide expanse of literature, where a diet emphasizing intake of vegetables, fruits, beans, lentils, whole grains, nuts, seeds, olives, avocado, fish, lean meats, and dairy is recommended. Judicious additions of red wine and dark chocolate are advisable as well. All such foods are advisable in amounts appropriate for dietary balance and maintenance of stable and healthful weight.

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Diet and Hypertension

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INTRODUCTION

Epidemiologic data have long shown variations in average blood pressure in diverse populations. Though there are many potentially confounding variables to these observed differences, there is growing evidence that dietary variation is a contributing factor. In particular, epidemiology suggests and clinical trial data affirm an effect of sodium chloride intake and overall dietary pattern on blood pressure. There is decisive evidence that modification of the overall dietary pattern can be effective in modulating blood pressure and may even be a substitute for pharmacologic treatment in some patients. In addition, there is clear evidence that weight management is often effective in reducing blood pressure in overweight patients (1), an issue of increasing public health importance as the prevalence of obesity steadily rises. Data also suggest that a variety of micronutrients, in addition to sodium, may modify blood pressure independent of the overall dietary pattern (2).

OVERVIEW

Hypertension is unusually prevalent in the United States at 29% to 45% of the adult population (3,4), above the estimated 25% to 28.5% prevalence in high-income countries globally (5). Trends had been favorable over recent decades, with data demonstrating relatively stable prevalence of hypertension—defined as a systolic blood pressure ≥130 mm Hg and/or a diastolic blood pressure ≥80 mm Hg (see Table 8.1)—and improvement in the prevalence of controlled hypertension (3). However, there is still a long way to go: In 2020, a call to action from the U.S. Surgeon General cited up to 71% of patients with hypertension failing to achieve adequate blood pressure control. This report focuses on three goals: to make hypertension control a national priority, to cultivate community supports, and to optimize patient care for hypertension. The report also attempts to use a health equity framework while aiming to address the contributions of social determinants of health, briefly addressed in this chapter (6).

TABLE 8.1

Classification of Blood Pressure Levels

Category	Systolic BP[a]		Diastolic BP[a]
Normal	<120	and	<80
Elevated blood pressure	120 to 129	or	<80
Stage 1 hypertension	130 to 139	or	80 to 89
Stage 2 hypertension	≥140	or	≥90

[a]*BP = blood pressure. All measures are in mm Hg.*

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Adapted from Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents (available at https://pediatrics.aappublications.org/content/140/3/e20171904); and 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults (available at https://www.onlinejacc.org/content/71/19/e127?_ga=2.213860700.938095644.1589579871-1123892624.1589579871).

Populations

Transcultural comparisons show higher rates of hypertension in industrialized nations, and these data provide a basis for the association between diet and hypertension. However, such comparisons are intrinsically limited by a plethora of confounding variables, leading to use of migration studies to support the impact of diet and lifestyle. Migration studies in numerous populations confirmed a rise in population blood pressures with environmental changes, specifically "Westernization" (7–9).

In the United States, hypertension is less common among those with normal weight compared to those who are overweight, and less common among vegetarians than those who eat meat (10,11). Isolating the direct effects of diet on blood pressure is difficult due to the prevalence of obesity in the United States and the strong association between obesity and hypertension (see Chapters 5 and 6). The association between higher body mass index (BMI) and hypertension may be especially strong for African Americans (12,13). A number of mechanisms have been proposed to account for obesity's causative role in the development of hypertension: increased sodium retention, activation of renin-angiotensin system, intrarenal compression by adipose tissue, and sleep disturbance (14,15).

Secular trends in the epidemiology of hypertension also suggest an important influence of obesity (16). Obesity, insulin resistance, and visceral adiposity are risk factors for both hypertension and cardiovascular morbidity (17,18). Up to 50% of individuals who have hypertension without obesity may also be insulin resistant (19). Similar to the effects of obesity, insulin resistance and compensatory hyperinsulinemia also promote hypertension by increasing renal sodium reabsorption, stimulating sympathetic nervous system overactivity, and by inducing a proinflammatory state (15). These affects appear additive when patients with hypertension also have metabolic syndrome by increasing cardiovascular risk. (20,21). Fortunately, weight loss and dietary pattern may have both independent and additive effects on blood pressure (22). The topics of obesity and insulin resistance are addressed fully in Chapters 5 and 6, respectively.

From a practical perspective, patients have comparable benefit from dietary interventions, which either lower blood pressure directly or produce weight loss and thereby indirectly lower blood pressure (see Table 8.2). There is decisive evidence that weight loss among patients with obesity and hypertension frequently results in blood pressure reduction. Modest weight loss—as little as 3 kg—may lower blood pressure in patients who do not reach their ideal body weight (23); this benefit may be attenuated when weight loss is achieved pharmacologically (24).

TABLE 8.2

Lifestyle Interventions for Blood Pressure Control Recommended by the National Heart, Lung, and Blood Institute

Intervention	Specific Guidance
Weight	

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reduction	Maintain a normal body weight (BMI 18.5–24.9 kg/m2). Weight loss is recommended in adults who are overweight or have obesity. 5%–10% weight reduction also conferring significant benefits
DASH eating plan	Adopt a diet rich in fruits, vegetables, and low-fat dairy products with reduced content of saturated and total fat
Dietary sodium reduction	Reduce dietary sodium to ≤2,300 mg (or at least reduce by 1,000 mg/day)
Aerobic physical activity	Regular aerobic physical activity (e.g., brisk walking) at least 30 minutes/day, most days of the week
Moderation of alcohol consumption	Men: limit to ≤2 drinksb/day. Women and lighterweight men: limit to ≤1 drinkb/day

[a]*In patients with hypertension*.

[b]*One drink equals 0.5 oz of 15 mL ethanol (e.g., 12 oz. beer, 5 oz. wine, 1.5 oz. 80-proof whiskey)*.

Adapted from National Heart, Lung, and Blood Institute recommendations for treatment and prevention of hypertension. More details and resources are available through their website: https://www.nhlbi.nih.gov/health-topics/high-blood-pressure; accessed 8/13/2020.

Dietary Patterns

In general, diets associated with optimal blood pressure control are similar to diets associated with a variety of other health benefits (see Chapter 45). Recent meta-analyses suggest the Dietary Approaches to Stop Hypertension (DASH) and Mediterranean diets may be the most effective dietary patterns to reduce blood pressure (11,25). The association between dietary pattern and blood pressure was confirmed by the results of the DASH study, which demonstrated that adherence to a diet high in fruits and vegetables, along with reduced saturated fat, and substitution of low-fat dairy in place of regular fat dairy, was effective in lowering blood pressure among randomized subjects with hypertension (26). The DASH sodium trial demonstrated independent effects on blood pressure by restricting sodium to 1,200 mg/day, with noted additive benefits by combining the two approaches. While the impact was greatest in patients with the highest baseline values, blood pressure reduction was observed in all groups (27) (**Table 8.3**).

TABLE 8.3

Review of Dietary Patterns

Diet	Description
DASH diet (1)	Whole grains, legumes, vegetable, fruits, 2-3 servings low-fat dairy/fat-free dairy, low sodium, 1-2 servings animal protein lean, nuts/seeds Low intakes: red and processed meats, sweets, less-saturated fat
Vegetarian diet (2)	Diets with larger basis on plant protein though with subtypes ranging from vegan (no animal products at all) to semivegetarian (non-fish, meat consumed but <1/week). Relies upon whole grains, vegetables, fruits, plant-based proteins (legumes, soy, nuts, seeds); some include dairy or milk alternatives, eggs or cheese
Mediterranean	Whole grains, legumes/beans/peas, vegetables, fruits, plant-based proteins

diet (3)	(nuts/seeds/soy products), olive oil, small portions animal proteins (seafood, chicken, eggs). Limit red meat and butter/cream. Some suggest drinking red wine
High protein diet (4)	Recommend >20% of total calories from protein, including both animal and plant proteins. Limit fat to <35% of total calories
Low carbohydrate diet (4)	<25% of total calories consumed from carbohydrates, higher amount of animal and plant proteins and higher intake fat
Nordic diet (3, 4)	Whole grains, fruits especially berries, vegetables, fish, nuts, low-fat dairy, rapeseed oil
Low glycemic index diet (5)	Low in refined carbohydrates and sugar while higher in complex carbohydrates (containing fiber). Foods measuring Glycemic Index <55 are considered low. Foods to include: legumes, beans, vegetables, fruits, high fiber. Decrease added sugar foods and sugar-sweetened beverages

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The PREMIER trial tested the value of established lifestyle approaches to blood pressure reduction—weight loss, sodium reduction, increased physical activity, and limited alcohol intake—alone and in combination with the DASH diet. Significant reductions in systolic blood pressure were seen in both groups, and the greatest reductions were observed in the combined treatment group (28). These effects were somewhat greater in men than in women and in those with baseline higher blood pressure as compared with normotension; however, some effect was observed across all population subgroups (29). The DISC study suggests that the relationship between diet and blood pressure in children is similar to that in adults (30) and that growing children can safely adopt and maintain a cardioprotective diet (31–33).

Several studies have examined the effects of different dietary and macronutrient patterns on blood pressure (11,34,35). Reduction in blood pressure was observed with a higher intake of protein derived from either plant sources or lean meat (36,37) and with substitution of unsaturated fat in place of saturated fats (38). Intermittent fasting has also been thought to reduce blood pressure, though a 12-month trial comparing this pattern to a calorie reduction diet and to a control group did not show any difference in blood pressures among the groups (39). Additionally, many macronutrient comparison studies have not changed typical American carbohydrate sources, and therefore the diets vary significantly with respect to

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glycemic load. A low glycemic load may be achieved even with a diet high in carbohydrate by emphasizing foods like vegetables and certain varieties of fruits, also whole grains, beans, nuts/seeds, legumes, and lean meats over ultra-processed alternatives (see Chapter 6). When tested, following such a diet leads to favorable effects across various cardiovascular risk factors in addition to its beneficial impact on blood pressure (40,41). For example, the DASH diet has a relatively high carbohydrate and low glycemic index pattern and is one of the most effective dietary patterns to reduce blood pressure (11,25). In contrast, red meat intake is associated with hypertension and increased risk for cardiovascular disease, particularly in the case of processed red meat (42,43). Overall, the literature suggests nutritional management of blood pressure by following a dietary pattern that contains fruits, vegetables, whole grains, legumes, dairy, fish, and nuts/seeds but contains less red meat or added sugar (25).

Benefit from lifestyle changes has been noted at all levels of blood pressure, though higher levels such as stage 2 hypertension generally require pharmacotherapy in combination. Other studies like the TRIUMPH trial investigating lifestyle modification in resistant hypertension are ongoing (44). A practical approach to more advanced hypertension is to initiate pharmacotherapy as indicated along with lifestyle changes and then taper medications when the blood pressure is well controlled and the patient establishes recommended dietary and lifestyle modifications.

As with the prevention and modification of other cardiovascular risk factors, the optimal diet in managing incipient and established hypertension remains uncertain, and many diet patterns can be effective. Recommendations for calorie control, abundant intake of fruits and vegetables, whole grains, and legumes, and restriction of saturated and trans fat intake may be made with confidence. Of note, such a diet is naturally rich in the micronutrients associated with blood pressure lowering (see Table 8.4), relatively rich in fiber, and relatively low in sodium. Determining which of these modifications in dietary behavior is responsible for blood pressure control is important to advance our understanding but may be unnecessary to make recommendations likely to benefit patients with hypertension.

TABLE 8.4

Micronutrients and Supplements that Impact Blood Pressure

Name	Research
Calcium (1)	Doses of 1,000 mg–1,500 mg calcium/day reduced systolic blood pressure by 1.14 mm Hg Doses ≥1,500 mg calcium/day reduced systolic blood pressure by 2.79 mm Hg For both men and women, effect higher in those 11–35 years old (−2.11 mm Hg systolic blood pressure). Those over 35 years old: −0.96 mm Hg systolic blood pressure
Garlic (2)	May be helpful but evidence is weak, not enough high-quality studies
Magnesium (3, 4)	Increased amounts consumed associated with lower systolic blood pressure Magnesium supplementation (>370 mg/day) associated with a decrease in systolic blood pressure and diastolic blood pressure
Coenzyme Q10 (5)	Limited evidence that supplement would affect blood pressure Does not lower blood pressure compared to placebo (3 trials)
Amino Acids (3, 6, 7)	Methionine and alanine associated with higher blood pressure Threonine and histidine associated with lower blood pressure Comparison between different types of dietary patterns-not supplements Glutamic acid intake associated with decreased blood pressure Sulfur amino acids are not correlated with blood pressure

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Omega-3 or Omega-6 Fatty Acids (8, 9)	Theoretical benefit to lower blood pressure but mixed results from randomized controlled trials
Fiber (3, 4, 10)	Higher fiber intake from diet or soluble fiber supplements associated with reduced blood pressure
Cocoa (11)	Small amounts of dark chocolate/flavonoid-rich cocoa products may decrease blood pressure by a small amount
Alcohol (3, 12)	Shown to increase blood pressure and heavy alcohol intake increases risk of hypertension Those who drank more than two alcoholic drinks, reducing alcohol intake by 50% showed reduction in systolic blood pressure −5.50 mm Hg and DPB −3.97 mm Hg
Caffeine (13)	Coffee consumption of 3–5 cups/day is associated with 15% reduction in CVD Habitual coffee consumption has an inverse association with mortality

Note: 1. Cormick G, et al. Calcium supplementation for prevention of primary hypertension. *Cochrane Database Syst Rev*. 2015(6):CD010037.

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Genetics

Nutrigenomics, the study of the effects of diet on gene expression, is increasingly recognized as important to understanding the etiology and treatment of hypertension. Heritability of blood pressure is well recognized, with reported ranges from 30% to 70% (45), and the knowledge regarding how gene-diet interaction influences blood pressure is growing rapidly. One literature review identified multiple genes implicated in “salt sensitivity” including the expected genes of the renin-angiotensin system, sympathetic nervous system, and epithelial sodium channel, as well as others such as cytochrome P450 3A and endothelial nitric oxide synthase (46). One study tested genotype of the beta-2-androgen receptor in participants of the DASH-Sodium study and found the DASH diet was particularly effective at lowering blood pressure in individuals carrying the G46A polymorphism (47). Genes such as Neuropeptide Y and CYP4F2 have been implicated in blood pressure changes based on dietary fat intake, while aldehyde dehydrogenase deficiency and the apolipoprotein E phenotype are associated with increase in blood pressure related to alcohol consumption (48). As nutrigenomic technologies continue to develop, they will provide additional avenues to illuminate genetic predispositions and identify specific, tailored treatments.

Social Determinants of Health, Diet, and Hypertension

While studies demonstrate the efficacy of treating elevated blood pressure with dietary changes or pharmacotherapy, it is important to note that adherence in a controlled trial is generally greater than is achieved in practice (49), which has led to a broad category of research in improving patient adherence and acknowledging the role of social determinants of health. One important limiting factor for adherence with recommended dietary change is the access and affordability of healthier food options, a problem that may be particularly notable in patients with lower socioeconomic status and those adversely impacted by structural or racial inequities (50). Food insecurity contributes to poor dietary adherence and worsened control of hypertension (51,52). One explanation for the worsened blood pressure may be that potassium-rich diets are often inaccessible, and one study identified that individuals with food insecurity not only consumed less potassium but also had a higher dietary sodium-to-potassium ratio than those living in food-secure households (53). Differences in health literacy may also contribute to poor adherence, leading some care teams to provide targeted education to improve both adherence and outcomes (54,55). The association between socioeconomic status, diet, and blood pressure begins even in childhood (56), and interventions to improve diet in childhood and adolescence have a disproportionate impact on blood pressure among children of lower income families compared to those with higher income (31).

Drug Interactions

There are also several diet-drug interactions that clinicians should be aware of when treating patients with hypertension. For example, grapefruit juice increases the bioavailability of calcium-channel blockers and interferes with their metabolism by CYP3A4 inhibition (57). African wild olive, a plant thought to have hypotensive effects of its own, may also increase the absorption of propranolol and

diltiazem (58). Anti-hypertensive medications have also been implicated in some micronutrient deficiencies, such as angiotensin-converting enzyme (ACE) inhibitors, leading to zinc depletion and beta-blockers depleting Coenzyme Q10 (59).

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NUTRIENTS, NUTRICEUTICALS, AND FUNCTIONAL FOODS

Sodium

Sodium is the most extensively studied nutrient influencing blood pressure. Evidence from a variety of sources, including epidemiologic studies as well as intervention trials, conclusively indicates that sodium contributes to blood pressure elevations on both a population and an individual basis (60,61). As many previous studies evaluated sodium intake based on dietary recall for a 24-hour period, more recent studies have investigated urine sodium excretion over various time periods to assess intake more accurately. One such study of 24-hour urine sodium excretion in adult participants of NHANES showed a linear association between blood pressure and increased sodium excretion (62). At a population level, global data suggest reduction to 2,300 mg of sodium intake will reduce systolic blood pressure by 3 to 4.5 mm Hg (63). A recent meta-analysis confirmed that sodium reduction leads to blood pressure reduction in all populations, particularly those with higher cardiovascular risk, such as older patients and patients with higher baseline blood pressures. The same study also revealed a greater effect the longer a low-sodium diet is maintained (64). Based on evidence regarding risk of hypertension and of cardiovascular disease, the 2019 Dietary Reference Intakes (DRI) for sodium established a chronic disease risk reduction intake (CDRR) sodium level and recommends reducing sodium intake if above 2,300 mg in adults or above 1,800 mg in children (65) (Table 8.5).

TABLE 8.5

Sodium Intake: Chronic Disease Risk Reduction Intake

		Chronic Disease Risk
Ages (years of age)	**Adequate Intake (mg/day)**	**Reduction Intake (mg/day)**
Children		
1–3	800 mg/day	Reduce if above 1,200 mg/day
4–8	1,000 mg/day	Reduce if above 1,500 mg/day
Males		
9–13	1,200 mg/day	Reduce if above 1,800 mg/day
14–70	1500 mg/day	Reduce if above 2,300 mg/day
Females		
9–13	1,200 mg/day	Reduce if above 1,800 mg/day
14–70	1,500 mg/day	Reduce if above 2,300 mg/day

Adapted from Sodium Dietary Reference Intakes; available at https://www.ncbi.nlm.nih.gov/books/NBK545448/

There has been some controversy regarding whether there is harm in consuming too little sodium (66), including concern that insufficient sodium intake may increase cardiovascular morbidity (61). This leads to broad debate regarding the level of sodium restriction. For example, the NUTRICODE group estimated

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an increased cardiovascular mortality with sodium intake above 2,000 mg/day; however, the PURE study suggests a significantly higher threshold of 5,000 mg/day (63,67). Despite these concerns, historical intake was estimated to be less than 800 mg of sodium/day in our paleolithic ancestors (68), and many other reservations regarding dietary reduction of sodium have been thoroughly debunked (69). Though a true lower limit of intake is not known, the NASEM has set adequate intake at 1,500 mg for adults due to extensive proof of safety; they also note that in trial populations, intake as low as 949 mg/day were studied without any deficiency symptoms reported (70). While there may be consequences of consuming too little sodium, given our population's prevailing sodium intake levels, this is less likely to be encountered in practice. Eighty percent of children and adolescents in the United States consumed above the CDRR intake level of 1,800 mg daily, and 80% of adult women and 97% of adult men ingested more than 2,300 mg (65). Recommendations to limit sodium intake below prevailing levels in the United States can therefore be made with considerable confidence, and advocating a generally health-promoting diet will result in sodium restriction by reducing the intake of fast foods and other highly processed foods.

The Food and Drug Administration (FDA) drafted voluntary target recommendations to reduce sodium in "commercially processed and prepared food" over a 10-year period of time (71). There has been some concern around such population-based recommendations leading to extremes of abnormally low intakes of sodium and thereby increasing morbidity. Although these concerns are valid, it should be understood that current intake of sodium in the U.S. diet (3,400 mg/day) is far too high, and suggestions to adopt more universal strategies to reduce sodium in some of the most sodium-rich items in the U.S. diet is likely to bring more benefit than harm. These recommendations do not eliminate sodium from the diet completely but would recommend restrictions in some of the most consumed foods in the country (71).

The efficacy of sodium restriction in the management of hypertension is well supported by clinical trial data, but establishing real-world effectiveness is a greater challenge. Adherence to a low-sodium diet is difficult for most patients (72), and such diets typically introduce other lifestyle changes that may also contribute to blood pressure reduction. Because of this difficulty, it has been suggested that achieving recommended sodium intake levels in the United States with any consistency will require appreciable changes to the food supply (72). All member states of the World Health Organization agreed with that approach at the World Health Assembly in May 2013 and set a target of reducing salt intake by 30% by 2025 (73). Population-based strategies, including government-directed policies, to reduce sodium intake are estimated to be cost effective in respect to quality-adjusted and disability-adjusted life years as well as in respect to reduced healthcare costs (74,75).

Patients should also be advised of the importance of reading food labels. The sodium content of many breakfast cereals is comparable to that of potato chips and pretzels, although the taste of salt in such products is masked by the sugar (see Chapter 38). As evidenced in the DASH diet, intake of unprocessed or minimally processed foods has significant health benefits. This concept is the basis of the NOVA scale, developed in Brazil, which classifies food and drink based on the type and amount of processing (76). More than 70% of sodium in the U.S. diet is associated with prepackaged and prepared processed foods. Sodium is often used to enhance flavor and palatability, and it is well known that foods that are more processed tend to be significantly higher in a number of nutrients and additives such as sodium (77). One useful guideline for consumers is to limit foods with more milligrams of sodium than calories per serving size or keep to less than 140 mg of sodium/serving (78). Consumer selection and acceptance of sodium-reduced foods and decrease in discretionary salt use both in cooking and in use of a salt shaker are all key components of reducing dietary sodium intake. Data overall suggest that these changes may be most tolerable and sustainable when the reduction is gradual (79,80). As with other dietary changes, salt restriction is more palatable as it becomes familiar: Those accustomed to a lower sodium diet begin to

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taste salt more readily and to prefer lower intake levels, while acclimation to a high-salt diet has the opposite effect (81) (see Chapter 38).

Salt Substitutes

So-called salt substitutes replace sodium salts with potassium or calcium salts and can aid individuals in adhering to a salt-restricted diet. There is some evidence suggesting that the preference for dietary salt may vary with factors other than taste perception (82), so acceptance of salt substitutes is variable. However, their use may be encouraged as clinical trials have demonstrated some favorable outcomes of salt substitution on blood pressure (83,84).

Potassium

Growing evidence suggests that increased potassium intake is associated with improvements in blood pressure (85). Specifically, dietary potassium intake that equals or exceeds sodium intake is associated with lower blood pressure (62,86–88). The average intake of sodium in the United States, estimated from NHANES data, is 3,600 mg/day, while the average daily intake of potassium is approximately 2,800 mg (89). Our prehistoric ancestors are estimated to have consumed less than 1,000 mg of sodium/day but more than 7,000 mg of potassium/day (68). As potassium is abundant in a variety of fruits and vegetables, high intake of potassium is generally associated with other dietary changes that may independently lower blood pressure. The INTERSALT study demonstrated that blood pressure rose with age in all populations who consumed more sodium than potassium but not in those who consumed more potassium than sodium (90). Additionally, African Americans with hypertension may demonstrate larger reductions in blood pressure compared to Caucasians with equal potassium intake (91). Data also suggest a role for monitoring random urine sodium-to-potassium ratios both to assess anticipated response to dietary change, as there is largest BP reduction among patients consuming more potassium than sodium, and for evaluating adherence to dietary recommendations (62,86,92).

CLINICAL HIGHLIGHTS

There is strong evidence that specific dietary regimens are associated with reductions in blood pressure in people with hypertension and preservation of blood pressure in those who are normotensive. These include diets rich in fruits, vegetables, grains, and nonfat dairy products; diets limited in saturated and trans fats; and diets low in highly processed products. Evidence suggests that restriction of dietary sodium to less than 2,300 mg/day improves blood pressure control in most individuals. Weight control, regular physical activity, and moderation of alcohol intake confer significant benefits as well. Combining these strategies is most effective and offers benefits beyond blood pressure regulation (see Chapter 45).

Most individuals can expect to be acclimated to a salt-reduced diet over a period of weeks so that preference for higher salt intake abates. Adherence to the dietary recommendations advisable both for blood pressure control and health promotion will lead naturally to a salt intake far closer to the recommended 2,300 mg than the current higher consumption typical in the United States. There is also some evidence for the hypotensive effects of potassium, calcium, and magnesium, which are fortunately abundant in the diets that are routinely advocated for blood pressure control.

Patients with hypertension should be advised to carefully consult nutrition labels and limit consumption of processed foods with high levels of sodium content. Supplemental calcium, which is of value in the prevention of osteoporosis in many patients (see Chapter 14), may contribute slightly to blood pressure control. Alcohol should be restricted or avoided until blood pressure is normalized and its consumption

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moderated in those with normal blood pressure. Salt substitutes have a role in reducing sodium intake and lowering blood pressure as well. Caffeine should be restricted in individuals with poorly controlled hypertension; moderate intake is acceptable for all others. Patients with blood pressure in the high-normal or elevated blood pressure (formerly prehypertension) range are at risk to develop hypertension and should be encouraged to modify their diet as a means to slow or prevent such progression. Future efforts to improve dietary adherence in patients with hypertension, including educational interventions and addressing food insecurity, may hold promise in improving hypertension-related morbidity in those at risk.

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Chapter 9

Diet and Hemostasis

Xinyin Jiang

OVERVIEW

Nutrition plays a vital role in both the manufacture of blood products and the homeostatic mechanisms involving the aggregation of platelets, the coagulation cascade, and fibrinolysis (1). Hematopoiesis requires an adequate intake of both energy and an array of micronutrients, including minerals such as iron, vitamins such as folate and B_{12}, and specific amino acids. The manufacture of clotting factors II, VII, IX, and X is dependent on adequate intake of vitamin K and normal hepatocyte function. There is also extensive bidirectional feedback between hemostatic and inflammatory pathways (2), and both systems are involved in the pathophysiology of obesity, cardiovascular disease (CVD), diabetes, and other chronic diseases.

Provided that both macronutrient and micronutrient intake meet or exceed recommended levels, diet is unlikely to be a limiting factor in hematopoiesis. However, variations in dietary pattern and in the metabolic responses to such variations appear to play an important and as yet incompletely understood role in modifying hemostasis. Roles for total energy intake, adiposity, dietary pattern, alcohol, the quantity and type of dietary fat, and various micronutrients have been tentatively or reliably identified in promoting or inhibiting thrombotic tendencies.

NUTRIENTS, NUTRICEUTICALS, AND FUNCTIONAL FOODS

Energy Intake and Weight Management

Severe energy intake deficiency leading to extremely low body weight is associated with decreased bone marrow cellularity, causing thrombocytopenia (3).

Excess energy intake leading to obesity appears to be associated with increased thrombotic tendencies. Obesity is associated with increased levels of fibrinogen, factor VII, factor VIII, and plasminogen activator inhibitor (PAI-1), as well as increased blood viscosity (4,5). Adipose tissue is considered a true organ, made up of fat and vascular cells, and capable of producing hormones, as well as inflammatory mediators. Adiposity, as measured by the waist circumference, has been positively correlated with fibrinogen levels (4) and may be particularly associated with a prothrombotic tendency (6). Faber et al. explain that adipose tissue induces thrombocyte activation by the production of adipose tissue-derived hormones, called adipokines, which directly and indirectly (via insulin resistance) affect platelet function (7). Recent evidence suggests that the nonfat cells (8) produce PAI-1 (9,10). The molecule PAI-1 is the major physiologic inhibitor of tissue-type plasminogen activator in plasma, thus preventing thrombolysis in vivo and increasing one's risk of myocardial infarction. Numerous studies have demonstrated significant associations among increased serum concentration of PAI-1, insulin resistance, and central adiposity, suggesting that PAI-1 can be considered part of the metabolic syndrome complex and may contribute to the impaired fibrinolysis in type 2 diabetes (11–13) (see Chapter 6). One

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study found that both weight loss and medication-induced improvement of insulin sensitivity significantly decreased platelet activation in obese women, suggesting that insulin resistance is itself an independent contributor to platelet activation (14). In fact, another study demonstrated that patients with metabolic syndrome who take aspirin have higher levels of serum thromboxane B(2), indicating less effective inhibition of cyclooxygenase-1 (COX-1) and a higher risk of clot formation (15).

Beneficial effects of weight loss on hemostasis have been reported. Short-term studies have shown variable effects on fibrinogen, apparently mediated by fluctuations in the levels of free fatty acids (4). Rapid weight loss may elevate fibrinogen because of free fatty acid mobilization, whereas more measured weight loss, as well as the maintenance of such loss, appears to be associated with reduced levels of both fibrinogen and other prothrombotic factors (4,16). Even weight reduction in obese children has been associated with decreased levels of fibrinogen, IL-6, C-reactive protein (CRP), and other inflammatory mediators (17). Both modest and substantial weight loss have been found to significantly reduce PAI-1 levels (18). Weight loss has also been associated with reductions in factor VII coagulant activity (factor VIIc), an effect that may be mediated through reductions in plasma triglycerides (19).

Physical Activity and Other Lifestyle Interventions

Physical activity appears to influence hemostasis, reducing levels of fibrinogen, factor VII, and PAI-1; however, these effects have been notably found only with regular exercise; acute exercise reduces PAI-1 as well but is associated with increases in fibrinogen and plasma viscosity (20). The benefits of regular activity may be especially robust in people with diabetes, suggesting that improved insulin sensitivity may reduce thrombotic tendencies. In healthy, untrained adults, moderate exercise significantly elevates fibrinolytic activity, while strenuous exercise enhances coagulation as well as fibrinolysis; however, it appears that hemostasis remains in balance after both moderate and strenuous activity (21). Athletes show even higher rates of fibrinolytic activity via increased antithrombin III levels and markedly decreased PAI-1, suggesting greater vascular efficiency in this group (22). In contrast, unfavorable hemostatic changes at the extremes of exercise intensity may predispose to the formation of intravascular thrombus and may contribute to the phenomenon of sudden cardiac death after exercise (23). It has been found that strenuous exercise promotes thrombin generation by shear stress that causes the release of procoagulant microparticles from platelets, and this phenomenon seems to be more important in sedentary people (24). Thus, very strenuous physical activity such as marathon running may not be beneficial to some people, and one of the mechanisms behind this may be an unequal activation of the coagulation and fibrinolytic cascades.

Intensive lifestyle interventions that combine a healthy diet with increased physical activity appear to have the greatest benefit on hemostatic factors. The Finnish Diabetes Prevention Study found a significant beneficial long-term effect of such an intervention on fibrinolysis, measured by reduced levels of PAI-1, in obese subjects with impaired glucose tolerance (25). Likewise, Lindahl et al. (26) showed that intense behavioral intervention producing significant weight loss also produced significant reductions in PAI-1. Although the intervention subjects also showed declines in tissue plasminogen activator (tPA), these effects were smaller than those on PAI-1, suggesting enhanced fibrinolysis. The Diabetes Prevention Program clinical trial, which studied the effect of an intensive lifestyle intervention or metformin on progression to diabetes in adults with impaired glucose tolerance, found modest but significant reductions in fibrinogen levels in the lifestyle group compared to both metformin and placebo (27).

In a randomized trial of physical activity and a low-fat diet with or without daily fish in type 2 diabetics, Dunstan et al. (28) found some prothrombotic and some antithrombotic effects of the interventions. Interestingly, electroacupuncture, which can induce analgesia and thus decrease

inflammation, has been shown to reduce PAI-1 and fibrinogen levels in women with polycystic ovarian syndrome (29).

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Dietary Patterns

The Dietary Approaches to Stop Hypertension (DASH) diet, characterized by fruits and vegetables, nuts, low-fat dairy, whole grains, and lean meat, has been demonstrated to reduce systemic inflammation in an array of studies (30). In addition, implementation of the low-sodium DASH diet in patients with diabetes for 8 weeks resulted in decreased plasma fibrinogen levels as compared to a standard diabetic diet (31).

Adherence to the Mediterranean diet, which is high in fruits and vegetables, nuts and seeds, as well as high-quality fats, especially olive oil, is associated with lower levels of CRP and fibrinogen (32). Following the Mediterranean style diet versus a high-fat diet for 1 month increased bleeding time, indicating less interaction of platelets with the vascular wall (33). The recent PREDIMED trial demonstrated that following the Mediterranean diet versus a low-fat diet for 1 year led to lower levels of circulating microvesicles (cMV), which are pro-atherothrombotic (34). As reviewed by Delgado-Lista et al., maintaining a basic Mediterranean diet leads to decreased factor VII, tissue factor, PAI-1, and thromboxane levels (35). The Mediterranean diet is rich in mono- and polyunsaturated fatty acids (MUFA and PUFA). The association of these fatty acids with hemostasis, however, remains controversial (discussed later in this chapter).

The association between vegetarianism and hemostasis is inconclusive. Cross-sectional studies have found reduced levels of prothrombotic factors and enhanced fibrinolytic activity in vegetarians compared to nonvegetarians (36–37). However, vegetarian diets, especially vegan diets, are also associated with increased platelet aggregation, an index of thrombosis, which may be explained by lower consumption of marine fish rich in long-chain (LC) n-3 PUFAs, leading to lower platelet levels of LC n-3 PUFA, such as eicosapentaenoic acid (EPA) (38,39). Incorporation of EPA into platelet membranes displaces arachidonic acid, a precursor to the potent platelet aggregator thromboxane A2. Preliminary investigations have begun to identify the antithrombotic potential of specific fruits, vegetables, and other components of diets shown to have overall hemostatic benefit. Tomatoes (40), certain berries (41,42), whole grains (43), and commonly used herbs and spices, such as thyme, rosemary, and cardamom, have shown significant antithrombotic activity in vitro and in vivo (42,44).

Vegetarian diets are associated with reduced cardiovascular risk (see Chapters 7 and 43), as is a Mediterranean pattern characterized by a relatively generous intake of PUFA and MUFA (see Chapters 7 and 45). Thus, whether individual dietary components yield consistently favorable effects on hemostasis is debatable; however, their net effect on overall cardiovascular risk is clearly beneficial.

In addition to obesity and CVD, the impact of diet on inflammation is also seen in deep venous thrombosis (DVT), further evidenced by the occurrence of holiday thrombosis. This phenomenon entails acute thrombosis due to an accumulation of holiday-related factors, such as overindulgence, travel, increased alcohol intake, and emotional stress (45). Patients with DVT are at risk of life-threatening pulmonary embolism, stroke, and other end results of embolic phenomena. As reviewed by Cundiff et al. (46), epidemiological evidence suggests that a diet made up mostly of fruits and vegetables (i.e., Mediterranean diet) rather than meat may significantly reduce the risk of DVT; however, the DASH diet does not appear to affect risk of DVT (47). In 2012, Varraso et al. investigated the impact of diet on the development of DVT among 129,430 US women and men in the Nurses' Health Study and Health Professionals Follow-up Study (48). They found that adherence to a Western diet, and intake of red meat and trans-fatty acids, were associated with an increased risk of DVT in men but not in women, while vitamins E and B6 and fiber were beneficial in preventing DVT. Randomized, controlled, prospective

noninferiority trials are needed to substantiate these claims.

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Alcohol

Light to moderate alcohol intake (1–2 drinks/day for men and 1 drink/day for women) has been shown to lower levels of fibrinogen, activate fibrinolysis through increased tPA, and reduce platelet aggregation over time (49,50). Overall, at a dose of 10 to 30 g/day, alcohol appears to impart greater antithrombotic than prothrombotic effects, accounting for some portion of its association with reduced risk of cardiovascular events (51). However, heavy alcohol consumption (>21 drinks/week) is associated with impaired fibrinolytic potential (49). Moreover, alcoholism, with resultant cirrhosis, is associated with a severe and potentially life-threatening coagulopathy, due to impaired production of vitamin K-dependent clotting factors and other effects.

Whether the effect of alcoholic beverages on hemostasis depends on the type of alcohol consumed is debatable. Tousoulis et al. randomized healthy young individuals to receive equal amounts (30 g) of alcohol as either red wine, white wine, beer, whisky, or water. They found that Von Willebrand factor was only decreased in the beer and red wine groups, suggesting an improvement in endothelial function (52). However, all alcoholic beverages led to similar decreases in collagen-induced platelet aggregation and plasma fibrinogen levels, suggesting that the beneficial effect of moderate alcoholic drink consumption on primary hemostasis is attributed to ethanol rather than other components.

Red wine contains resveratrol, a polyphenolic compound naturally found in certain fruits and nuts, which shows antioxidant (53) and antiplatelet properties (54). A randomized controlled study (RCT) demonstrated that taking a resveratrol-rich grape supplement (resveratrol 8 mg) for 6 months followed by a double dose for the next 6 months in patients undergoing primary prevention for CVD significantly decreased CRP, Tumor Necrosis Factor (TNF)-alpha, PAI-1, and Il-6/Il-10 ratio, and increased Il-10 (antiinflammatory) levels (55). Further, alcohol and resveratrol may act synergistically to mitigate the process of atherosclerosis as well as coagulation (56). However, because red wine typically contains less than 2 mg/L of resveratrol, wine consumption alone cannot safely achieve a clinically relevant daily dose of resveratrol (57).

Dietary Fiber

A higher intake of dietary fiber such as oat husk fiber (58) and guar gum (59) has been associated with reduced PAI (58–60), fibrinogen (61), and CRP levels (63). Increasing dietary fiber intake may also improve fibrinolytic activity by increasing levels of tPA (64). Although Fehily et al. found that adding cereal fiber to diet of healthy adults did not affect fibrinogen levels (65), the majority of evidence supports that dietary fiber correlates inversely with thrombotic tendency. The mechanism by which fiber may influence hemostasis is uncertain and may be confounded by other concomitant changes in the diet such as fat and energy reduction (26). A reduction in visceral adiposity, which is known to be associated with inflammatory mediators, may be the link between fiber and inflammation (see Chapter 6). Emerging evidence suggests that fiber may also interact with the gastrointestinal microbiome to modulate inflammatory response (66).

Fat

High dietary fat intake is associated with relatively high levels of factors VIIc and X, PAI-1, and tPA (4). Increasing fat intake impairs fibrinolytic activity (4). Elevated serum lipids associated with high dietary fat intake may promote thrombosis both directly and indirectly (4). Conversely, lowering fat intake decreases PAI-1 levels (4). However, moderate reduction in fat intake, from 39% to 31%, did not change

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coagulation or fibrinolytic profiles, suggesting substantial reductions may be needed to elicit beneficial effects (67). The influence of dietary fat on hemostasis likely vary with the composition of dietary fat, as well as with its quantity, and may also be determined by certain genetic factors (68). Interestingly, Delgado-Lista et al. demonstrated that irrespective of the type of fat consumed, a single high-fat meal induces a postprandial procoagulant tendency (69). The influence of specific types of fat on coagulation is discussed later.

n-3 Fatty Acids

PUFAs, including n-3 PUFAs, are substrates of COX-1 and 12-lipooxygenase (12-LOX) that produce oxylipins, which regulate platelet function and thrombus formation (70). Animal data suggest that LC n-3 PUFAs reduce platelet aggregation (71,72). However, the evidence in humans remains controversial (73,74) and may be affected by the source and quantity of PUFAs and whether they are consumed in food or dietary supplements.

Plasma n-3 and n-6 fatty acids were independently inversely associated with CRP and fibrinogen, but the ratio of n-6/n-3 fatty acids was positively correlated with the hemostatic and inflammatory biomarkers studied (75). However, whether modifying the n-6/n-3 ratio is meaningful for cardiovascular health is unclear (76). Intakes of both alpha-linolenic acid (ALA) from a plant-based diet and LC n-3 PUFAs like EPA and Docosahexaenoic acid from marine foods are associated with cardioprotective effects in epidemiological studies, as reviewed by Fleming et al. (77). However, there are also exceptions, such as the Coronary Artery Risk Development in Young Adults Study, showing no effects of fish, long-chain PUFAs, or ALA intake on fibrinogen, factor VII, factor VIII, or von Willebrand factor (78). The OPTILIP trial of older adults also found that decreasing the n-6:n-3 ratio to approximately 3:1 through increased intake of EPA and DHA lowered triacylglycerol concentrations but had no significant effect on hemostatic markers (79).

A review of RCTs published through 2005 by Robinson and Stone (80) found no consistent effects of n-3 supplementation on hemostatic parameters; approximately half of 24 trials reviewed demonstrated increased fibrinogen with n-3 supplementation, while the other half showed no effect or reduced levels. Likewise, a recent study measuring the effect of 6-week supplementation with OMACOR® fish oil in 150 patients with peripheral arterial disease receiving aspirin and statin therapy revealed no change in von Willebrand factor, fibrinogen binding, platelet aggregation, or CRP levels (81).

It is possible that effects may vary depending on the composition of the fish oil. Supplementation for 3 months with DHA, a key n-3 PUFA in fish oil, did not appreciably alter hemostatic factors in a group of healthy young adults (82). Further, fibrinogen levels may only be lowered by fish oil if vitamin E is concomitantly administered (83). As reviewed by Thijssen et al., the most consistent finding is the potential beneficial effect of moderate amounts of fish oil on platelet aggregation (84).

A recent meta-analysis of 10 trials involving 77,917 individuals found that EPA and DHA supplementation did not prevent major cardiovascular events and all-cause mortality, negating the benefit of these n-3 PUFAs for primary prevention of CVD (85). However, use of LC n-3 PUFA for clinical treatment of high-risk patients is expected to provide benefit. Taking 4 g of icosapent ethyl in the REDUCE-IT trial reduced the risk of cardiovascular death in statin-treated patients (86). A meta-analysis by Gapinski et al. (87) reported promising effects on clinical end points, including a nearly 14% reduction in the risk of restenosis at 6 months after coronary angioplasty with intake of 4 to 5 g/day of n-3 fatty acids. Studies evaluated by Gapinski et al., such as that of Dehmer et al. (88), demonstrated a benefit of n-3 fatty acid supplementation in conjunction with aspirin use. In the context of coronary stenting and use of GpIIb/IIIa inhibitors, Gajos et al. demonstrated that adding 1 g/day of omega-3 PUFAs to dual

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antiplatelet therapy actually decreases thrombin formation in patients undergoing percutaneous coronary intervention (89). Likewise, giving fish oil to patients with severe congestive heart failure leads to a dose-dependent decrease in platelet activation and antiinflammatory effects evidenced by decreased Il-6 and TNF-alpha levels (90).

Monounsaturated Fatty Acids

Although initial in vitro data suggested MUFA may increase in platelet aggregability (91), more recent clinical trials have found that a high-MUFA diet has beneficial effects on platelet aggregation (92). Sustained MUFA supplementation has also been associated with reduced postprandial activation of factor VII (93–95). In a randomized crossover study examining effects of diets rich in varying compositions of fatty acids, Pacheco et al. (96) observed increases in postprandial concentrations of tissue factor (prothrombotic effect) and PAI-1 (antifibrinolytic effect) when the ratio of oleic to palmitic acid decreased (i.e., MUFA:SFA). The replacement of saturated fats with MUFA yields a graded reduction in the aggregation response of platelets to Adenosine diphosphate, as well as decreased factor VII, tissue factor, PAI-1, and thromboxane levels, suggesting a favorable effect on thrombotic tendency (97). MUFA has also been inversely correlated with inflammatory markers CRP and IL-6 levels (75). A presidential advisory from the American Heart Association concludes that MUFA substitution for saturated fat decreases CVD risk (98).

Saturated Fatty Acids

Inconsistent effects of saturated fatty acids on thrombotic tendency have been observed. Irrespective of the type of fat consumed, fatty meals induce a postprandial procoagulant state, which may be enhanced by increased intake of saturated fatty acids (69). Tholstrup et al. (99) administered meals rich in either stearic or myristic acid to 10 healthy men and found variable effects on thrombotic factors including PAI-1, factor VIIc, and beta-thromboglobulin. Both fatty acids diminished platelet aggregability in the postprandial phase (100). Other studies have reported increased levels of factor VIIc induced by a high saturated fat diet relative to a high monounsaturated fat diet in women (101,102), and Lahoz et al. (103) reported increased thromboxane excretion in association with a high saturated fat test diet. A study on palmitate demonstrated increased levels of the procoagulant molecule, tissue factor, via extracellular release of histone H3 (104). Evidence to date does not strongly support assignation of cardiac risk associated with saturated fat intake to effects on hemostasis, although increased levels of activated factor VII and PAI-1 induced by diets rich in saturated fat may raise the risk of occlusive thrombosis from preexisting unstable atheromatous plaques (51). The chain length of fatty acids may lead to differential influence. LC-saturated fatty acids have been associated with increased platelet aggregation, while short- and medium-chain fatty acids showed a negative correlation (105). C12–C16 saturated fatty acids are considered as major determinants of Factor VII antigen (106).

Antioxidant Vitamins

Animal data suggest that both vitamins E and C can inhibit platelet aggregation and delay thrombus formation (107,108). Serving as antioxidants, vitamins E and C decrease oxidative stress, which is a mediator of endothelial dysfunction. However, investigations into the antithrombotic effects of these antioxidants in humans have had mixed results.

An observational study has demonstrated that vitamin C intake was inversely correlated with CRP and tPA levels (109). A short-term RCT among people with type 2 diabetes demonstrated that 2-g vitamin C supplementation for 4 weeks decreased prothrombotic factors such as tPA and von Willebrand factor

(110). However, other RCTs among healthy and people with type 2 diabetes did not show significant effects of vitamin C on hemostasis (111,112).

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One study of short-term vitamin E supplementation (400 IU/day) in hypercholesterolemic subjects demonstrated reduced platelet aggregation after 6 weeks (113). It has also been shown that 600 mg of vitamin E daily for 2 weeks leads to normalization of 8-iso-PGF2-alpha urinary excretion and decreased thromboxane metabolite excretion (114). Enhanced anticoagulant effect in response to high-dose vitamin E supplementation has been reported in patients taking oral anticoagulants, prompting preliminary investigations into possible antagonistic effects of vitamin E on vitamin K (115). In contrast, a recent trial of vitamin E supplementation in healthy volunteers showed no significant effects on the coagulation profile or platelet aggregation (116). Meta-analysis of vitamin E supplementation also did not support its positive influence on vascular outcome in patients with a low or high risk of vascular accidents (117).

Studies of antioxidant supplements, including vitamins E and C, for cardiac risk reduction have generally been disappointing (see Chapter 7). Most of these studies have used alpha-tocopherols only; further studies of vitamin E supplementation in the form of mixed tocopherols, shown to have greater potency in inhibiting platelet aggregation, may be warranted (118).

Vitamin K

Vitamin K plays a crucial role in hemostasis, as it is required for the formation of clotting factors II, VII, IX, and X, which can be disrupted in fat malabsorption syndromes (such as cystic fibrosis, short gut, celiac disease, and chronic pancreatitis). In addition, neonates are inherently deficient in vitamin K. It is suggested that adaptive hepatic mechanisms are present to compensate for the variable intake of daily phylloquinone. The highest concentrations of vitamin K (400–700 mcg/100 g) are found in green vegetables, but other foods such as fruits and grains contain as low as 1 to 10 mcg/100 g (119). Oral anticoagulant drugs that act as vitamin K antagonists are often prescribed for patients at risk of thromboembolic events to reduce the production rate of clotting factors. Preliminary evidence suggests that dietary vitamin K may interfere with anticoagulation stability in patients on oral anticoagulants (120). High vitamin K diets lead to decreased warfarin sensitivity indices and thus decreased international normalized ratio (INR), which measures bleeding time, leading to higher anticoagulant dosage requirements; however, diets low in vitamin K are more likely to cause unstable anticoagulation than diets higher in the vitamin. Patients receiving warfarin should be advised to keep their dietary intake of vitamin K stable and consider supplementation with 100 to 150 mcg/day, which may even help improve INR stability (119).

Vitamin D

Vitamin D deficiency has adverse effects on hemostasis in both in vitro and animal studies (121). Although the mechanism is not entirely understood, vitamin D may act through the vitamin D receptor (VDR) to regulate expression of genes in the hemostatic and inflammatory pathways (122). Lower serum 25(OH)D levels were correlated with higher tPA, PAI-1, fibrinogen, and D-dimer in clinical studies (123–125). Whether vitamin D supplementation reduces the risk of thrombosis is unclear. Several trials demonstrated that vitamin D supplementation protected against unprovoked venous thromboembolism in women with low vitamin D concentrations (126) and enhanced the anticoagulant effect of warfarin in vitamin D-deficient patients with DVT or pulmonary embolism (127). Vitamin D supplementation also led to lower risk of thrombotic events in patients with prostate cancer (128). However, supplementation with vitamin D for 1 year in obese/overweight subjects did not influence PAI-1 or tPA, despite increases in serum vitamin D levels (129). Vitamin D supplementation also did not affect hemostatic factors in another

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pilot intervention in patients with peripheral artery disease (130). Overall, preventing vitamin D deficiency seems to be critical for hemostasis, yet the effectiveness of vitamin D supplementation for thrombotic risk reduction requires further research.

Flavonoids

Flavonoids, a family of polyphenol compounds found in a variety of foods, including grapes, berries, nuts, and cocoa, have been shown to inhibit platelet aggregation and thrombin activity in vitro (131). Human studies are not yet conclusive but suggest beneficial effects. A randomized, controlled crossover study in 23 patients with coronary artery disease demonstrated that 200 mg of Pycnogenol/day for 8 weeks led to decreased isoprostane levels and improved endothelial function (132). Additionally, Pycnogenol may have protective antithrombotic properties for individuals following a thrombotic event and are synergistic with compression stockings for the prevention of postthrombotic syndrome (133). Another study showed that both in vitro incubation and oral supplementation with purple grape juice reduced platelet aggregation in healthy subjects (134). A small trial by Hermann et al. (135) found flavonoid-containing dark chocolate to induce a rapid, significant improvement of platelet function in smokers, a demographic known to have baseline platelet dysfunction. A critical review of 25 wellcontrolled human intervention studies confirmed the platelet-inhibiting effect of cocoa-related products (136). However, there have also been some contradictory findings (137), including studies examining soy isoflavone phytoestrogens, which found no effect on the hemostatic system (138).

Arginine

Arginine is a precursor in the manufacture of nitric oxide by the vascular endothelium; nitric oxide levels may influence platelet–endothelium interactions. Animal data have been reported suggesting that L-arginine supplementation reduces levels of thromboxane relative to prostacyclin and inhibits platelet aggregation (139). A study on New Zealand white rabbits showed that L-arginine was even more effective than aspirin in reducing platelet aggregation (140). Administration of L-arginine has been shown to inhibit platelet aggregation in healthy human subjects (141); Neri et al. (142) found this effect to be reproducible in pregnant women with normal blood pressure and with chronic hypertension but not in the preeclamptic state. However, an older study of L-arginine supplementation in subjects with hypercholesterolemia showed no favorable effects on levels of endothelin or platelet adhesion molecules (143).

Diet/Drug Interactions

Not only does nutrient intake play a role in disease development and progression, but it also affects pharmacological treatments for CVD.

Aspirin (an acetylated salicylate) has widespread applications and while generally safe in low doses, it does put patients at risk of gastrointestinal bleeding and renal damage. Caffeine increases the rate of appearance, the maximum concentration of salicylate in the blood plasma, and its time to excretion; however, the specific mechanism is unclear (144). Drinking alcohol while taking aspirin may enhance platelet dysfunction and dangerously prolong bleeding time, and significantly increase the risk of gastrointestinal or other bleeding (145,146).

Fluctuations in vitamin K intake lead to variations in the requirement of the antithrombotic medication warfarin, as mentioned earlier in this chapter. Common herbs also affect vitamin K metabolism, including biliberry, bromelain, danshen, dong quai, feverfew, garlic, ginger, gingko biloba, ginseng, horse chestnut, meadowsweet, St John’s wort, turmeric, and willow. It is thus recommended to maintain a stable diet

while on antithrombotic medications, especially if taking warfarin over the long term.

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Nutrigenetics

Developments in nutrigenetics provide the opportunity to use nutriceuticals to prevent and manage thrombosis in people with inherited mutations in genes associated with hemostatic abnormalities (147). The R353Q genetic polymorphism in the *FVII* gene is one of the most studied. People with the R allele demonstrated greater concentrations of FVII Ag after a saturated fat-rich diet (148), and the RR homozygotes had stronger inverse correlation between fiber intake and FVII:C (149). However, there were also studies that did not find a difference between these genotypes (150,151). Other genetic polymorphisms can modify the dietary influence on hemostasis as well. For example, the methylene tetrahydrofolate reductase (MTHFR) enzyme converts methylenetetrahydrofolate to 5-methyltetrahydrofolate, the form of folate that provides a methyl group for the conversion of homocysteine to methionine. Two known single nucleotide polymorphisms (C677T and A1298C) on this gene cause reduced MTHFR enzyme activity, resulting in hyperhomocysteinemia, which is a prothrombotic condition. Folic acid supplementation can effectively prevent and treat homocysteinemia in these individuals (147). A recent study in adults with hypertension in China provides some evidence that folic acid supplementation can significantly reduce stroke risk in individuals with elevated homocysteine (152).

Microbiome

Increasing evidence suggests that the intestinal microbiome plays an important role in hemostasis. Microbiome alterations are related to increased susceptibility to thrombosis in both animals and humans (153). Fecal microbiota transplant (FMT) from healthy donors to 35 patients with metabolic syndrome prolonged the thrombinography lag time after 6 weeks, suggestive of modest suppression of thrombin generation (153). How the gut microbes mediate hemostasis is not well understood. One theory suggests that gastrointestinal microbial metabolites such as trimethylamine Noxide (TMAO) may trigger prothrombotic platelet function and promote arterial thrombus growth (154). TMAO can be derived from the microbial metabolism of choline and carnitine. Both antibiotic treatment and a choline-deficient diet can prevent some of the TMAO-related thrombotic abnormalities in mice. However, whether inhibiting the TMAO synthesis in humans is fruitful for human disease risk reduction is uncertain. Administration of probiotics to mouse models of acute and chronic colitis attenuated thrombogenesis and inflammation (155). Future research on the microbiome will likely yield new therapeutic possibilities for diseases related to dysregulated hemostasis.

CLINICAL HIGHLIGHTS

Hemostatic factors, such as fibrinogen, PAI-1, and factor VIIc, are strongly associated with the risk of cardiovascular events (156,157). Evidence from a variety of sources indicates that dietary pattern may play an important role in influencing hemostasis. However, due in part to the wide range of circulating factors involved in hemostatic mechanisms and in part to the difficulties of controlled dietary interventions, little is known with certainty about the effects of specific foods or nutrients on overall thrombotic tendency (158). Evidence available to date suggests that dietary recommendations to reduce risk of thromboembolic disease are consistent with recommendations to lower risk of CVD. Protective factors include the avoidance of excess energy intake and obesity; the avoidance of excess fat consumption; physical activity; abundant dietary fiber, especially soluble fiber; moderate alcohol consumption; sufficient n-3 fatty acids; and micronutrients such as vitamins C, D, and E (158). A shift of

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calories from saturated fats to unsaturated fats and increased intake of fruits, vegetables, and concentrated sources of flavonoids such as cocoa, berries, and green tea all conform with the weight of evidence, although definitive knowledge of hemostatic effects is lacking in each case. Weight loss in obese patients may be of particular importance. Before definitive dietary recommendations can be offered to modify hemostasis for clinical benefit, observational and ideally interventional studies of diet and clinically important thrombotic events rather than surrogate markers will be needed. Careful monitoring prior to anticoagulation therapy may be indicated for patients on ketogenic diets (159), as well as those with high dietary consumption or supplementation of vitamin K or n-3 fatty acids. Microbiome, nutrigenetics, and nutrigenomics highlight the future direction of precision nutrition for hemostatic management.

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Chapter 10

Diet and Cerebrovascular and Peripheral Vascular Disease

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INTRODUCTION

Stroke is the fifth leading cause of death in the United States, just behind heart disease, cancer, unintentional injuries, and chronic lower respiratory diseases and accounts for approximately 148,000 deaths annually (1). Most strokes are the result of thromboembolic events and are associated with atherosclerotic vascular disease. Peripheral vascular disease is the result of systemic atherogenesis and is associated with the same predisposing factors as coronary atherosclerosis. Therefore, dietary recommendations for the prevention and modification of cardiovascular risk generally are pertinent for peripheral vascular disease and stroke risk reduction as well. However, some evidence shows that dietary fat restriction may be associated with increased stroke risk and suggests a possible disparity in the optimal dietary interventions for the two conditions. The weight of evidence would still favor fat restriction, and particularly saturated/transfat restriction, below levels currently prevailing in the United States. The leading modifiable risk factor for stroke is hypertension, which is amenable to dietary prevention and management, as described in Chapter 8. Approximately 87% of all strokes are ischemic, and the prevention of ischemic heart disease might most effectively eliminate events in this category. Approximately 10% of all strokes are hemorrhagic (2–5). Evidence from the 1950s to 1970s suggested that the incidence of hemorrhagic stroke was elevated in Inuit populations with high intake of marine oils rich in n-3 fatty acids (6,7). The hypothesis was that the risk of intracranial hemorrhage may be elevated by excessive intake of platelet-inhibiting nutrients and gave rise to the idea that n-3 fatty acids in lower doses may improve cardiovascular health. A recent study among the Inupiak in Alaska found that palmitic and myristic acids were adversely associated with most CVD risk factors, whereas marine n-3 fatty acids were beneficially associated with CVD risk factors (8). However, as indigenous populations have experienced the effect of the global nutrition transition, more recent studies among Inuit peoples in Greenland and First Nations and Alaska Native populations in North America show a similar risk of ischemic and hemorrhagic stroke compared to white populations (8–11). The overall evidence that stroke can be prevented by dietary means is compelling, but the understanding of the exact mechanisms and definitive intervention studies are still limited (12).

OVERVIEW

Diet

The risk of stroke is strongly correlated with both systolic and diastolic blood pressure, and advances in the pharmacologic management of hypertension are thought to be the principal explanation for declining stroke incidence and mortality over recent decades. Nonetheless, stroke remains the fifth leading cause of

death and a leading cause of long-term disability among adults in the United States (1,13).

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Elevated levels of total cholesterol, low-density lipoprotein (LDL), triglycerides, and very low-density lipoprotein, as well as depressed levels of high-density lipoprotein (HDL), are linked with atherosclerotic heart disease. Atherosclerosis is known to be a systemic disease, and the same lipid patterns are inferentially linked to cerebrovascular disease (14). A case-controlled study by Hachinski et al. (15) showed total cholesterol, LDL, and triglyceride levels to be significantly higher and HDL to be significantly lower among subjects with thromboembolic stroke compared to matched controls. The Women's Health Study with 27,937 US women aged ≥45 years showed that total cholesterol, LDL-C, total cholesterol to HDL-C ratio, and non-HDL-C remained significantly associated with increased risk of ischemic stroke (14) By contrast, Nagaraj et al. reported no difference in the serum lipid profiles between controls and patients with thrombotic stroke (16). A recent large-scale prospective population-based study demonstrated increased rates of ischemic stroke among men and women with low HDL levels (17). Among adults with diabetes, both elevated TG and low HDL-C are associated with increased risks of stroke (18).

Reduction of cholesterol levels in high-risk patients has been shown to reduce significantly the incidence of stroke (19). Whereas most trials have used pharmacotherapy, namely, statin drugs, for lipid reduction, the achievement of lipid reduction by dietary means is thought to confer similar benefit. The possibility that statin-related stroke risk reduction is due to effects other than lipid lowering complicates inferences about diet, serum lipids, and stroke risk (20). Lifestyle intervention to reduce cholesterol would also induce diverse effects, however (see Chapter 45), and thus might lower stroke by other means as well. Additionally, although statins are commonly used and well-tolerated medications, a recent meta-analysis reviewed 20 statin trials with more than 200,000 participants and determined that statin therapy is associated with a 44% increased risk of incident diabetes. However, other meta-analyses have shown a reduction in all-cause mortality and a 22%–25% reduction in stroke risk for each 40 mg/dL reduction of LDL-cholesterol with statin use (19,21).

Dietary patterns associated with optimal lipid profiles are described in detail in Chapters 7 and 45. In general, restriction of energy from saturated fat to less than 7% of total calories and energy from trans fat to less than 1% of total calories (22); a substitution of healthful unsaturated oils from nuts, seeds, olives, and avocado; an abundant intake of fruits, vegetables, and whole grains; regular consumption of fish, beans, and lentils; and moderate intake of lean meats would be indicated. Plant-based diets have been shown to confer a significant reduction in lipid levels when compared with diets that include animal products. A systematic review and meta-analysis showed that vegan and vegetarian diets are associated with lower mean concentration of total cholesterol and LDL, as well as a decrease in HDL but with no significant effect in triglyceride levels. Vegan diets were associated with larger LDL-C reductions than lacto-ovo vegetarian diets (23).

Cholesterol is exclusively found in animal-based products; however, it is likely that the benefit from a plant-based diet is due to a reduction in saturated fats rather than a reduction in dietary cholesterol. Recent systematic reviews have shown that the consumption of dietary cholesterol is not associated with serum lipid profiles and the risk of cardiovascular disease (24,25). The 2015–2020 *Dietary Guidelines for Americans* (DGA) removed the recommendations for restricting dietary cholesterol (26). It is important to note that foods from four-legged animals that are rich in cholesterol are also high in saturated fatty acids and therefore may increase the risk of CVD. Although high in cholesterol, shellfish and eggs do not contribute to serum cholesterol (24,27,28). Intervention studies have found no significant effect of egg consumption on markers for CVD risk (25,29).

There is a comprehensive body of evidence demonstrating the benefits of the Mediterranean diet on

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cardiovascular health (30). The Mediterranean diet has been shown to be significantly associated with lower risk of coronary heart disease and decreased stroke risk in epidemiological studies and randomized controlled trials (30). The Mediterranean diet consists of abundant intake of fresh vegetables, fruits, legumes, olive oil, and nuts and minimally refined cereals. Protein sources include moderate amounts of fish, shellfish, and poultry; moderate amounts of cheese and fermented dairy products; low amounts of red meat and processed foods; and moderate amounts of red wine with meals (31,32). A recent multicenter randomized trial compared cardiovascular end points in participants at high cardiovascular risk on two versions of the Mediterranean diet (one with olive oil supplementation and one with nuts) with a control low-fat diet (33). There was a significant risk reduction for major cardiovascular events in the Mediterranean diet groups relative to the control group (olive oil group: HR, 0.69; 95% CI, 0.53–0.91; nuts group: HR, 0.72; 95% CI, 0.54–0.95) (33).

Recommendations for cardiovascular disease prevention include restriction of saturated fat to less than 10% of total calories, avoidance of trans fat, with 15% of calories from monounsaturated fatty acids, and 10% to 15% from polyunsaturated fatty acids. The ratio of n-3 to n-6 polyunsaturated should be between 1:1 and 1:4 (see Chapters 2, 7, 44, and 45), achieved by including fish, seafood, and flaxseed in the diet routinely and/or taking a fish oil supplement. However, the diet recommendations regarding saturated fat have been challenged (34,35). Saturated fats are often lumped together as one group but should be considered as a diverse class of compounds (36,37). Stearic acid, found in dark chocolate, and lauric acid, found in coconut oil, have been hailed as healthy foods (28). However, other saturated fatty acids also found in coconut oil, such as palmitic and myristic acid, have been shown to be associated with inflammation and atherogenesis (38). A recent systematic review and meta-analysis of clinical trials found that in comparison to other plant oils (e.g., corn, soy peanut, and palm oil), coconut oil increased total cholesterol by 15–26 mg/dL, increased LDL by 10.5 mg/dL, and increased HDL by 4 mg/dL (35). Additional evidence suggests that coconut oil results in poorer lipid profiles than polyunsaturated fats, although it may be less atherogenic than saturated fats from dairy and beef (39).

The relationship between fat intake and stroke risk may be less clear. An observational study by Gillman et al. (40) followed 832 men in the Framingham cohort over 20 years for incident strokes. Dietary intake was assessed using a single 24-hour recall at baseline. Total intake of fat, saturated fat, and monounsaturated fat was negatively associated with stroke risk. The reliability of dietary intake assessment in this study is suspect, as is the control of confounders. Nevertheless, these results have been reproduced by subsequent epidemiological investigations (41,42), which have found inverse associations between intake of animal fat and risk of stroke. Recent diet intervention studies have also found no difference or higher adjusted stroke mortality in subjects advised to eat lower fat diets (43). A recent meta-analysis of 14 prospective cohort studies demonstrated that higher dietary saturated fatty acid intake is associated with a decreased risk for stroke (RR, 0.87; 95% CI, 0.78 to 0.96). In addition they found a linear relationship between saturated fatty acids and stroke, where the pooled risk of stroke decreased by 6% per 10 g/day increase in saturated fatty acid intake (44). These findings are certainly provocative and suggest a need for more research but should not, on their own, refute the weight of evidence favoring restriction of potentially atherogenic fat for health promotion.

Tobacco, a sedentary lifestyle, and obesity (45–47) have all been shown to contribute to stroke risk. In 2010, the American Heart Association proposed the Life's Simple 7 Score (LS7) to define optimal behavioral and clinical cardiovascular risk factors (48). In a national population-based US cohort study with 22,914 subjects, the score provided 2 points for ideal, 1 point for intermediate, and 0 points for poor level of each of the seven behaviors: smoking, diet, physical activity, BMI, blood pressure, total cholesterol, and fasting glucose. Each 1-point increase in LS7 score (0–14) was associated with an 8%

lower risk of stroke (49).
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Hypertension is the single most important modifiable risk factor for stroke, and improved detection and treatment of hypertension is thought to be the principal explanation for declining rates of cerebrovascular disease (5,50). The primary prevention of hypertension is often feasible, with diet playing a major role (see Chapter 8). The consistent prevention of hypertension by dietary means would almost certainly result in the prevention of cerebrovascular events as well (20).

Recent reports have demonstrated that stroke incidence in younger adults has been increasing (51), possibly secondary to increasing obesity in children and adolescents. A recent retrospective population-based study also demonstrated rising rates of acute ischemic stroke in adolescents and young adults (aged 15 to 44), along with a concurrent increase in the prevalence of hypertension, diabetes, obesity, and tobacco use in that age group. A meta-analysis of prospective studies demonstrated that overweight and obesity in young adulthood were independently associated with increased risk of ischemic stroke (RR, 1.40; 95% CI, 1.24 to 1.58) and (RR, 1.78; 95% CI, 1.03 to 3.16), respectively, and similar increased risk for hemorrhagic stroke was observed (52).

Type 2 diabetes mellitus is a strong predictor of cardiovascular disease and appears to be an independent risk factor for stroke (53). HbA1c levels and smoking appear to be associated with increased risk for first stroke among diabetics (54). As with nondiabetics, tight blood pressure control significantly reduces stroke incidence (55,56).

Consumption of dietary fiber via whole grains has been shown to predict lower risk of total and ischemic stroke (57,58); influence of glycemic load on serum lipids, glucose levels, and insulin sensitivity may play a role in this association. Studies funded by Quaker Oats Company have shown that oat consumption lowers blood pressure (59–61), although this has been challenged (62). In a recent systematic review, examining the evidence for a cardioprotective effect of whole grain, cereal fiber, and bran were associated with lower risk of various CVD-related risk factors and outcomes (63).

The hypothesis that antioxidant nutrients may prevent stroke was tested in the Chicago Western Electric Study. A total of 1,843 men contributed to 46,102 person-years of observation, during which 222 incident strokes occurred (64). Although reported intakes of beta-carotene and vitamin C were inversely associated with stroke risk, the relationships did not achieve statistical significance. Subsequent studies of antioxidant supplementation have been inconclusive to date, although diets rich in foods containing such micronutrients have shown strong evidence of benefit (65–67). A recent systematic review and dose-response meta-analysis found an inverse association between milk consumption and stroke risk (68). The authors suggest that milk consumption might reduce stroke risk due to the high calcium content contributing to risk reduction.

The importance of adequate micronutrient intake to stroke prevention is supported by data from the Linxian Nutrition Intervention Trial. Subjects from a rural Chinese population with a micronutrient-poor diet had reduced rates of hypertension and stroke when given a multivitamin/multimineral supplement rather than placebo; the effect was more pronounced in men than in women (69). A recent systematic review found some evidence of blood pressure–lowering effect of vitamin and mineral supplementation but that the lowering effect was likely too small to prevent future hypertension effectively (70).

Population data have shown consistently that fruit and vegetable consumption is associated with reduced stroke risk (66,67,71–73). A recent review by Hu et al. (74) used subgroup analysis to demonstrate that the risk of stroke decreased by 32% (RR, 0.68; 95% CI, 0.56 to 0.82) and 11% (RR, 0.89; 95% CI, 0.81 to 0.98) for every 200 g/day increment in fruit and vegetables, respectively. Data from the Zutphen study were used to determine the role of specific micronutrients in this association (75). A total of 42 strokes occurred among 552 men followed for 15 years. Dietary histories were obtained at

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three times, after 5-year intervals. A strong and statistically significant relationship between flavonoid intake, particularly quercetin from black tea, and reduced stroke risk was reported (RR, 0.27 by quartile; 95% CI, 0.11 to 0.7). A weaker, inverse association with stroke risk was observed for carotenoids. Data extracted from a cohort of young adults in Spain suggest that high fruit consumption, whole-grain consumption, or consumption of at least 1 serving/week of cruciferous vegetables may be protective against CVD in young Mediterranean populations (76).

Partial substitution of protein for carbohydrates in a balanced diet has been shown to improve blood pressure and lipid profiles and decrease cardiovascular risk (77,78). However, the source of the protein may have a strong influence on stroke risk. With respect to coronary heart disease, red meat and high-fat dairy products have been associated with increased risk, while nuts, fish, and poultry protein sources were associated with a lower risk (79). A recent prospective study of men and women observed that both unprocessed and processed red meat was linked to a higher risk of stroke (80). In comparison to a serving of red meat, a serving per day of poultry, nuts, fish, low-fat dairy, and whole-fat dairy were associated with 27%, 17%, 11%, and 10% lower risk of stroke, respectively.

Fish consumption is associated with reduced risk of cardiovascular disease (81,82). The association between stroke and fish consumption was assessed in the Chicago Western Electric Study. Among 1,847 men followed for 30 years, stroke incidence was highest among subjects in the highest quartile of fish intake (83), thus failing to suggest any benefit. However, the accumulating prospective studies investigating associations between fish intake and risk of stroke have generally found significant inverse associations (84–86). A meta-analysis found that eating fish 3 times a week was associated with a 6% decrease in total stroke, and a subanalysis of studies with stroke subtypes demonstrated a 10% reduction in both ischemic and hemorrhagic strokes (87). An 18-year prospective cohort study with 34,033 Dutch participants found that eating ≥1 portion/week of either lean fish (HR, 0.70; 95% CI, 0.57 to 0.86) or fatty fish (HR, 0.63; 95% CI, 0.39 to 1.02) was associated with lower incidence of ischemic stroke (84).

In addition to its role in stroke prevention, diet may play a role in recovery. Evidence suggests that a large proportion of patients with acute stroke have preexisting malnutrition or develop malnutrition within 1 week after the event (88). Protein-energy malnutrition in this group significantly predicts poor outcome, including death (89). Dietary interventions to build and maintain lean body mass may offer benefit; dietary consultation is generally warranted.

Although stroke can be prevented by the pharmacologic treatment of hypertension, projections from Framingham, National Health and Nutrition Examination Survey (NHANES), and other cohort study data suggest that a population-based approach would confer additional benefits (50,90). Modeling by Cook et al. (91) suggests that a reduction of 2 mm Hg in the mean population diastolic blood pressure achieved through lifestyle modification could prevent 67,000 cardiovascular events and 34,000 strokes annually in the 35- to 64-year-old age group. In 2017, the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines issued new hypertension guidelines that lower the definition of high blood pressure (92). Those changes could have implications for future detection, prevention, management, and treatment of high blood pressure (see Chapter 8). Direct linear relationships between body weight and sodium consumption account for age-related increase in blood pressure (93). In contrast, an inverse dose–response relationship between potassium intake and stroke risk shows that a potassium intake of 90 mmol (≈3,500 mg)/day is associated with the lowest risk of stroke (94). Non-pharmacologic and behavioral recommendations included maintenance of healthy weight or weight loss, physical activity, lowering of dietary sodium, increasing dietary potassium from fruits and vegetables, and moderate alcohol consumption (92–94). Adherence to the so-called Mediterranean diet, rich in fruits and vegetables, fatty fish, and whole grains, has been associated with reduced risk of total and ischemic

stroke (30).
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Alcohol taken in low doses may protect against cerebrovascular disease, whereas higher intakes appear to increase risk (95). Wine may offer increased protection over other alcohol types (96). Modest alcohol intake—approximately 15 to 30 g/day of ethanol, or the equivalent of two drinks—may independently of other behaviors reduce the risk of atherosclerosis in the carotid arteries (97) (see Chapter 40). However, alcohol consumption increases the risk of hemorrhagic stroke in a dose-dependent manner (98).

Moderate coffee, tea, and cocoa consumption has been shown to be correlated with a lower risk of stroke (99). A recent large prospective study in Japan observed that coffee and green tea consumption was associated with an inverse risk of cerebrovascular disease and stroke (100). Other smaller prospective studies have demonstrated that consumption of coffee and tea may reduce the risk of ischemic stroke in male smokers (99,101) and both ischemic stroke and subarachnoid hemorrhage in women (102).

Physical activity appears to protect against both incident stroke and the degree of functional disability resulting from stroke (103). Moderate and high levels of activity are associated with reduced risk of total, ischemic, and hemorrhagic strokes (104). Exercise contributes directly to blood pressure control, produces favorable influences on both serum lipids and glucose, and helps control body weight, all of which may influence stroke risk.

Elevated homocysteine levels have been associated with cardiovascular disease and, to a lesser extent, cerebrovascular disease (105–107). There has been some evidence linking reduction of homocysteine with reduced carotid intimal thickness (108). A diet rich in B vitamins and folate, or a supplement containing these nutrients, may confer some protection against stroke in vulnerable individuals (109). Recent prospective trials have demonstrated, however, that while B vitamin supplementation lowers homocysteine, there is no clear evidence of protection against cardiovascular or cerebrovascular events; an adverse influence is even a possibility (110,111). Despite these data, the relatively high prevalence of vitamin B_{12} deficiency in the population at risk for ischemic stroke suggests that additional supplement trials may be warranted (112).

Magnesium supplementation, particularly in magnesium-deficient individuals, may mitigate stroke risk by inhibiting spasm of intracranial vessels. A prospective study evaluating the relationship between dietary magnesium intake (comparing highest and lowest quintiles of magnesium intake) and cardiovascular disease demonstrated an inverse relationship between dietary magnesium intake and mortality from hemorrhagic strokes in men (HR, 0.68; 95% CI, 0.48 to 0.96) and from total (HR, 0.47; 95% CI, 0.29 to 0.77) and ischemic strokes in women (HR, 0.50; 95% CI, 0.30 to 0.84) (113).

Higher sodium intake is associated with hypertension and increased cardiovascular morbidity and mortality (see Chapter 8). The CDC's Sodium Reduction in Communities Program estimates that reducing daily sodium intake to the recommended 2,300 mg/day could save between 280,000 and 500,000 lives and nearly $100 billion in healthcare costs over 10 years (114,115). A meta-analysis reported that each increment of just 1 g/day salt intake was associated with a 6% greater risk of stroke (RR, 1.06; 95% CI, 1.02 to 1.10) (116). Studies have shown that a reduction in salt intake is a cost-effective public health measure, with a significant impact on morbidity and mortality (117). However, several studies have suggested that there are potential harms associated with too little sodium intake in normotensive populations (118). An observational study of over 133,118 patients used salt excretion as a proxy for salt intake and determined that there was J-shaped association between sodium excretion and cardiovascular events. Among patients with hypertension, sodium excretion of >7 g/day and <3 g/day were both associated with increased risk of death and major cardiovascular disease events (118).

Peripheral Vascular Disease

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Peripheral vascular disease is the result of systemic atherosclerosis and shares risk factors with coronary and cerebrovascular disease. Dietary interventions to modify coronary artery disease risk, described in Chapter 7, should be applied in peripheral arterial disease as well. There is evidence that clinicians tend to modify risk factors less aggressively in peripheral than in coronary arterial disease (119). As in patients with stroke, malnutrition is common in people with peripheral vascular disease and may lead to poorer outcomes (88). Peripheral vascular disease is associated with elevated plasma homocysteine and, therefore, may be amenable to intervention with B vitamin and folate supplementation in certain patients (105,106), although as noted, vascular benefit of homocysteine lowering is increasingly uncertain. As is the case for atherosclerotic disease in general, dietary modification of risk factors should be coupled to other lifestyle interventions, such as smoking cessation and increased physical activity, as well as all indicated pharmacologic interventions (48,120). A trial found that 1 year of daily supplementation with n-3 fatty acids, oleic acid, and vitamins B_6 and E significantly ameliorated peripheral vascular disease (121).

Plasma levels of n-3 fatty acids have been reported to correlate inversely with risk of peripheral vascular disease, and evidence from prospective trials to date is promising but inconclusive (122,123). A strong positive association between smoking and peripheral vascular disease has been consistently reported (124). Elevated postprandial insulin and dyslipidemia associated with insulin resistance also appear to contribute to risk, suggesting that dietary intervention to improve glycemic control (see Chapter 6) may play a role in the prevention and control of peripheral vascular disease (125,126).

NUTRIENTS, NUTRICEUTICALS, AND FUNCTIONAL FOODS

Nutrients and nutriceuticals pertinent to the prevention or management of atherosclerosis and dyslipidemias are discussed in Chapter 7, those related to the control of hypertension in Chapter 8, and those related to control of insulin levels in Chapter 6. Evidence is generally insufficient to characterize the role of single nutrients in the prevention or amelioration of cerebrovascular or peripheral vascular disease independent of these effects. The literature offers some support for seafood consumption, fish oil, and algae supplementation (12,127–129). Intravenous magnesium as a therapy in acute stroke is a topic of an ongoing investigation. A recent meta-analysis found some improved global outcome among patients with ischemic stroke only (130) but is not yet referable to standard care. An association between low levels of vitamin D in circulation and increased stroke risk has been observed, but implications for risk reduction are as yet speculative (131,132). Studies of vitamin E supplementation have demonstrated no significant clinical benefit to using vitamin E for stroke prevention (133,134).

An evolving area of discussion is how the interaction between genetic variation and dietary intake impacts the development of cerebrovascular disease. The gene coding for apolipoprotein A-I (apo A-I), a component of HDL, is highly variable, and a particular single nucleotide polymorphism in its promoter region (−75 G>A) results in a rare *A* allele that has been associated with increased apo A-I concentrations (135–137). A study of 755 men and 822 women demonstrated that higher dietary intake of polyunsaturated fatty acids was associated with higher HDL concentration in women who had the *A* allele, but the inverse effect was seen in women who had the *G* allele. This effect was not seen in men with either allele (136–138). Polyunsaturated fatty acids are also thought to interact with genetic polymorphisms in the peroxisome proliferator-activated receptor alpha-family (Leu162Val). For both men

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and women, those with the *V162* allele experienced decreased fasting triglyceride concentrations with increased polyunsaturated fatty acid intake, while those with the L162 allele did not experience any association between polyunsaturated fatty acid intake and fasting triglyceride levels (138). Nutrigenomic considerations in cerebrovascular disease is an evolving field, and further research is needed in order to be able to provide dietary recommendations based on genotype (136).

Dietary compounds can also interact with pharmacotherapy. Statins, other than pravastatin, are metabolized via cytochrome P-450, so the consumption of grapefruit juice may inhibit cytochrome P-450 and reduce the metabolism of many statins (139). Additionally, research suggests that oils rich in polyunsaturated fats could interact with statins and lead to greater protective effects than either alone (140). A small study demonstrated that patients on statins who consumed olive oil rather than sunflower oil had improved lipid profiles (141).

CLINICAL HIGHLIGHTS

The predominant risk factor for stroke is hypertension, which can be prevented and modified by dietary interventions (see Chapter 8). Additional risk may be conferred by low dietary intake of n-3 fatty acids, obesity, hyperinsulinemia, hyperlipidemia, micronutrient deficiencies, and elevated plasma homocysteine. The possibility exists that excessive fat restriction may increase stroke risk, although the data are not definitive. Certain factors that reduce the risk of thromboembolic stroke, such as platelet-inhibiting nutrients—notably fish oil—may increase the risk of hemorrhagic stroke in a dose-dependent manner.

Dietary recommendations for prevention of stroke and peripheral vascular disease parallel recommendations for general health promotion. Dietary cholesterol is not associated with serum lipid profiles, but a plant-based diet has been shown to confer a reduction in lipid levels. Total dietary fat intake should be moderate (approximately 25% to 30% of total calories), with a preponderance of monounsaturated and polyunsaturated fatty acids. The possibility exists that saturated fat consumption may not be associated with increased stroke risk.

Consumption of fish and the use of flaxseed oil to increase the proportion of n-3 fatty acids in the diet appear safe and reasonable in efforts to prevent stroke and peripheral vascular disease, although risk of hemorrhage is raised if consumption is extreme. Fish oil, which provides eicosapentaenoic acid and docosahexaenoic acid, provides more certain benefit than flaxseed, which provides alpha-linolenic acid. Supplemental fish oil at a dose of 1 to 2 g/day is reasonable for most patients, barring intolerance or contraindications (e.g., hypersensitivity, coagulopathy).

A variety of fruits and vegetables may provide all needed micronutrients, but a multivitamin/multimineral supplement is a reasonable precaution against isolated, subclinical deficiencies, the most pertinent of which are apt to be B vitamins, vitamin D, and folate. Definitive evidence of benefit is lacking. Dietary sodium restriction and generous intake of potassium, magnesium, and calcium may lower blood pressure. Regular physical activity and smoking cessation are essential elements in lifestyle management of risk for both stroke and peripheral vascular disease. Alcohol intake should not exceed the range consistent with health promotion (i.e., 15 to 30 g/day of ethanol) and at this dose may confer benefit (see Chapter 40). The value of micronutrient supplements in megadoses for the prevention or modification of either stroke or peripheral vascular disease is unsubstantiated at present, although investigation of various nutrients (e.g., magnesium, vitamin D, vitamin E, flavonoids, L-arginine) is ongoing, and thus recommendations in this area will evolve.

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Chapter 11

Diet and Immunity

May May Leung and and Elizabeth Eilender

INTRODUCTION

The overall function of the immune system is to prevent or limit infection. Physical barriers—skin and mucous membranes—serve the purpose of delimiting exposure to foreign materials and thus comprise important constituents of immunity. To the extent that nutrition influences the structure and function of such barriers, see Chapters 18, 22, and 23 for gastrointestinal (GI) tract, skin, and wound healing, respectively. However, when immunity is discussed, it is most often the actions of the antibody and cell-mediated systems in defense of the body against microbial and toxic invasions that are implied.

The immune system is a complex system that protects one's body from countless pathogenic microbes. It comprises two kinds of response mechanisms: the innate and the adaptive response. The innate response is an immediate first response to an invading pathogen and usually less effective than the adaptive response. Cells of the innate immune response include phagocytes (such as macrophages and monocytes), neutrophils, dendritic cells, eosinophils, and others.

The adaptive immune response is more effective as it has the ability to specifically recognize a pathogen and recognize it if exposed to it again, even years after initial exposure. As memory cells, if they encounter antigens again, they can respond efficiently and effectively by releasing a rapid, pathogen-specific immune response. Because the immune system is capable of destroying a broad spectrum of microbial cells and clearing a range of both toxic and allergenic substances, it is critical that the immune response be able to recognize and differentiate between self and non-self entities. This is crucial so that the body does not release destructive mechanisms against one's own tissues. Mistakes in such differentiation can be made as not all immune responses are salutary. Atopy and autoimmune diseases represent aspects of the immune function, albeit undesirable ones (see Chapters 20 and 24).

T cells (or lymphocytes) play a critical role in recognizing antigens and coordinating the immune response. There are various T cell subtypes that coordinate different types of immune responses. In general, they are divided into the cytotoxic T cells, which bear the CD8 receptor ($CD8^+$ T cells) and the T helper (Th) cells, which bear the CD4 receptor ($CD4^+$ T cells). The cytotoxic T cells are involved in direct destruction of tumor cells and host cells infected with pathogens, while the Th cells play a crucial role in coordinating the responses of other immune cells.

The other lymphocytes of the adaptive immune system are the B cells, which are responsible for antibody or immunoglobulin (Ig) production. Like T cells, B cells respond specifically to an antigen. They can differentiate into plasma cells, which produce one of five classes of immunoglobulins (Ig)—IgM, IgD, IgG, IgA, and IgE. Igs are pathogen-specific molecules, which help the adaptive immune system not only to recognize but also to destroy invasive pathogens. Each class of Ig has a specialized role. For example, at the mucosal surface, IgA is the first line of defense as it inhibits bacterial and viral adhesion to epithelial cells.

Optimal immune response depends on an adequate diet and nutrient balance as after immune cell

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activation, metabolic needs are met by increased utilization of glucose, amino acids, and fatty acids (FAs). Also, specific nutrients play a role in the rate limiting production of immune system components. This chapter highlights the importance of optimal nutrient status to support the functions of the immune system.

OVERVIEW

Diet

Diet is an important modulator of the immune system. Overnutrition may lead to chronic inflammation and increased risk of immune disorders (1,2). In fact, obesity and over nutrition are strongly associated with greater risk for numerous chronic diseases that have chronic systemic inflammation as an underlying feature, including cardiovascular disease, stroke, type 2 diabetes mellitus (T2DM), asthma, cancer, and chronic liver disease (3,4). The Western diet, which consists of foods high in sugar and trans and saturated fats and low in complex carbohydrates, fiber, micronutrients, polyphenols, and omega-3 FAs, is a well-known risk factor (5,6). Specifically, obesity has been shown to impair immune function through alteration of inflammatory mediators and the subsequent derangement of leukocyte counts and the cell-mediated immune response (7). Meanwhile, excess intake of dietary fat may interfere with reticuloendothelial system function, which is the system of phagocytic cells involved in the immune response. Phagocyte function is impaired by hyperglycemia in diabetes; however, the role of dietary sugar in nondiabetics is less clear.

Undernutrition, whether due to food shortages, famines, or a result of malnutrition from prolonged hospitalizations, is well understood to impair immune function and increase mortality due to severe infections (8). Malnutrition during gestation apparently can result in prolonged immunocompromised system even if the diet is adequate during the neonatal period. Low birth weight is associated with impaired development of the spleen and thymus and possibly impaired placental transfer of maternal IgG (see Chapter 26).

Protein-energy undernutrition, which is the most fatal form of malnutrition in developing countries, increases susceptibility to multiple infectious diseases (9,10) through the suppression of Th cells, while T-suppressor cells are spared or even generated at an increased rate. One study testing the impact of protein-energy malnutrition on immunity and influenza found that mice fed a very low protein (VLP) diet, comprising 2% protein, displayed more severe disease following influenza infection (11). Furthermore, mice maintained on a VLP diet showed lower virus-specific antibody response and a reduction in influenza-specific $CD8^+$ T cells compared to mice fed an adequate protein (AP) diet, comprising 18% protein. Notably, switching diets (from VLP to AP) resulted in improved virus clearance, as well as protective immunity. While these findings were observed in mice, they nonetheless underscore the benefit of a nutritional intervention for addressing influenza (and potentially other viruses) in certain malnourished populations. However, some authorities have speculated that malnutrition actually may result in some enhancement of immune function or merely render the body less accommodating to microbial pathogens as, in general, the rate of infection in states of extreme malnutrition is lower than the immune system disruption would suggest.

Fasting or calorie restriction (CR), which has been studied for effects on longevity and chronic and autoimmune disease prevention and treatment, may enhance immune function. Recent research suggests chronic CR and other dietary restrictions, such as intermittent fasting or a fast-mimicking diet (FMD), have potential to prevent many age-related diseases, possibly by delaying aging (12). However,

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compliance challenges exist with chronic CR, and long-term studies in monkeys suggest that diet composition may have a greater role in disease prevention, compared to energy restriction (13,14). In contrast, a FMD (followed by refeeding) appears to decrease the biological rate of aging and promote anti-inflammatory effects (15,16).

Other diets that have shown to support the immune system positively include the Mediterranean diet, which is rich in vegetables, fruit, nuts, legumes, fish, and *healthy* dietary fats. The Mediterranean diet is associated with a reduced risk of chronic disease, such as cardiovascular disease, cancer, and, more recently, Alzheimer's disease (17). Although the nutrient complexity of whole foods makes nutrient-specific causality difficult to establish, potential benefits have been proposed for vitamins, minerals, sterols, fiber, and antioxidant phytochemicals. Furthermore, the range of polyphenols found in fruits and vegetables provides a protective effect via immunomodulatory and anti-inflammatory mechanisms and thus reduces the risk of chronic diseases attributed to chronic inflammation (18). Additional studies have also shown decreased immune cell activation associated with the Mediterranean diet (19).

Similarly, vegetarian diets also appear to enhance the immune system. A recent systematic review and meta-analysis suggests that individuals following vegetarian-based diets may have lower levels of C-reactive protein (CRP), leukocyte, and fibrinogen, which are prominent markers of inflammation, compared to their non–vegetarian-based counterparts (20). Given that CRP is implicated in atherosclerosis development, results of the review may partly explain the lowered incidence of cardiovascular events observed in the vegetarian populations (21,22). Furthermore, the lowered leukocyte and fibrinogen levels observed in vegetarian-based diets is certainly favorable as elevated leukocyte and fibrinogen biomarkers have been associated with increased risk of mortality, T2DM, metabolic syndrome, and coronary heart disease (23–25). There have also been several reports demonstrating the clinical benefit of a vegetarian diet for patients with rheumatoid arthritis (RA). A study examining laboratory variables in RA patients treated with a vegetarian diet observed a decrease in several inflammatory markers, notably leukocyte count and IgM rheumatoid factor (26). Additionally, a systemic review analyzing the effect of a vegetarian diet on patients with RA showed a statistically and clinically significant long-term disease improvement with the dietary intervention (27).

NUTRIENTS, NUTRICEUTICALS, AND FUNCTIONAL FOODS

Zinc

Zinc deficiency is considered one of the most prevalent nutritional deficiencies worldwide due both to limited dietary intake and the presence in the food supply of phytic acid, a zinc chelator (found in wheat bran, whole grain cereals, and many raw vegetables). Zinc is an essential cofactor in more than 90 metalloenzyme systems; its deficiency interferes with cellular replication. Zinc deficiency, in particular, appears to arrest T-cell maturation. Studies in mice have shown that moderate-to-severe zinc deficiency leads to bone marrow depletion of B lymphocytes and to peripheral lymphopenia. Further, observational studies in humans have demonstrated that inadequate zinc stores were a risk factor for pneumonia in older adults (28).

These studies suggest that zinc deficiency leads to chronic elevation of glucocorticoid levels, which in turn suppress immunity. The combination of zinc deficiency and elevated cortisol is thought to augment apoptosis of prelymphocytes. Phagocytic cells, representing a first line of defense, may be favored over lymphocytes during periods of malnutrition. Fortunately, zinc repletion appears to restore normal immunity in zinc-deficient organisms within as little as 2 weeks. Following zinc supplementation, older

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subjects developed increased plasma zinc levels and subsequently decreased oxidative stress markers and inflammatory markers (29). Zinc has also been suggested to improve symptoms of the common cold. In a double-blind randomized controlled trial (RCT), patients with common cold symptoms took 13.3 mg of zinc as long as symptoms were present (30). Compared to a placebo, zinc significantly reduced the duration of common cold symptoms, from 7.6 to 4.4 days. However, it is important to note that excessive zinc supplementation may adversely affect immune function (31).

Iron

Iron plays a key role in the immune system as it helps to fight off infections by enabling T-lymphocyte immune cell proliferation and maturation, as well as regulating cytokine production and action against bacteria (32,33). Iron deficiency is highly prevalent globally. During extended periods of iron deficiency, antibody production is typically reduced. This has been shown in studies with mice exposed to the influenza virus (34) and also in older adults, where iron deficiency impaired innate and adaptive immunity (35). Supplementation may be beneficial to certain at-risk populations, as noted in one study where iron supplementation of hospitalized children resulted in a reduction of recurrences of respiratory tract infections, urinary tract infections, and gastroenteritis (36). However, supplementation should be utilized with caution as iron excess is also associated with impaired immunity, along with susceptibility to tumorigenesis.

Essential Amino Acids

Deficiency of any of the essential amino acids appears to suppress immunity, whereas intake of nonessential amino acids appears not to be limiting, given adequate total protein intake. Animal studies suggest that imbalances of protein intake can impair immunity even in the absence of overt deficiency. For example, excessive dietary leucine has been shown to reduce antibody responses in animals. Sulfur-containing amino acids involved in the synthesis of glutathione may be in particular demand during infection and inflammation due to the increased oxidative stresses, suggesting that supplementation might be beneficial (37).

Arginine is a conditionally essential amino acid (see Chapter 3). Studies in animals and in vitro suggest that supplemental L-arginine may be immunostimulatory (38). The use of L-arginine in states of human immunodeficiency has been proposed. Reduced hospital stay following surgery has been observed in supplemented patients. Arginine is an essential nitrogen donor in nitric oxide synthesis. Macrophages produce nitric oxide after Toll-like receptor activation, which is consequently toxic to several pathogens and, thus, plays an important role in the innate arm of the immune response. Of note, certain pathogens have inherent arginase activity, which blocks arginine availability for nitric oxide synthase (39). The effects of nitric oxide on the vasculature are potentially an important component of the response to severe infection (40); enhancement of endothelial function with arginine supplementation has been reported (41–43). Immune enhancement has been ascribed to both glutamine (44) and taurine (45) as well.

Vitamin C

Normal vitamin C nutriture is vital to skin integrity and wound healing, which are vital components of the immune system (see Chapters 22 and 23). Vitamin C also has an important role as an antioxidant by attacking free radicals. In addition, vitamin C supports both the innate and adaptive immune response as it stimulates neutrophil apoptosis (which helps to protect host tissue from significant damage (46), aids in macrophage removal (47), and plays a role in the differentiation and maturation of T cells (48,49)).

While megadosing of vitamin C is not recommended, positive effects have been found in some

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intervention trials. A systematic review found significant benefits of vitamin C supplementation in patients with pneumonia (50). For example, in a double-blind RCT, older participants receiving 200 mg/day of ascorbic acid for 4 weeks improved their respiratory condition (51). In a recent meta-analysis of nine RCTs, vitamin C supplementation (0.7–0.8 g/day) reduced duration, shortened time of indoor confinement, and relieved symptoms of the common cold (52).

Vitamin A and Carotenoids

Vitamin A deficiency is associated with disruption of mucosal and epithelial barriers, as well as inhibited innate and adaptive immune system antibody responses. Thus, it is not surprising that low vitamin A status has been associated with impaired functioning of neutrophils, macrophages, as well as T cells and B cells (53). The relationship between vitamin A and infection appears to be bidirectional; for example, infection with *Schistosoma mansoni* has been reported to deplete vitamin A (54). Malaria has been reported to induce acute-phase reactants that deplete carrier proteins and thereby lower levels of serum carotenoids and retinol. Thus, the reliability of serum measures of these micronutrients during acute infection is highly suspect (55). Vitamin A supplementation of children in the developing world has been established as a means of preventing infectious disease and death, specifically decreasing diarrhea and mortality in malnourished or human immunodeficiency virus (HIV)–infected children (56). However, high-dose supplementation of vitamin A may cause immunosuppression.

B Vitamins

B vitamins are involved in numerous energy-related enzymatic processes. While there is still much to be learned about how various B vitamins may support the body's immune system, there is some evidence that highlight the role of certain B vitamins. For example, low plasma pyridoxal 5 phosphate (PLP), the active coenzyme form of vitamin B_6, has been significantly associated with impaired antibody and cell-mediated immunity (57–59). In critically ill patients, vitamin B_6 supplementation increased plasma PLP levels associated with increased total lymphocyte cells, including Th and T-suppressor cells (60). In regards to folate (vitamin B_9), high-dose folic acid supplementation had a positive impact via altered mRNA expression in cytokines and decreased cytotoxicity of natural killer cells (part of the innate immune response) in healthy participants (61). Studies have also shown that cobalamin (vitamin B_{12}) may act as an immunomodulator (62). Vitamin B forms have also been effective in decreasing inflammation caused by viral infection. Specifically, vitamin B_3, vitamin B_6, and vitamin B_{12} intake (in the form of niacin, pyridoxine, and cobalamin) have been significantly associated with lower inflammation levels (e.g., decreased CRP) in patients with HIV (63).

Vitamin E

Vitamin E, a term that actually refers to a group of related compounds of both the tocopherol and tocotrienol chemical classes, is important to immune function both in its role as an antioxidant and as a cell membrane constituent. A relatively high amount of vitamin E is found in the membranes of immune cells since they are highly susceptible to oxidative damage (64). There is suggestive evidence that vitamin E supplementation can enhance both humoral and cellular immunity. Vitamin E may be of particular importance in combination with n-3 FAs (see Essential Fatty Acids). The recommended dietary allowance (RDA) for vitamin E intake may not be optimal with regard to immune function, particularly in older adults (65). A randomized trial of vitamin E supplementation for 4 months in healthy older subjects demonstrated enhancement of clinically relevant measures of T-cell function (66). A dose of 200 mg/day

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was superior to both higher and lower doses. The possibility of adverse effects of high doses of vitamin E on immune function and other aspects of health is noteworthy, particularly for at-risk populations such as people with diabetes and those with a history of heart attacks (67–69).

Optimal dosing, nutrient context, and formulation remain uncertain. Vitamin E is found in foods in the company of polyunsaturated fat, and it mitigates the effects of n-3 polyunsaturated fatty acid (PUFA) on various aspects of immune function (70). Thus, some combination of vitamin E and fish oil supplementation may offer benefits as yet to be clarified. A total daily intake of vitamin E from both food sources and supplements up to but not exceeding 200 mg/day seems prudent while awaiting further research.

Vitamin D

The active form of vitamin D, 1,25-dihydroxyvitamin D (3), regulates bone formation and additionally modulates multiple immune cells, including monocytes, macrophages, dendritic cells, and lymphocytes. Additionally, immune cells contain vitamin D–activating enzymes, which allow local activation within the immune system. Multiple epidemiologic reports have associated vitamin D deficiency with increased risk of chronic infections, specifically from *Mycobacterium tuberculosis* and autoimmune disorders. Studies have shown that active vitamin D has multiple effects on the immune system, including increase in chemotaxis (e.g., movement of leukocytes toward inflammation sites), phagocytosis, and T-cell activation. Supplementation has been associated with a decreased overall mortality in an RCT (71) and has been reported to increase sputum clearance of acid-fast bacilli (bacteria causing tuberculosis and other infections) and promote radiologic improvement of patients with tuberculosis (72). Vitamin D supplementation has also shown benefits in patients with chronic obstructive pulmonary disease and a baseline deficiency by reducing the incidence of exacerbations (73). A recent review reported that vitamin D supplementation reduced risk of influenza, COVID-19 infections, and mortality (74), mainly due to related inflammatory status and by modulating adaptive immunity, such as reducing Th cell responses. This is supported by a meta-analysis of RCTs, in which researchers found that vitamin D had protective effects against respiratory tract infection (75).

Essential Fatty Acids

Dietary FAs are essential sources of energy and foundational components of cell structure. They also play important roles in the modulation of innate and adaptive immune responses through such mechanisms as modifying membrane composition and acting through specific receptors. Consumption of unsaturated FAs can either protect or increase risk of development of many immune-related and metabolic diseases depending on the balance of n-6/n-3 polyunsaturated FAs in one’s diet. For example, diets high in n-6 PUFAs appear to promote tumorigenesis. Dietary n-3 PUFAs inhibit the generation of arachidonic acid and inflammatory eicosanoids. This effect may be beneficial in states of chronic inflammation, as discussed in Chapter 20. A randomized trial involving 40 healthy adults over age 65 showed that 2 months of supplementation with black currant seed oil, a source of both n-6 and n-3 essential FAs, enhanced delayed-type hypersensitivity skin responses and reduced production of prostaglandin E_2 (76). However, a more recent study demonstrated that fish oil supplementation may be beneficial in reducing neutropenia secondary to chemotherapy (77). There has long been speculation that increasing n-3 FA intake may serve to reduce the risk of chronic, inflammatory diseases, such as atherosclerosis but potentially at the cost of increased vulnerability to certain infectious pathogens (78). Benefits of fish oil supplementation in chronic inflammatory states, such as RA, have also been reported (79) (see Chapter 20). The clinical significance of these results is as yet uncertain. Thus, at present, arguments that total

dietary n-3 PUFA, the ratio of n-3 to n-6 PUFA, or the total amount of each of these fat classes in the diet is most germane to health outcomes (70).

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Selenium

Selenium is an essential trace element that affects various aspects of human health, including optimal immune function. Through its incorporation into selenoproteins, this trace element is involved in regulating oxidative stress, redox, and other critical cellular processes involved in immune responses (80,81). Selenium deficiencies have been associated with viral infections, such as influenza, by influencing both innate and adaptive immunity responses. Supplementation in selenium-deficient individuals has also been shown to mitigate cancer risk. Some of the most convincing evidence has been derived from a study in the Linxian province in China, an area with selenium-deficient soil and hyperendemic rates of upper GI tumors (82). However, caution must be used when considering selenium supplementation as it has been associated with increased T2DM incidence (83). While the topic has been extensively reviewed (84–87), more research is needed, particularly related to clinical trials.

Probiotics and Prebiotics

The majority of immune cells within the human body are found within the gut-associated lymphoid tissue, highlighting the important role this tissue has in maintaining overall health. The gut microbiota within the gut lumen provide antigens and signals that can interact with local and systemic immune cells. Alterations to the microbiota, whether through antibiotics or sanitation efforts, may predispose patients to a variety of diseases, including allergies, asthma, autoimmune diseases, diabetes, heart disease, and cancers (88–90).

Probiotics can enhance specific aspects of immune function as measured in vitro. Further, in vivo studies in mice demonstrated that probiotic mixtures can reduce T-cell and B-cell responsiveness and downregulate production of certain cytokines, which may be beneficial in certain autoimmune disease (91). A review of studies examining probiotic effect on immune function has shown that probiotic use improves phagocytosis, natural killer cell activity, and mucosal IgA production (92). Studies in infants have also shown that probiotic use may decrease episodes of diarrhea and prevent necrotizing enterocolitis (93,94). However, a clear mechanism for the influence of probiotics on infection or immune disorders over time remains to be established. Studies show that these effects are closely related to specific bacterial strain supplementation and individual responsiveness (3,95). The use of probiotics specifically for gastrointestinal disorders is addressed in Chapter 18.

Prebiotics, which are substrates utilized by probiotics, in the form of non-digestible dietary fiber, have a major impact on gut health (96). During dietary fiber fermentation, short-chain fatty acids (SCFAs) are produced. These FAs are considered key regulators of inflammatory diseases by controlling migration of immune cells to inflammatory sites, as well as enabling accelerated pathogen clearance (97,98). In addition to SCFAs, dietary fiber has been reported to increase the diversity of gut microbiota and promote health-associated bacteria, such as *Bifidobacterium* spp. and *Lactobacillus* spp. (99). While human studies linking diet, gut microbiota, and infection are still limited, it is important to acknowledge the highly promising role of the microbiome, its influence on responses to viral infection, and its modulation by dietary interventions.

SPECIAL TOPICS

Physical Activity

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An abundance of evidence demonstrates the significant impact that exercise can have on the immune system. Moderate, regular physical activity facilitates weight control, improves vascular health, and generally supports optimal immune function. Specifically, it has been shown to improve immune responses to vaccination and lower chronic low-grade inflammation, and improve various immune markers related to such diseases as cancer, HIV, cardiovascular disease, diabetes, and cognitive impairment (100–102). Moreover, intense exertion (often performed by athletes) has been associated with suppressed mucosal and cellular immunity, increased symptoms of upper respiratory tract infection, and impaired immune responses to vaccines and antigens (103–105). The current body of research supports the viewpoint that regular bouts of moderate-intensity exercise lasting up to 45 minutes are "immunoenhancing," whereas repetitive bouts of intense exercise that lasts greater than 2 hours can be 'immunosuppressive' (106).

Breast Milk

Breastfeeding is addressed in Chapter 27. Breast milk imparts to the neonate preformed antibodies that supplement innate immunity. Increasing evidence suggests that breast milk also functions in priming the acquired immune system of the newborn. There is speculation that the substitution of formula for breast milk may be a contributing factor to increases in the prevalence of atopy, asthma, and autoimmune disease (107).

Aging

Gradual attenuation of immune function with aging is well established and may be an important contributor to functional deterioration with age. Reduced T-cell function may be the earliest harbinger of age-related immunocompromise (31). Although a decline in immune function with age has been deemed normal, epidemiologic evidence suggests that age-related immune dysfunction may be due, at least in part, to nutritional deficiencies. The regulation of T-cell function tends to deteriorate with age, whereas Ig levels tend to rise. Specific antibody responses diminish. Protein and zinc deficiencies appear to be particularly prevalent and important contributors to dysregulation of immune function in older individuals. Limited evidence suggests that supplementation can confer clinical benefit (108). There is some evidence that a daily multivitamin or multimineral supplement for 6 to 12 months in older adults improves measures of cell-mediated immunity (31). Given that deficiencies of one or more micronutrients are found in up to one-third of all free-living older adults, a multivitamin or multimineral supplement for all individuals over age 50 is likely to be both appropriate and cost-effective. Also as suggested in a previous section, FMDs may be effective interventions in treating age-related diseases, such as cancer, cardiovascular disease, and Alzheimer's disease.

Human Immunodeficiency Virus Infection

Energy expenditure rises with HIV infection, and depletion of vitamin B_{12}, vitamin D, folate, zinc, and selenium have been reported as the $CD4^+$ count falls below 500 (109). The acquired immunodeficiency syndrome (AIDS) is associated with wasting; the wasting syndrome seen in HIV infection is an AIDS-defining condition (110). Loss of 10% or more of baseline body weight generally is associated with diminished functional capacity.

In addition to appropriate antiretroviral therapy, nutritional supplementation and appetite stimulation have been considered important adjuvants in this syndrome (111). However, a recent Cochrane systematic review concluded that there are no "consistent clinically important benefits with routine multiple

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micronutrient supplementation" in people living with HIV (112). The evidence for high-dose supplementation is not as clear; however, in one RCT, high-dose supplementation did not confer added benefits and may increase alanine transaminase (liver function biomarker) levels as observed in an RCT (113). Of note, vitamin B, C, and E supplementations did not reduce mortality in HIV-exposed infants in another RCT (114), yet there has been evidence supporting zinc supplementation and prevention of immune failure and diarrhea in patients with HIV (115).

Vitamin D deficiency is common in both pediatric and adult patients with HIV and may be related to various comorbidities in pediatric patients with HIV, including infections, growth failure, and wasting (116,117). An imbalance between caloric intake and the metabolic demands imposed by the primary HIV infection, as well as any secondary opportunistic infections, is thought to be the principal antecedent of wasting, but effects of specific inflammatory cytokines have been suggested (111). Reviews conducted in the past two decades address the role of pharmacologic support with megestrol acetate, dronabinol, and/or testosterone analogs, as well as growth hormone (111,118–120). Clinical trials suggest that resistance training may offer the benefits of anabolic steroids without the attendant adverse metabolic effects (121,122); the inclusion of exercise in the treatment of AIDS-related wasting should be routine (120).

Nutritional supplementation should focus on adequate total energy to prevent ongoing weight loss, as well as balanced intake of macronutrients and micronutrients. Of note, the authors of the Cochrane review do not suggest that their findings be interpreted as a reason to not take micronutrient supplementation where specific deficiencies may be occurring or where a patient is insufficient in meeting the recommended daily allowance of vitamins and minerals (114).

Nutrition counseling is apparently more effective when combined with an appropriate oral supplement than when given alone (123). The role, if any, of potentially immune-enhancing nutrients, such as zinc, arginine, or n-3 FAs, in HIV in general, and the AIDS wasting syndrome specifically, is unknown. There has been recent evidence suggesting a relationship between selenium deficiency in patients with HIV and worse outcomes. Certain randomized trials suggest that selenium supplementation in patients with HIV may reduce morbidity and CD4+ cell counts (124).

Coronavirus Infection

The coronavirus disease (COVID-19) is a rapidly emerging infectious disease that the World Health Organization has classified as a global pandemic (125). In severe cases of COVID-19, complications can include acute respiratory distress syndrome, multiple organ dysfunction syndrome, and death (126–128). These complications are believed to be related to what can best be described as a cytokine storm, where an unusually strong release of cytokines and other immune-related stimuli results in hyper-inflammation (129).

Data continue to emerge about this infectious disease and potential strategies on how best to prevent and treat it. However, as of the time of writing (September 2020), some current best practices include consuming foods that support optimal immune status, such as fruits and vegetables (rich in antioxidants, flavonoids, and carotenoids), nuts and seeds (rich in vitamin E), legumes (rich in zinc), and seafood (rich in omega-3 FAs, zinc, and vitamin D) (130). Vitamin supplementation may also have benefits as new research has explored its direct effects on virus-receptor binding. Interestingly, vitamin D supplementation promoted binding of the coronavirus cell entry receptor angiotensin-converting enzyme 2 (ACE2), which reduced the number of virus particles that could attach to ACE2 and invade the body (131). A recent retrospective study (including 780 confirmed cases of COVID-19 infection) concluded that older and male cases who had preexisting conditions and below-normal vitamin D levels had

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increased odds of death—those with vitamin D deficiency were nearly 13 times as likely to have died (132). Also, the nutritional supplement, quercetin (a bioflavonoid compound found in a variety of plants), may have a beneficial effect on the incidence and duration of respiratory tract infections in certain populations through its regulation of the expression of certain genes associated with cytokine production and its help in increasing zinc uptake into cells (130,133). While this evidence is promising, much more research is needed to understand how the immune system responds to the coronavirus and potential dietary and nutrition supplementation interventions as this global pandemic continues to evolve rapidly.

CLINICAL HIGHLIGHTS

An association between nutritional status and immune function is of clear clinical importance. Less clear is the means for optimizing immune responses when overt nutritional deficiency is not a threat. Although the evidence supporting immune enhancement by specific nutrients in humans is preliminary, the confluence of lines of evidence from animal, in vitro, in vivo, and epidemiologic studies allows for some general recommendations. The maintenance of macronutrient balance, including adequate protein intake with regard to both quantity and quality, is essential for immunocompetence across the lifespan. Abundant intake of fruits and vegetables is advisable on the basis of epidemiologic evidence, even as the potential mediators of immune effects (e.g., vitamins, minerals, sterols, flavonoids) are investigated.

Multivitamin or multimineral supplementation for all individuals over age 50 offers potential benefit and virtually no known toxicity. Additional supplementation with zinc (up to 30 mg/day) and vitamin E (200 IU/day) may confer additional benefit as well. Excessive dosing of single nutrients may have adverse effects and should be discouraged; zinc is a notable example.

Inclusion in the diet of n-3 FAs from plant or marine food sources may be beneficial. Notably, a balance of n-3 and n-6 FAs is critical—a ratio of not less than 1:4 is supported by available evidence. Recommendations for probiotic use are still difficult to provide due to variations in strains and individual responses. Regular, moderate physical activity and prevention of obesity may confer benefit to immune function and are advisable on other grounds.

Optimizing the maternal diet during gestation should be a high priority in all populations at risk for nutritional deficiencies (see Chapter 27); such deficiencies during fetal development appear to produce long-lasting immunologic impairment, regardless of the quality of the perinatal diet. However, megadosing of micronutrients, regardless of life stage, may be hazardous as nutrients of clear benefit to immune function, such as zinc, iron, and vitamin E, are immunoinhibitory at high doses. Furthermore, although adequate iron, in conjunction with adequate levels of transport proteins, supports optimal immune status, iron repletion during acute infection, particularly if globulin levels are low, should be avoided, as the iron under such conditions is preferentially available for bacterial metabolism.

There is some preliminary evidence of benefit from the administration of immunomodulating nutrients in the setting of acute illness. The combination of uracil, arginine, and n-3 FAs supplementation has shown particular promise. (A proprietary product, Impact [Sandoz], offers this combination in an enteral formula.) Even though conclusive evidence from outcome studies of infectious disease in humans to support a role for dietary interventions in the enhancement of immunity is lacking, the available evidence supports a diet consistent with recommendations supported by other lines of evidence. New trends are supporting a new paradigm to nutrient supplementation to treat disease. The new paradigm, labeled pharmaconutrition, tailors nutrient supplementation directly with the underlying disease process (98). Similar evidence supports daily supplementation with a multivitamin or multimineral. Recommendations for a diet that may enhance immune function may be made to patients with confidence in the probability of

overall health benefits and the improbability of toxicity.

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Chapter 12

Diet and Cancer

Lise Alschuler

INTRODUCTION

Diet has a contributory role in the development of cancer, supported by in vitro, animal, and epidemiologic studies. Decisive intervention trials are for the most part lacking, however, because of the protracted time course of carcinogenesis and a lack of reliable surrogate markers in most cases. An exception is studies in populations with well-defined nutrient deficiencies that increase the risk of specific cancers, where supplementation may dramatically reduce risk; the Linxian study in rural China is noteworthy in this regard (1,2). Most reviews of diet and cancer cite the work of Doll and Peto (3) and suggest that one third or more of all cancer is related to nutritional factors and potentially preventable by nutritional means. Dietary factors may influence cancer initiation, promotion, and progression via direct effects on DNA and the tumor microenvironment (4), and via indirect effects on immune function (see Chapter 11), and overall vitality (see Chapter 45).

As is the case for atherogenesis, the process of carcinogenesis may be affected both favorably and unfavorably by micronutrients and macronutrients. Initiation is fostered by mutagenic exposures, including nutrient compounds, and promoted by tissue disruption (5) characterized by the Hallmarks of Cancer (6) (sustained proliferation signaling, evasion of growth suppression, defective apoptosis, cellular immortality, induction of angiogenesis, activation of invasion and metastasis, genomic instability, inflammation, altered energy metabolism, and immune evasion) (see Fig. 12.1). The hallmarks of carcinogenesis, culminating in cancer promotion and progression, appear to be more meaningfully associated with macronutrient intake and overall health than with specific nutrient compounds, although the aggregate influence of certain nutrient groups, such as antioxidants, flavonoids, and essential fatty acids, may be considerable. Procarcinogens in the diet include heterocyclic amines (HCAs) and polycyclic aromatic hydrocarbons (PAHs) that result from pyrolysis (i.e., charring); acrylamide formed when starchy foods are cooked at high temperature (7); nitrosamines used or produced in the curing of meats; naturally occurring contaminants, such as aflatoxin B-1; naturally occurring chemicals in plants; and chemicals added to the food supply as a result of agricultural practices and food handling. While all of potential importance, the net effect of carcinogenic compounds in foods is generally thought to be small relative to the effects of dietary pattern on general health, and its profound influence on cancer risk. This contention is highlighted by the presence of naturally occurring mutagens in many plant foods, yet a consistent and strong inverse association between the consumption of such foods and cancer risk. Also germane is the issue of chemical contamination of food; there is widespread concern that pesticide residues on produce, for example, may at times be carcinogenic (8). If so, voluminous data largely from observational trials suggest that the benefits of a generally nutritious diet clearly outweigh any harmful effects of such residues on otherwise healthful foods. Nonetheless, a potential benefit from choosing organic alternatives—particularly in certain food groups (9)—is worthy of both consideration and study.

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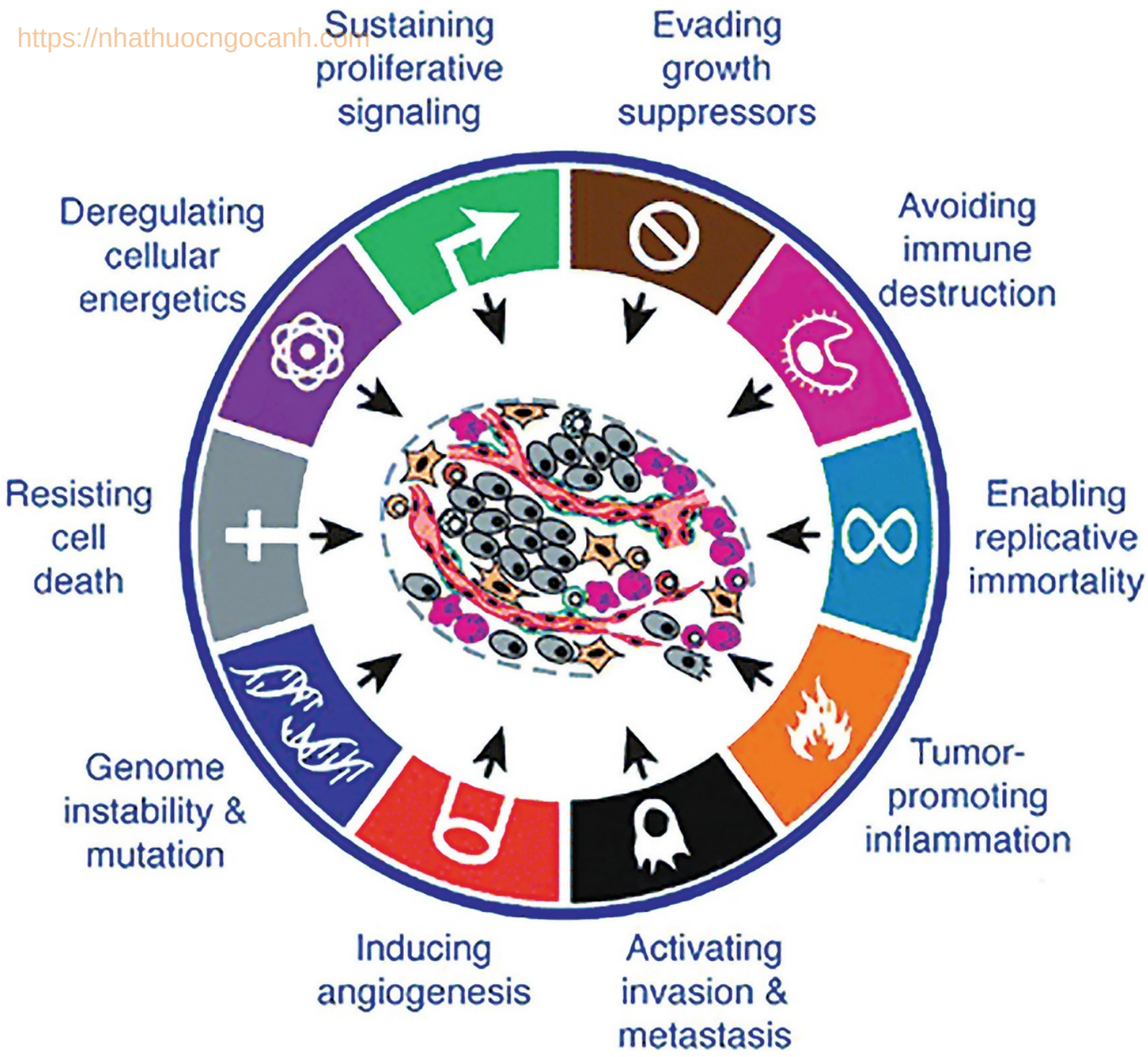

FIGURE 12.1 Hallmarks of cancer as defined by Hanahan and Weinberg (3).(Reprinted with permission from Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell*. 2011;144(5):646–674. Copyright © Elsevier.)

Whereas mutagenicity has been demonstrated for most of the compounds noted earlier, there are, of course, no intervention trials demonstrating carcinogenicity directly in humans. Epidemiologic studies support an association between excess saturated fat intake and cancer incidence at a variety of sites; a relative excess of n-6 polyunsaturated fats has been implicated as well. The literature linking trans fat to cancer risk is limited but suggests the association may be especially strong (10,11). Overall, balance in dietary fat intake may be an important determinant of cancer risk (see Chapters 2, 7, and 45) as may the balance of dietary fat to other macronutrients. Carbohydrate content may be of particular concern with

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high-glycemic-load carbohydrates potentially increasing the risk of cancer (12–20), possibly through insulin and insulin-like growth factors (21-26). Also, diet may lead indirectly to cancer by contributing to obesity, which is consistently and strongly associated with the risk of almost all cancers and particular importance in breast and prostate cancer (27). Associations with cancer incidence have been suggested for both excess dietary protein of animal origin and excessive intake of simple sugars. Additionally, the consumption of ultra-processed foods is associated with increased cancer risk, such that for every 10% increase in ultra-processed foods, the risk of cancer increases 12% (28). The most convincing evidence for the cancer-fighting potential of diet supports a high total intake of fruits and vegetables. Increasing public interest in organic foods, apparently motivated by concerns for both personal and planetary health, while a welcome trend, has the potential to exaggerate the dangers of chemical residues on produce. A net benefit of higher intake of fruits and vegetables is not limited to organic produce only. Thus, any harms attached to chemical residues on plant foods appear to be overwhelmed by the benefits of produce intake, as noted previously. Recent data reaffirm that the prevailing intake of fruits and vegetables in the United States falls well short of recommended levels (29,30).

Less extensive evidence suggests that energy restriction may reduce cancer risk, either directly or indirectly through effects on body fat and insulin resistance (31). Conversely, overweight and obesity are convincingly associated with increased cancer risk (32), worsened cancer prognosis and cancer-related morbidity (33). Dietary fiber and a variety of micronutrients to be discussed are thought to reduce cancer risk. Nutrients with antioxidant properties are thought to be particularly important in cancer prevention by neutralizing the carcinogenic potential of free radicals ingested or generated by metabolism, inflammation, and radiation exposure. Efforts to isolate the “active ingredients” from cancer-fighting foods and diets, however, have been largely disappointing to date. Whether this is due to errors in dosing and/or choice of compound or to the differential effects of nutrients in the native context of foods versus isolation in supplements is at present unknown.

In clinical practice, dietary recommendations may be made based on available evidence to reduce both aggregate cancer risk and the risk of certain specific cancers. Similar recommendations are indicated for secondary prevention. In general, dietary recommendations for cancer prevention are entirely consistent with recommendations for health promotion (see Chapter 45) and substantially confluent with those for cancer recovery (34). In areas where dietary recommendations for cancer prevention rest on slight or inconclusive evidence, alternative, stronger sources of evidence consistently support very comparable recommendations.

As clinically overt cancer is invariably a catabolic process, nutritional support is important in the management and tertiary prevention of cancer. Malnutrition is a frequent concomitant of cancer and its treatment, with the potential to forestall recovery and impair functional ability. Strategies to promote and preserve lean body mass during cancer treatment likely warrant greater attention than they have received to date (35–37). Limited study of branched-chain amino acids suggests that certain combinations provided as a dietary supplement may meaningfully enhance lean body mass reserves and cancer recovery (38–41). Additionally, given the underlying role of inflammation in cachexia, supplementation with anti-inflammatory omega-3 fatty acids merits consideration (42).

OVERVIEW

Diet

Cancer as a pathologic category is diverse and complex, as is the literature associating carcinogenesis,

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and its suppression, with diet. Numerous attempts have been made to review and summarize the pertinent literature (3,43–60), but none is truly conclusive. While the identification of specific dietary causative factors has remained elusive, epidemiological evidence demonstrates a clear association between dietary patterns and cancer risk (61–64). The lack of readily measurable and modifiable risk factors for cancer renders the study of human carcinogenesis extremely difficult. The genomic, epigenomic, and physiological heterogeneity of each malignancy complicates the assessment of nutritional factors on tumor development and growth. Surrogate markers of cancer risk are improving but do not compare to those relied on routinely to assess the cardioprotective effects of lifestyle interventions (see Chapter 7). Prospective interventions still must rely on actual cancer or precancerous dysplasia/neoplasms as endpoints. Of necessity, such interventions are lengthy and large and often prohibitively expensive. In addition, the study of cancer prevention by dietary means may be obviated by assessing individuals in whom signs of increased risk or damage done are already evident, if the benefit of diet pertains to initiation and the earliest stages of promotion. Further complicating the relationship between diet and cancer is the prevailing view that cancer is a nonthreshold risk. Establishing a dose–response relationship between any isolated dietary factor and cancer may prove daunting.

Despite the complexity of both cancer and nutritional epidemiology, there is considerable uniformity in published recommendations for prevention of cancer by dietary means. As summarized by the American Cancer Society, current guidelines for the dietary prevention of cancer include achievement and maintenance of healthy weight, a generous intake of vegetables and fruits, and a relative abundance of other plant-based foods such as cereals and grains; regular physical activity; and limitation of alcohol intake (65,66). These recommendations are generally consistent with those for the prevention of both heart disease and diabetes, inspiring a joint effort by the American Cancer Society, American Heart Association, and American Diabetes Association to promote the same basic pattern of healthful lifestyle change (67).

Evidence in support of these recommendations derives principally from observational and retrospective studies and is of varying strength with regard to specific cancers and specific aspects of diet (43). A mechanistic understanding of nutrients in the prevention of cancer is developing and should guide future studies and recommendations.

Diet and Specific Neoplasms

Colon Cancer

Colon cancer is the leading cause of cancer death in the United States, and diet and obesity are thought to be potent determinants of colon cancer risk (68–70). Diet and nutrition are estimated to explain as much as 30% to 50% of the worldwide incidence of colorectal cancer (71). Evidence of an inverse association between dietary fiber intake and the risk of colorectal cancer has been established, (50,72,73); however, high fiber intake does not have any effect on colonic adenoma (precancerous growth) recurrence (74). This suggests that the greatest impact of high fiber is in primary prevention, supported by the finding that intake of high-fiber beans is associated with lower risk of colon adenomas (75), and high intake of fruits and vegetables is associated with reduced risk (although the extent to which this is due to fiber or other nutrients is uncertain).

High fiber intake is thought to lower risk by any of several possible mechanisms, including dilution of mutagens, reduction of gastrointestinal transit time, alteration of pH, and alteration of the gut flora and microbiome (76,77). The prospective Scandinavian HELGA cohort study, which examined 108,081 subjects, found that fiber from cereal foods may play a particularly strong role in the prevention of colon

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cancer (78). Another study found that high compliance with a low-fat, high-fiber diet is in fact associated with reduced risk of adenoma recurrence (79). Furthermore, data from the Iowa Women's Health Study, obtained prospectively over a 5-year period, demonstrated an inverse association between vegetable and fiber intake and colon cancer risk, although the associations were not statistically significant. The protective effect of garlic was confirmed in a 2020 meta-analysis of 11 epidemiological studies, with the highest garlic intake conferring a 29% reduced risk of colorectal cancer (80).

Negative studies of fiber and colonic polyp recurrence have raised doubts about the potential for dietary fiber to reduce colon cancer risk in high-risk individuals. In one such study (81), subjects with a prior history of colonic polyps were randomly assigned to receive counseling conducive to high dietary fiber intake or a control condition. The rate of recurrent polyp development did not differ between groups. In the second (82), more than 1,000 subjects with colonic polyps were randomly assigned to high (13.5 g) or low (2 g) daily supplements of wheat-bran fiber. Again, no difference was seen in the rate of polyp recurrence between groups. An accompanying editorial by Byers (83) appropriately concludes that these studies, while suggesting lack of short-term benefit of fiber in the prevention of polyp recurrence, provide little information about the potential role of fiber in colon cancer prevention. In particular, the long latency of cancer and the segregation of its pathogenesis into initiation, promotion, and expression raise the possibility that preventive measures may need to occur years before clinical features might otherwise develop to exert a meaningful influence. Injury to colonic epithelial cells is apt to have occurred years earlier in these study participants (i.e., long before polyps first appeared). Thus, these studies cannot be inferred to offer meaningful information about the impact of varying lifelong fiber intake on colon cancer risk (83). While provocative, these short-term studies do not refute the weight of evidence suggesting a benefit of high fiber intake for a lifetime. The European Prospective Investigation of Cancer and Nutrition (EPIC) suggests an approximate 9% reduction in the risk of colorectal cancer for each quintile increase in total dietary fiber intake (84). An examination of seven cohort studies suggests that methodological differences may account for inconsistencies in previous studies evaluating the inverse association between fiber intake and colorectal cancer risk (85). The studies do, however, raise important questions about the timing, reliability, and magnitude of preventive benefit from fiber over the lifespan. The negative evidence generated by such trials should neither be exaggerated nor dismissed. Perhaps dietary fiber offers protection against colon cancer only by preserving the health of an uninjured colon but provides no safeguard against polyps or cancer once injury related to diet and luminal pressures has accrued. Further studies will be needed to make such determinations.

In an innovative application of factor analysis, Slattery et al. (86) studied nearly 2,000 cases of colon cancer in comparison to 2,400 controls. They found that a "Western"-style diet (with a high intake of fat, cholesterol, and protein and a high body mass index [BMI]) was associated with significantly increased risk compared to other dietary patterns. These data are consistent with those of most other studies but are novel in providing an assessment of associations with overall dietary patterns (87). In the dietary arm of the Women's Health Initiative, nearly 50,000 postmenopausal women were randomly assigned to a fat-reduced diet with abundant intake of fruits and vegetables or to a control group given information about the current dietary guidelines. After 8 years of follow-up, colon cancer rates did not differ between groups (88). However, the dietary patterns achieved differed minimally between groups, and the advice to restrict all varieties of dietary fat indiscriminately is at odds with current thinking. Thus, the study has been criticized for methodologic failings and is not generally seen as refuting other evidence regarding the protective effects of fruits and vegetables or of restricting dietary fats selectively.

A 2020 meta-analysis of 13 prospective cohort studies found that greater adherence to a Mediterranean-style diet, replete with fruits, vegetables, whole grains, nuts, seeds, olive oil, fish, and

minimal processed and refined foods, was associated with a 10% reduced incidence in colorectal cancer (89).

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Overall, recommendations supported by the weight of available evidence include a diet rich in vegetables and other plant-based foods and still support a high intake of insoluble fiber from whole grains, beans, and lentils, along with vegetables and fruits. A prudent dietary pattern, essentially a diet that emphasizes vegetables, fruits, and unprocessed foods, is associated with reduced risk of colon cancer whereas a Western dietary pattern (rich in meat and processed foods) is associated with an increased risk. A 2020 systematic review and meta-analysis found that the plant-predominant diet was associated with a 19% reduced risk (RR 0.81; 95% CI 0.73, 0.91), whereas the Western dietary pattern was associated with a 25% increased risk (RR 1.25; 95% CI 1.11, 1.40) (90).

Consumption of red meat (at least conventionally raised, factory-farmed red meat) and particularly processed meat should be moderate. Alcohol intake should be kept at moderate levels. There may be a particular benefit from including dairy foods in the diet. To date, no definitive evidence supports micronutrient supplements as a specific strategy for preventing colon cancer, although arguments may be made for calcium, vitamin D, folate, lycopene, probiotics, and glutamine (see Chapters 4 and 18).

While observational studies have demonstrated a positive association between high intake of dietary red and processed meats with colon cancer, there is significant inconsistency among studies, likely an artifact of the heterogeneity of the diets studied as well as challenges presented by confounding variables in observational studies in (91). Prospective data from the Nurses' Health Study demonstrate an association between animal fat consumption and colon cancer risk (92). Meta-analyses have shown that individuals with high consumption of cured meats and red meat are at increased risk of colorectal cancer, with no association between low-fat meats, specifically fish and skinless poultry, and colon cancer risk (93)

Of all types of meat consumed, evidence suggests that processed red meats have the strongest association with cancer, potentially because meat cooked at high temperatures may form carcinogenic compounds such as PAHs and HCAs. A recent observational study of more than 120,000 individuals found that a daily increase of 3 oz of red meat was associated with a 10% greater risk of cancer mortality (94). Pastured or "grass-fed" beef has a different fat composition than "conventional" factory-farmed beef, and this difference could be meaningful for cancer risk in general and colon cancer specifically (95). Grass-fed beef is higher in ω-3 polyunsaturated fatty acids (PUFAs), which may be protective, and lower in ω-6 PUFA, which may be harmful (96). Moreover, the beef fat from cows raised on grass (cow's natural diet) is very different than beef fat from factory-farmed cows raised on grain, offal, and various industrial chemicals. There is interest in how fat-stored pesticides, antibiotics, and other growth promoters from factory farming might impact on human disease, but evidence at this time (notwithstanding health effects through environmental damage) is mostly speculative.

A case–control study conducted by Neugut et al. (97) using patients with colorectal adenomatous polyps as cases demonstrated an increased risk of colon cancer among those in the highest quartile of saturated fat intake, red meat consumption, and total dietary fat. Other studies further support an association between high red meat consumption and colon cancer risk (98,99). High dietary fat intake is thought to influence colon cancer development through effects on bile acid production and bacterial flora (68). High consumption of fiber showed a strong protective effect.

Physical inactivity and obesity may increase colon cancer risk, with physical activity associated with a reduced risk of both proximal colon and distal colon cancers (100). Results of the Health Professionals Follow-up Study suggest an inverse association between physical activity and colon cancer risk and an independent association between BMI and colon cancer risk. The association was even stronger for the

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waist-to-hip ratio than for BMI, suggesting that adiposity and fat distribution may influence colon cancer development (101). Data from Calle et al. (23) reveal a relative risk increase of 50% or more for cancer death in those with a BMI above 40 as compared to those of normal weight. Newer data increasingly links obesity with both increased risk and poor prognosis (69). Obese individuals have elevated insulin growth factor-1 (IGF-1) and proinflammatory cytokines, which likely underlie the association between obesity and colon cancer risk (102).

The hypothesis that calcium, vitamin D, and/or dairy products rich in both reduce colon cancer risk is currently among the most provocative topics in the field (103). A 2020 systematic review and meta-analysis that included 15 cohort studies and 14 case–control studies found that dairy consumption was associated with a 20% reduction in colorectal cancer risk (104). This risk reduction was independently seen with total milk intake and also with cheese intake for reducing the risk of proximal colon cancer. One possible explanation for the beneficial influence of dairy is that dairy is a source of vitamin D. Higher serum 25-hydroxy vitamin D is associated with lower colorectal cancer risk (105). Another theory is that dairy consumption increases the colonic concentration of lactic acid bacteria, which, in turn, exert anti-inflammatory actions and which activate phagocytic destruction of malignant cells (106).

Diet is thought to be one of the most potent determinants of colon cancer risk (68). High dietary fat intake is thought to influence colon cancer development through effects on bile acid production and bacterial flora (68). High fiber intake is thought to lower risk by any of several possible mechanisms, including dilution of mutagens, reduction of gastrointestinal transit time, modification of intestinal microbiome, and alteration of pH. Garlic, beans, and dairy are each independently associated with reduced colorectal cancer risk.

Breast Cancer

Evidence linking dietary factors to breast cancer risk is based on a combination of animal studies, ecologic studies between and among populations, retrospective studies within populations, observational cohort studies, and, to a lesser extent, intervention studies.

The American Cancer Society recommends avoidance or limitation of alcohol intake, avoidance of obesity, maintenance of physical activity, and abundant intake of vegetables and fruits as means to lower breast cancer risk (107). The evidence is stronger for vegetable and vegetable fiber, alcohol, and obesity than for other aspects of diet.

A 2017 meta-analysis of 83 studies found that adherence to a Mediterranean diet results in a 6% reduction in breast cancer, an effect most significantly seen with vegetable, fruit, and grain intake.[10] Dietary fiber intake has a singularly protective effect with the highest intake associated with a 5% reduction in breast cancer risk compared to the lowest intake in a meta-analysis of 16 prospective studies (108). Cereal fiber and soluble fiber had the strongest protective effects.

Kushi et al. (109) assessed the association between breast cancer incidence and intake of vitamins A, C, and E, retinol, and carotenoids among more than 34,000 women in the Iowa Women's Health Study. No protective effect was found for women with high intake of any of these nutrients. Some protective effect was noted for supplementation with vitamins C and A, but the associations did not reach significance. Similar results were reported from the Nurses' Health Study, where intake of vitamins C and E showed no association with breast cancer risk; vitamin A intake was inversely associated with risk in this study (110), a finding supported by a meta-analysis (111). This inverse relationship may be mediated by the effect of vitamin A on reducing oxidative stress (112). An analysis of data from a large case–control study in Italy, Mezzetti et al. (113) suggests that modification of dietary antioxidant intake, body weight, alcohol consumption, and physical activity level could eliminate up to one third of breast cancers in the

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Dorgan et al. (114) compared serum levels of carotenoids, retinol, selenium, and α-tocopherol between 105 breast cancer cases and matched controls. Only lycopene emerged as significantly protective, whereas the trend for β-cryptoxanthin was favorable but did not reach statistical significance. Lycopene is found principally in tomatoes, and β-cryptoxanthin is found in tangerines, nectarines, oranges, peaches, papaya, and mango.

Legumes, particularly soy foods, are associated with reduced risk of breast cancer and its recurrence. In a meta-analysis of 18 studies, the highest intake of soy was associated with a 12% reduced risk of breast cancer compared to the lowest intake (115). The protective effect is strongest among premenopausal women (21% reduced risk) and for estrogen receptor-negative breast cancer (29% reduced risk).

The association between dietary fat intake and breast cancer risk is both controversial and complex. Animal studies and cross-cultural comparisons in humans suggest that total fat, saturated fatty acids, and n-6 PUFAs may increase breast cancer risk (116), whereas n-3 PUFAs and possibly MUFAs decrease risk (117–120). The PREDIMED randomized controlled trial found a 68% reduction in breast cancer risk in association with a Mediterranean diet supplemented with extra virgin olive oil and a 41% reduced risk when a Mediterranean diet was supplemented with nuts (121). Dietary fat may have disparate effects on pre- and postmenopausal women, possibly conferring a protective effect on premenopausal women, while elevating cancer risk in postmenopausal women (122) In contrast, in a long-term follow-up (average 19.6 years) of the Women's Health Initiative trial, obese postmenopausal women benefit from a 15% reduction in mortality from breast cancer in association with fat intake less than 20% of total caloric intake (123). Obesity is a risk factor, especially for estrogen receptor-positive breast cancer in postmenopausal women. Central obesity is associated with increased risk of triple-negative breast cancer, more common in premenopausal women (124). This is likely due to the metabolic and inflammatory abnormalities associated with abdominal obesity.

A case–control study in Italy found an inverse association between intake of unsaturated fat and breast cancer and a positive association for starch (119). Among post-menopausal women diagnosed with estrogen receptor-positive breast cancer whose tumors expressed IGF-1 receptors, stable or increased simple carbohydrate intake resulted in a 5.5-fold increase in recurrence risk while decreasing simple carbohydrates by 27 g daily halved recurrence risk (125). Thus, the dietary contributors to breast cancer risk may vary with population characteristics, type of breast cancer, and prevailing dietary patterns.

Evidence linking moderate to heavy alcohol consumption to breast cancer risk has been fairly consistent, as reported in several meta-analyses by Smith-Warner et al. (126), Schatzkin et al. (127), and van den Brandt et al. (128). The pooled data suggest a relative risk of approximately 1.4 among moderate to moderately heavy drinkers (30) to 60 g of ethanol per day (two to five drinks) compared with nondrinkers. Light alcohol consumption (one drink, or 5–15 g of alcohol daily) is associated with a modest (5.9%) increase in the relative risk of breast cancer incidence (129). In a long-term follow-up of over 12,000 women in the After Breast Cancer Pooling Project (a consortium of three prospective trials), daily consumption of alcohol was not associated with increased risk of recurrence except in women who were postmenopausal at diagnosis, in whom 6 g or more alcohol per day was associated with a 20% increased risk of recurrence (130).

A diet rich in fruits, vegetables, and grains, with modest to no alcohol intake, and without excess meat, saturated fat, calories, and obesity, is consistent with recommendations for health promotion. The aggregated evidence suggests that such recommendations may serve to reduce breast cancer risk as well (131–133). A seminal 2007 study suggests better breast cancer survival among women who are

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physically active and eat an abundance of vegetables and fruits (134). An online database is available that provides summary evidence for a wide array of potential carcinogens that might contribute to breast cancer risk (8).

Lung Cancer

As is widely known, tobacco is by far the most important modifiable risk factor for lung cancer. However, as only a minority of smokers develop cancer, there are likely to be other important exposures, as well as variability in genetic susceptibility (135). There has long been evidence of a protective effect of fruit and vegetable intake. American Cancer Society data indicate that obesity is a risk factor for lung cancer (27).

The association of reduced risk of lung cancer with consumption of green and yellow vegetables suggested a protective effect of β-carotene (135) and other carotenoids and flavonoids. The results of randomized clinical trials have largely refuted a role for supplemental β-carotene in cancer prevention. Specifically, with regard to lung cancer, two negative trials are noteworthy. In the CARET (β-carotene and retinol efficacy trial) trial, current smokers and asbestos-exposed workers had a statistically significant increase in risk of both incident lung cancer and lung cancer mortality when taking supplemental β-carotene as opposed to placebo (136). Similarly, β-carotene supplementation was associated with a higher incidence of lung cancer than placebo in the Alpha-Tocopherol, Beta-Carotene (ATBC) Cancer Prevention Study (137–139). Conversely, consumption of foods rich in flavonoids such as vegetables, tea, and wine is inversely associated with lung cancer risk among smokers (140). The results of a large cohort study conducted in Finland suggest that flavonoids, particularly quercetin, confer protection against cancer in general and lung cancer in particular (141). The primary source of flavonoids in the study population was apples (142). The results of this study were relatively unaffected by adjusting for intake of vitamins C and E and β-carotene. A recent study found little evidence of a link between B vitamins or methionine and lung cancer risk (143). Overall, there are suggestions in the literature of protective effects against lung cancer of several antioxidant nutrients (144).

The lowest quintile of dietary glycemic index is associated with a 51% reduced risk of lung cancer compared to the highest quintile (145). This association was most evident among never-smokers and for squamous cell lung carcinoma. Greater adherence to an anti-inflammatory diet (high intake of non-starchy vegetables, fruits, nuts, cereals, legumes, fish, and low intake of red and processed meat and alcohol) is associated with an 80% reduced risk of lung cancer among heavy smokers (146). A meta-analysis that included 11 epidemiological studies, 7 case–control studies, and 4 cohort studies found that soy consumption was inversely associated with lung cancer risk, especially in nonsmokers (147). Specifically, daily consumption of 100 g of tofu could result in approximately one-third fewer cases of lung cancer. In a case–control study of lung cancer among nonsmoking women, Alavanja et al. (148) reported increased risk in association with red meat and dairy intake and particularly total and saturated fat intake; a protective effect of vegetables was not seen. Combined, these studies suggest that dietary flavonoids and antioxidants exert a mitigating effect on cigarette-derived carcinogens. The association of total and saturated fat intake with increased lung cancer risk was demonstrated in a large pooled analysis of 10 prospective studies (149). These positive associations were most significant among smokers, and for squamous and small cell lung carcinoma. Importantly, high polyunsaturated fat intake was associated with an 8% decreased risk of lung cancer. A case–control study among men in Sweden identified low vegetable intake and high milk consumption as lung cancer risk factors in a mixed group of smokers and nonsmokers (150). A subsequent meta-analysis in the United Kingdom suggested an overall survival advantage with dairy consumption, limited not just to cancer (151). In a review of studies of lung cancer

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risk factors among nonsmoking women in China, the dietary factors reported to be most consistently associated with increased risk were low intake of vegetables and fruits, particularly vegetables and fruits rich in carotene and vitamin C (152).

A separate case–control study in Chinese women identified frequent consumption of fried food as a risk factor and frequent carrot consumption as protective (153). At least one case–control study in China demonstrated a decreased risk of lung cancer with increasing intake of meat as well as vegetables among men in a mining town (154). The discrepant findings with regard to red meat are likely due to variable population characteristics; red meat may be protective when diet is marginal and harmful when diet tends to be excessive. Alternatively, as yet unspecified confounders may account for the observed associations between meat consumption and lung cancer.

The sum of available evidence supports recommendations to consume a low-glycemic index diet, with an abundance of fruits and vegetables, soy, polyunsaturated fats, and dairy products. Recommendations to limit meat are reasonable. Recommendations to consume any particular micronutrient cannot be made with confidence (50).

Prostate Cancer

There is considerable interest in dietary and lifestyle risk factors for prostate cancer. Ecologic and migrant studies suggest that the dietary patterns of industrialized countries, associated with high saturated fat and protein intake and relatively low intake of fruits and vegetables, contribute to increased risk (155). World Cancer Research Fund (WCRF) guidelines for prostate cancer risk reduction include maintenance of a normal BMI, avoidance of sugary drinks, at least five servings of non-starchy vegetables and fruits daily, at least 25 g of cereals and legumes, less than two drinks of alcohol daily, less than 2.4 g of sodium daily, and at least 30 minutes of vigorous or 60 minutes of moderate exercise daily. Adherence to at least four of these guidelines is associated with a 38% reduced risk of aggressive prostate cancer (156). Similarly, adherence to a Mediterranean diet is also associated with a lower risk of aggressive prostate cancer (157). There is evidence of an increased risk in association with high intake of saturated fat from animal and dairy sources (158–160). However, fat intake was not predictive of risk in a case–control study in England, thought to be due in part to a high mean fat intake and a relatively narrow range (161). Based on the results of a case–control study in Sweden, Andersson et al. (162) suggest that the association between prostate cancer risk and dietary fat is eliminated by controlling for total energy intake. The discrepancies in the available literature may be interpreted as suggesting that intake of saturated fat or total energy, or both, is among the factors contributing to population risk for prostate cancer, but that other important factors remain to be identified to further stratify the risk among members of a population with high or low mean fat and energy intake.

As with virtually all other cancers, there is an association between prostate cancer risk and obesity. American Cancer Society data suggest a marked increase in prostate cancer risk with rising BMI (27).

Fish intake may not protect against prostate cancer incidence but may have a decided benefit for prostate cancer mortality (163). Although a recent trial showed higher prostate cancer risk with higher plasma level of long-chain ω-3 PUFAs (like those derived from fish intake) (164), commentators have been critical of the plasma measure used in the study, which does not accurately reflect long-term intake, and of the conclusion, which may erroneously attribute disordered ω-3 partitioning to high consumption (165). Still, meta-analyses of a shorter-chain ω-3 PUFA (specifically α-linolenic acid) show inconsistent findings; there may be an increased risk of prostate cancer overall with higher intakes, blood levels, or adipose concentrations, but prospective studies do not show a clear association (166,167).

Soy consumption is inversely associated with prostate cancer, with a 2018 systematic review meta-

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analysis of 18 studies finding that regular soy consumption was associated with a 29% reduced risk of prostate cancer (168).

A variety of micronutrients have been suggested to protect against prostate cancer, although for most, the evidence is limited. However, as virtually all of the putatively protective nutrients are found in fruits and vegetables, the evidence is more convincing that fruit and vegetable intake may be protective (160). The evidence in support of a specific protective effect of tomatoes and/or their lycopene content raises the possibility that high fruit and vegetable intake is a marker of high tomato intake (155). Data from the Health Professionals Follow-up Study suggested an inverse association between prostate cancer risk and intake of lycopene but not other carotenoids (169). A systematic review and meta-analysis of 26 studies established a trend between higher lycopene consumption and lower prostate cancer risk (170). This was confirmed in a subsequent systematic review and meta-analysis that included 30 studies. This review found that tomato products, cooked tomatoes, and sauces were associated in a dose-response manner to reduced prostate cancer risk (171).

Preliminary evidence has suggested protective effects of vitamins D and E, (158,172); however, prospective intervention trials have failed to demonstrate a preventive benefit for prostate cancer (173,174). Data from the ATBC trial suggest that α-tocopherol may inhibit the transformation of clinically latent to clinically active prostate cancer. The same study showed a decrease in prostate cancer risk in non-alcohol drinkers receiving β-carotene (like lycopene, also concentrated in the prostate [175] but an increased risk in drinkers [176,177]). Long-term follow-up of 7 to 12 years of participants in the SELECT trial found that vitamin E supplementation with (synthetic) alpha-tocopherol was associated with an increased risk of prostate cancer (178). The results of this study do not necessarily apply to naturally occurring vitamin E isomers found in diet given the distinct biological role of racemic alpha-tocopherol acetate from naturally occurring tocopherols and tocotrienols.

An inverse association between intake of retinoid (which regulates epithelial cell growth and is chemically related to vitamin A) and prostate cancer risk has been reported fairly consistently. In contrast, intake of retinol—a first-generation retinoid—has been positively associated with risk in several studies (158). A pooled analysis of 15 prospective studies with total participants of 11,239 cases and 18,541 controls, analyzed the associations between serum concentrations of carotenoids, retinol, alpha-tocopherol, and gamma-tocopherol with prostate cancer risk (179). Lycopene was not associated with the risk of prostate cancer but was associated with a significantly reduced risk of aggressive prostate cancer. No other carotenoid was associated with prostate cancer risk. Retinol was positively associated with prostate cancer risk. Alpha-tocopherol was associated with both decreased prostate cancer risk and decreased risk of aggressive prostate cancer. Gamma tocopherol was not associated with prostate cancer risk.

Other Cancers

The principal modifiable risk factors for cancer of the esophagus appear to be tobacco, smoking and human papillomavirus, alcohol exposure, drinking very hot liquids (293), red and processed meat consumption (180), while fruit and vegetable intake, folate, fiber, beta-carotene, vitamin C, as well as physical activity and normal BMI are inversely associated with risk for esophageal cancer (181).

While the primary risk factor for gastric cancer is *Helicobacter pylori* infection, dietary factors also play a role. In a meta-analysis of 76 prospective studies with follow-up ranging from 3 to 30 years, the consumption of total fruit and white vegetables (but not total vegetable intake) was inversely associated with gastric cancer risk, while high-salt foods, beer, and liquor (not wine) increased risk (182). White vegetables include potatoes, cauliflowers, turnips, onions, parsnips, white corn, kohlrabi, and

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mushrooms. High fruit and vegetable intake has been consistently associated with reduced risk of gastric cancer (180).

The etiology of childhood cancers is poorly understood at present. An association between maternal consumption of cured meats containing N-nitroso compounds and brain tumor risk has been suggested (183). Recommendations to avoid such products are consistent with general dietary guidelines. There may be an association between excess caloric intake and childhood cancer, notably acute lymphoblastic leukemia (184).

Data from the Iowa Women's Health Study suggest that fat from animal sources and a diet high in meat may increase risk of non-Hodgkin's lymphoma (185); fruit consumption appeared to be protective. Data from the EPIC trial are suggestive of a protective benefit for lymphomas from adherence to a Mediterranean-style diet (186).

A 2015 meta-analysis of nine cohort and case–control studies concluded that high intake of cruciferous vegetables is inversely associated with pancreatic cancer risk (187). The prevailing consensus is that fruits and vegetables are protective, whereas high intake of meat, saturated fat, or both increases risk (188).

Several case–control studies have found that stewed and roasted meat and fried foods may increase bladder cancer risk, whereas fruit, yogurt, vitamin C from both diet and supplements, and multivitamin use may decrease risk (189,190). In the Italian population, greater adherence to a Mediterranean diet with increased consumption of legumes, vegetables, and fish was inversely associated with bladder cancer risk (191). Animal and in vitro studies implicate nitrates, nitrites, and N-nitroso compounds in bladder cancer, but no definitive evidence is available in humans (192). In a concise summary, Willett (43) made the following observations: Cancer of the oral cavity is inversely associated with fruit and possibly vegetable intake and positively associated with alcohol intake; esophageal cancer is inversely associated with fruit and vegetable intake and positively associated with alcohol and hot drink consumption; gastric cancer is inversely associated with fruit and vegetable intake, is positively associated with salt intake, and may be positively associated with egg and total carbohydrate intake; pancreatic cancer risk may be reduced by fruit, vegetable, and fiber intake and increased by intake of alcohol, meat, protein, and carbohydrate; both endometrial and renal cancers are convincingly associated with obesity; and fruit and vegetable consumption appears to be at least weakly protective against most cancers studied.

Obesity is associated with increased cancer risk (193), with 12% of cancers in men and 13% of cancers in women attributable to obesity (194). Obesity and adiposity have been associated with several tumors of hormonal tissues, including ovary, uterus, breast, and prostate. Obesity is thought to promote tumorigenesis by raising estrogen levels, by promoting insulin resistance and insulin-like growth factor, as noted earlier (50,193), and by increasing low-grade inflammation and oxidative stress. Obesity is a well-established risk factor for renal cell cancer (195). A large, ongoing American Cancer Society observational cohort study suggests an association between obesity and virtually all varieties of cancer (27). Summary recommendations of most agencies attempting to prevent cancer are consistent with these associations and include reduced fat intake; increased fruit, vegetable, and fiber intake; maintenance of body weight near ideal; and minimal consumption of salt-cured, pickled, and smoked foods, and alcohol (44). It should be noted that with our evolving understanding, total dietary fat may be less important for cancer prevention than the distribution of fats in the diet.

NUTRIENTS, NUTRICEUTICALS, AND FUNCTIONAL FOODS

The natural reductionist tendencies of Western science are perhaps nowhere more evident, for good or for

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bad, than in efforts to elucidate the relationships between dietary constituents and cancer risk. As stated earlier, the weight of evidence clearly favors a diet rich in fruits and vegetables. Whether or not isolated nutrients found in plant foods can provide the benefits of a prudent dietary pattern is far from established. Most studies to date in pursuit of such evidence have proved disappointing. Nonetheless, a variety of nutrients and nutrient categories have received considerable attention in both the professional literature and lay press, and they are addressed briefly here.

Vitamin C

Despite long-standing interest in the potential for vitamin C to prevent cancer by virtue of its antioxidant properties, to date there is no convincing evidence that supplementation effectively prevents or treats cancer. High dietary intake of vitamin C is consistently associated with reduced cancer risk, but such intake invariably is associated with high fruit and vegetable consumption (196). Notwithstanding, sufficient vitamin C is a component of cancer prevention. Vitamin C is necessary for essential immunity and is a cofactor in oxygenase enzymes, which regulate cell metabolism, phenotype, and proliferation (197). The evidence regarding vitamin C supplementation is summarized in Appendix E.

Carotenoids

There are more than 600 carotenoids in nature, most of which are widespread in plants, lending pigment that functions in photoprotection and photosynthesis (198). Approximately 50 carotenoids are retinoids, moieties with varying vitamin A activity (199). The hypothesis that carotenoids in general may prevent cancer is based on associations between cancer risk and dietary intake patterns (200) and on a mechanistic rationale (201). Notably, carotenoids induce apoptosis and inhibit DNA oxidation (202). However, no definitive evidence of benefit from isolated supplements has been produced to date.

β-Carotene

Abundant in dark green, yellow, and orange fruits and vegetables, β-carotene is the most extensively studied of the carotenoids. Interest in the cancer-fighting properties of the nutrient was derived from observational and ecologic studies. Intervention trials to date report consistently negative results, however, with isolated β-carotene in supplement form increasing cancer risk in smokers in both CARET (136) and the ATBC trial (138). β-carotene failed to reduce the development of colorectal adenomas in an intervention trial (203) and showed no benefit in a prospective study of prostate cancer (204). These and other studies resulted in recommendations to avoid supplemental β-carotene, particularly in smokers, and have shifted interest to other carotenoids, alone or in combination with each other and unrelated antioxidants. The evidence regarding β-carotene supplementation is summarized in Appendix E.

Lycopene

Lycopene is the carotenoid responsible for the bright red color of tomatoes. It differs from other carotenoids in several respects. Lycopene lacks a ring structure; therefore, it cannot be converted to vitamin A. Because of its 11-carbon chain of conjugated double bonds, lycopene has exceptional antioxidant capacity. Data from a large, prospective cohort study mitigate against a protective effect (205,206). A 2011 Cochrane review of lycopene in prostate cancer prevention included three randomized controlled trials with 154 total participants. Due to high risk of bias in two of the three studies, this review concluded that there is not enough evidence to support or refute the benefit of lycopene in prostate cancer prevention (207). The evidence regarding lycopene supplementation is summarized in Appendix E.

Vitamin E

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Vitamin E, inevitably provided as α-tocopherol, is a lipid-soluble antioxidant. Like β-carotene, it has been studied in cancer prevention with largely disappointing results. The ATBC and CARET studies both included α-tocopherol and showed no significant benefit (136,137). In contrast to β-carotene, α-tocopherol appeared relatively innocuous in these studies, although there have been hints of potential cardiovascular harms at high doses in other studies (see Chapter 7). Some interest persists in the potential role of vitamin E in combination with water-soluble antioxidants such as vitamin C in cancer prevention. Evidence supporting a role for supplemental vitamin E in cancer prevention is in the aggregate unconvincing at present (208–211). The evidence regarding vitamin E supplementation is summarized in Appendix E.

Selenium

Selenium is an essential mineral with antioxidant properties. Studies in China, where soil is generally selenium poor, provide definitive evidence for selenium in cancer prevention (212–215). In the United States, where selenium deficiency is rare, a role for supplemental selenium in cancer prevention is much less certain (216), although some trials have been suggestive (217). A study in the United States found that dietary selenium intake was associated with reduced risk of pancreatic cancer (218). There is evidence that individual variations in selenium metabolism and transport genes may alter the cancer preventive effect of selenium supplementation (219), a factor which may confound clinical trial findings. The evidence regarding selenium supplementation is summarized in Appendix E.

Fiber

Dietary fiber, a diverse group of indigestible components of plant cell walls, is thought to mediate cancer risk by several mechanisms (220). By increasing fecal bulk and reducing intestinal transit time, insoluble fibers may reduce the risk of colon cancer. Dietary fiber has shown inverse associations with colon cancer risk in both retrospective (221,222) and prospective studies (223). Wheat-bran fiber has been shown to reduce bile acid excretion in patients with resected colon adenomas, suggesting an additional mechanism by which colon cancer risk may be reduced (224). The effect of fiber on the microbiome is also an emerging area of interest. Fiber may exert its protective influence on colon cancer risk and irritable bowel disease partially through fermentation of butyrate, which may decrease the inflammatory response in the colon (225). Fiber from beans has been shown to alter the metabolome, specifically reducing carcinogenic metabolites (226). However, data from the Health Professionals Follow-up Study failed to demonstrate an association between fiber intake and colon cancer risk (227), as have intervention trials of polyp recurrence, as noted previously (81,82). As the overall evidence on the effects of fiber supplementation rather than fiber from dietary sources is mixed at best, use of supplemental fiber to reduce colon cancer risk has been discouraged (228). A protective effect of soluble fibers and cellulose in breast cancer has been reported from a large case–control study (229). This has been confirmed in a large prospective study in Japan that found that 18 g of daily fiber was associated with reduced risk of breast cancer, with the effect most evident for estrogen and progesterone receptor-negative tumors (230). The weight of evidence favors a diet rich in both soluble and insoluble fibers found in fruits, vegetables, beans, lentils, and whole grains. Evidence is insufficient to support supplementation as a means of reducing cancer risk (220). Soluble and insoluble fibers are discussed in Appendix E.

Green Tea

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There is considerable interest in a potential role for green tea, and a particular constituent, epigallocatechin gallate (EGCG), in cancer prevention, particularly for breast and prostate cancers with equivocal benefit in colorectal and liver cancers. Evidence to date derives from epidemiologic studies, animal research, and early-phase intervention trials (231–240). Evidence of benefit is as yet far from definitive, but such benefit is biologically plausible. The inclusion of green, black, white (the most concentrated in bioflavonoids), or oolong tea in the diet may be recommended as a strategy with some potential to confer health benefit and negligible, if any, potential to confer harm.

Olive Oil

Olive oil is among the salient components of the health-promoting Mediterranean diet, which has been associated with reduced rates of cancer as well as heart disease. There is conjecture that olive oil may offer specific protection against cancer (241,242). Such effects are attributed to high levels of monounsaturated fatty acids, squalene, tocopherols, and phenolic compounds (243). Whether or not definitive evidence ensues that olive oil protects against cancer, its inclusion in the diet as a health-promoting cooking oil is certainly advisable.

Ethanol

Ethanol is well established as a promoter of head and neck cancers, and its consumption is consistently associated with increased risk of cancers of the gastrointestinal tract, respiratory tract, and breast (244–247). These associations and their implications for advice to patients about alcohol intake are addressed in Chapter 40.

Artificial Sweeteners

The potential carcinogenicity of artificial sweeteners, particularly aspartame, but also sucralose and saccharin, is frequent fodder for the media (248). Such associations from animal research as have been seen are not coupled to any direct evidence in humans. Given the enormous population-level exposure to aspartame and other artificial sweeteners, even a very small but meaningful effect on cancer risk would likely have long since been discernible. While the topic is deserving of ongoing scrutiny, there does not appear to be cause for particular concern at present (see Chapter 42). In fact, data from the large NutriNet-Sante prospective trial found that consumption of artificially sweetened beverages is not associated with cancer risk, whereas consumption of sugary drinks and fruit juices is associated with increased cancer risk (249). Guidelines from the US National Cancer Institute report that there is no clear evidence that artificial sweeteners available in the United States are associated with cancer risk in humans (250).

Soy

The evidence linking soy intake and cancer risk is mixed for breast cancer as well as prostate cancer. Population studies generally show lower breast (and other) cancer rates in populations that eat more soy. Systematic reviews and meta-analysis consistently demonstrate that pre-diagnosis soy intake is associated with reduced incidence and mortality from cancer in general (251), colorectal (252), prostate (253), endometrial (254), and breast cancer (255) specifically.

Organic versus Conventional Food

Currently, there is no clear evidence that organic meat and produce lower cancer risk as compared to conventionally grown foods. A 2012 systematic review found no significant nutritional advantages to

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organic foods; however, organic foods have lower pesticide residues (256). Another systematic review and meta-analysis found that organic meat has greater PUFAs and less saturated fatty acids than conventional meat although minerals and antioxidants were comparable (257).

Conjugated Linoleic Acid

There is some preliminary evidence of an anticancer effect of conjugated linoleic acid (CLA) (258–260) (see Chapter 2). Such early reports are consistent with the expansive literature suggesting that the quantity and distribution of dietary fats may influence overall cancer risk substantially. The clinical implications for CLA in efforts to attenuate cancer risk are mixed but suggestive of benefit (261,262).

Folate

Low folate intake has been associated with increased risk of colorectal and cervical cancers (263). While these associations remain investigational (264), there are other compelling reasons to ensure that all patients (especially female patients) consume at least 400 μg of folate daily (see Chapters 4, 7, and 27), which may offer the added benefit of reduced risk of prostate cancer and potentially melanoma (265,266). However, there is cause for concern with synthetic folic acid supplementation as trials have shown increased cancer incidence, particularly prostate cancer, with folate supplementation (267,268).

Other Nutrients

To date, no other micronutrients have been studied adequately to permit definitive recommendations regarding a role in cancer prevention in humans. However, numerous substances are biologically plausible inhibitors of cancer and are supported in this role by preliminary evidence.

Allyl compounds, found in garlic, onion, chives, and leeks, demonstrate inhibition of tumor induction in vitro and are associated with reduced rates of cancer, particularly gastric cancer, in epidemiologic studies. Isothiocyanates, organic compounds distributed widely in plants and particularly abundant in cruciferous vegetables, appear to suppress carcinogen activation by the cytochrome P-450 system. Indole compounds, also abundant in cruciferous vegetables, demonstrate inhibition of carcinogenesis in mammary cell lines, possibly mediated by effects on estrogen. Flavonoids, organic antioxidants widely distributed in plants, may have cancer-fighting properties. This class of compounds includes flavones, flavonols, and isoflavones. Flavones found in citrus fruit have been shown to inhibit the growth of malignant cells in tissue culture. Of the flavonols, quercetin has been most extensively studied and has been shown to inhibit the growth of neoplastic cells.

Tea leaves used to prepare green, black, white, and oolong tea contain polyphenols, including catechins and flavonols. Quinones are produced when the tea is oxidized. The constituents of such tea have been shown to inhibit nitrosamine formation in vitro. Tea consumption has been associated with reduced cancer risk as described previously.

Soybeans are a rich source of isoflavones, which are converted by intestinal bacteria to substances with weak estrogen activity and the capacity to function as estrogen antagonists in certain tissues. These substances appear to inhibit the growth of mammary cell tumors as well as tumor-induced angiogenesis.

Terpenes, lipid-soluble compounds found in a variety of herbs, have demonstrated a variety of anticancer properties, including suppression of cellular proliferation and induction of apoptosis (269,270).

The list of nutrients with the potential to influence cancer risk by diverse mechanisms is long and continuously growing. The clinician is obligated to remain alert for significant trial results with potential clinical implications.

Acrylamide

Acrylamide, a carcinogenic compound formed when starchy foods are cooked at high temperature, has been identified in products as diverse as breakfast cereals and French fries (271). Whether acrylamide poses a meaningful risk to humans at typical exposure levels and what implications this may have for food manufacturing and preparation are as yet uncertain. A 2015 meta-analysis evaluating 32 relevant studies concluded there was no increased risk of most types of cancer from exposure to acrylamide, but a modestly increased risk for kidney cancer and for endometrial and ovarian cancers in never-smokers (272). The US National Toxicology Program states acrylamide is “reasonably anticipated to be a human carcinogen” and the US Environmental Protection Agency reports it is “likely to be carcinogenic to humans” (273).

Pesticide Residues

Many environmental contaminants, including pesticide residues on foods, are potential carcinogens (8). There is evidence for pesticides as risk factors for cancers of the thyroid (274), breast (275), and prostate (276). Concern about such associations contributes to widespread enthusiasm for organic foods. For example, arsenic—found in agricultural products such as insecticides—has been found in conventionally grown rice and rice products in the United States at levels high enough to cause of concern for some experts. While arsenic in insecticides is limited to organic arsenic, which is likely nontoxic, arsenic in groundwater and rice is inorganic and may be concerning for increased cancer risk. However, it is not clear that the levels of arsenic found in rice increase the risk of cancer, and indeed, the benefits of eating rice—especially whole grain brown rice, which has more arsenic than white rice—may outweigh the risks. Of course, alternative arguments may readily be made to support the preferential production and selection of organically grown foods.

Calorie Restriction

Energy restriction has been shown to have tumor-inhibiting properties in animal studies (277,278) A 2014 systematic review and meta-analysis of animal studies included 59 studies, of which over 90% found a cancer preventive effect from caloric restriction (279). The benefit was significant with a pooled OR (95% CI) of 0.20 (0.12, 0.34). No long-term studies of calorie restriction have been conducted in humans, nor do such studies seem probable. Most cancers, including breast, prostate, ovarian, endometrial, and renal, may be promoted by either high-calorie intake or the resultant high BMI (280). Energy restriction and decreased adiposity may be especially important for breast cancer prevention (281,282). Further study of calorie restriction in cancer prevention is warranted and may be most effectively approached in the context of secondary prevention studies (i.e., prevention of cancer recurrence following successful treatment). In that setting, however, restriction of calories would need to be judiciously balanced against the quality of the diet and nutritional support to preserve lean body mass.

Calorie restriction has been studied in the context of SIRT1 gene expression. SIRT1 is an enzyme with a range of cellular functions related to calorie restriction, insulin sensitivity, and cancer development. It acts as an important sensor of nutrient availability in cells and may protect adipose tissue from inflammation under normal feeding conditions. SIRT1 seems to be downregulated in cells with high insulin resistance and inducing its expression may increase insulin sensitivity (283). Evidence suggests SIRT1 enhances skeletal muscle insulin sensitivity during caloric restriction (284). Furthermore, a high-

fat diet may act to cleave the SIRT1 protein and promote inflammation and metabolic dysfunction (285).

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SIRT1 also plays a role in cancer metabolism. It has been suggested to have both oncogenic and tumor-suppressor effects, depending on the p53 gene status (286). SIRT1 expression in mice may be a key mediator of the influence of caloric restriction on improved longevity, as SIRT1 may serve to protect colonic mucosa from excessive cell growth (287).

Diet and Cancer Management

By a variety of mechanisms, cancer tends to induce malnutrition (288). Although there is theoretical concern that nutritional support might stimulate tumor growth, there is no evidence of such an effect in humans (289). While in part the result of cancer and treatment factors that may reduce nutrient intake, cancer cachexia differs from starvation in that it is an inflammatory catabolic process with increased basal energy expenditure, lipolysis, and protein turnover (290). Optimizing dietary quality to preserve lean body mass, reduce inflammation, and support immune system activity may have important implications for recovery (290–293).

Patients with cancer are at particularly high nutritional risk and often content with continuous loss of lean body mass. The American Society for Parenteral and Enteral Nutrition (ASPEN) guidelines state that at-risk patients should undergo nutritional screening and development of a nutrition care plan, if necessary. Clinical studies suggest that oral nutritional interventions may help maintain lean body mass in cancer patients and elderly individuals.

A 2012 systematic review and meta-analysis of 13 studies and 1,414 individuals conducted by Baldwin and colleagues found that oral nutritional interventions increase nutrition intake and improve some quality of life measures in patients with cancer, but do not seem to improve mortality (294). Similarly, Baier et al. (295) found that a simple amino-acid cocktail was effective for increasing lean tissue and protein turnover in elderly individuals.

Learned Food Aversions

Foods associated circumstantially with the unpleasant effects of cancer treatments may result in aversions. Nearly 50% of untreated cancer patients have such aversions, and new ones develop with treatment in more than 50% of all patients. Although several approaches have been tried to prevent learned food aversions from developing, the most promising approach to date is the administration of nutritionally unimportant foods near treatment times so that learned food aversions are directed toward such foods rather than those with important nutritional value (296).

CLINICAL HIGHLIGHTS

Inconsistent, weak, and sometimes conflicting literature on the relative effectiveness of specific nutrients in preventing cancer of various tissues may be seen as a challenging quagmire of evidence from which no meaningful message can be extracted. However, if one looks at dietary pattern rather than nutrient consumption, the literature is remarkably consistent. The risk for virtually all cancers influenced by diet can likely be reduced with a diet rich in whole plant-based foods like fruits and vegetables and cereals. Avoidance of conventionally produced red meat and processed foods has strong support. Dairy foods may be of benefit. Both obesity and high total energy intake, which are correlated with one another, appear to increase risk of most cancers. When fat intake is relatively high, the greater the proportion of fat that is n-3 polyunsaturated, such as that found in fish, the lower the cancer risk; such benefit appears to be absent when fat intake is low. Similarly, a variety of micronutrients that show benefit in populations with

marginal diets show no such benefits in populations with abundant diets.

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Genetic polymorphisms induce variable susceptibility to diet-related diseases of all kinds but may be especially important in carcinogenesis. Numerous trials highlight the potential importance of genetic polymorphisms and gene–nutrient interactions in cancer development and prevention. Advances in the field of nutrigenomics will undoubtedly foster tailored advice to patients about dietary strategies for minimizing personal cancer risk, but the field remains inchoate at present.

Patients wishing to minimize cancer risk using the knowledge presently at hand should be encouraged to eat a diet rich in fruits and vegetables and plant-derived fiber. Meat should be predominantly poultry and fish. Alcohol consumption should be limited. Ideal body weight should be maintained by prudent energy intake and regular physical activity. Regular consumption of green, black, white, or oolong (oolong is a partially oxidized tea, between green and black tea) tea might confer some benefit. Inclusion of soy in the diet also confers benefit, particularly if used as a substitute for red meat. The avoidance of charred food, deep-fried food, and smoke-cured food may be reasonably advised.

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Chapter 13

Diet and Hematopoiesis: Nutritional Anemias

Alicia Tucker

INTRODUCTION

Nutritional status is, of course, a vital determinant of all aspects of health. The influence of nutriture is more readily apparent in some aspects of physiology than others, however. In particular, tissues with a high rate of turnover and metabolic processes with high energy requirements are more likely to manifest impairments due to even nominal nutrient deficiencies than are more sedate aspects of physiology. One of the tissues with the highest rate of cellular turnover is the bone marrow, and thus, as would be expected, nutrient deficiencies are readily manifest as abnormalities in hematopoiesis.

Anemia can be defined as a reduced or insufficient number of circulating red blood cells, which can be measured through a variety of blood studies. However, many blood volume studies are not practical, cost effective, or generally available. As a result, *anemia* has been defined as a reduction in one or more of the major red blood cell (RBC) measurements obtained as a part of the complete blood count (CBC): hemoglobin concentration, hematocrit (HCT), or RBC count. In clinical practice, a low hemoglobin concentration or a low hematocrit is most widely employed for this purpose. Normative values vary by gender, age, race, and altitude. In many studies, the definition of *anemia* used is that suggested by a World Health Organization (WHO) expert committee nearly 40 years ago. However, this WHO criteria for anemia in men and women are <13 and <12 g/dL, respectively, were meant to be used within the context of international nutrition studies and were not initially designed to serve as *gold standards* for the diagnosis of anemia (1). Deficiencies of iron, folate, and vitamin B_{12} (cobalamin) will all eventually contribute to decreasing hemoglobin levels, though iron deficiency is thought to be the most common cause of anemia globally. Other nutritional deficiencies (including folate, vitamin B_{12}, and vitamin A) will all eventually contribute to decreasing hemoglobin levels and are the most important epidemiological markers affecting hematopoiesis (2,3). Nutritional supplementation may be therapeutic in a significant percentage of all anemias seen in primary care. Thus, awareness of and attention to nutritional anemias is incumbent upon all healthcare providers.

OVERVIEW

Diet

The production of blood cells is an energy-intensive process, and thus overall dietary adequacy is a critical determinant of the vitality of hematopoiesis. The manufacture of red and white cells consumes the building blocks of cells and cell components and thus depends on the availability of proteins and fatty acids, in particular. Hematopoiesis is maintained at optimal levels only when an adequate amount of high-quality protein and, more specifically, essential amino acids are consumed. Similarly, the composition of blood cell membranes requires the provision of essential fatty acids (4).

Micronutrients directly involved in hematopoiesis may also influence the rate of blood cell

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manufacture. These include iron, which is required in the construction of hemoglobin, as well as vitamin B_{12} and folate, cofactors required for erythrocyte Deoxyribonucleic acid (DNA) synthesis. Deficiencies of several other nutrients—including vitamin A, vitamin B_6, vitamin B_2 (riboflavin), vitamin C, vitamin E, and copper—may be associated with the development or exacerbation of anemia (5).

Roughly one-third of the world's population is affected by anemia, with preschool-aged children and women of reproductive age particularly affected. The prevalence of anemia varies by geographic region, with prevalence highest in developing countries (6,7). In the United States, the National Health and Nutrition Examination Survey (NHANES) from 2003 to 2012 estimated that 5.6% of the US population had anemia, with 1.5% having moderate to severe anemia. The NHANES data showed that anemia, and more severe levels of anemia, are more prevalent for specific subgroups such as blacks, Hispanics, older adults over 60 years, non-pregnant women of reproductive age, and pregnant women. For example, the estimated prevalence of anemia in pregnant women in the United States is 8.8%; however, this rises to 9.2% of Hispanic pregnant women and 24.2% of black pregnant women (8). Disparities are also seen among children in the United States. The overall prevalence of anemia in children 0 to 5 years of age was estimated at 6% in 2010. However, children enrolled in federally funded programs serving low-income children found that the prevalence of anemia in this population increased from 13.4% in 2001 to 14.6% in 2010. The highest prevalence (18.2%) was among children 12 to 17 months of age in this group (9). During this time period, there was also a rise in the prevalence of anemia for older adults between the age of 60 and 85, with a nearly 20% prevalence rate of anemia in some populations within this age group. These high rates of anemia are of particular concern because anemia is associated with disability and physical decline. Anemic older persons over 85 years have been found to be at risk for higher mortality rates than those without anemia. Prior data has estimated that nearly one-third of anemia cases in older adults were nutritional, with two-thirds being related to chronic disease or myelodysplastic in nature (8,10).

Iron-deficiency anemia (IDA) affects more than 2 billion people worldwide and remains the most common nutritional deficiency. This global prevalence is concentrated in preschool-aged children, menstruating women and girls, and pregnant women (11). In the United States, 2% of adult men, 9% to 12% of white women, and up to 20% of black and Mexican American women are estimated to have IDA. The racial differences are pronounced, especially in the African American population, most likely due to genetic variation. It is important to recognize that the WHO parameters were not meant to be an exact standard for all to follow but that it was meant to help establish a basic standard for the international community and that these cutoffs were developed at a time when testing and diagnosis varied widely. More recently, the NHANES III and Kaiser–Scripps database have allowed more specific data to be based on ethnic origin. This has allowed for a better understanding of the variation in the lower limit of normal based on age, race, and gender, with appreciably lower limits of normal hemoglobin concentrations for African Americans being recognized (1,8,12,13).

Due to the prolonged life span, 120 days, of the mature RBC, it is important to consider the stages necessary to reach IDA. The process of reaching IDA must first occur with a negative iron balance, followed by iron depletion (iron storage is low but the body is still able to maintain normal physiology), followed by iron-deficient erythropoiesis, and finally IDA (14,15). Iron deficiency is the result of an imbalance between the iron demand by the body and iron absorption from the diet. Typical causes include inadequate dietary intake in infants and children, absorption hindrances in older adults, and physiologic losses in menstruating women. Iron deficiency in adults may also be a sign of chronic blood loss and may stem from malignancy. Consideration of the most likely cause of anemia and a patient's risk factors based

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on age and dietary factors is important in clinical care as it may determine whether simply prescribing iron supplements or performing additional clinical testing for blood loss is warranted. This involves considering specific risk factors for IDA across the life cycle. Prenatal vitamins with iron are prescribed to all pregnant women, and compliance has been shown to reduce the number of low–birth-weight infants (16) (see Chapter 27). Infants may be at high risk if they are living in poverty, were preterm or low birth weight, or are fed primarily underfortified dairy milk (not breastmilk or formula) before 1 year of age, which has been demonstrated to increase blood loss and infections in infants (see Chapter 29). A higher prevalence of IDA is consistently observed among children and adolescents with overweight (Body Mass Index [BMI] 85–95th percentile) and obesity (BMI >95th percentile). This is clinically significant as an analysis of data collected from almost 10,000 children in the United States showed IDA was more prevalent in overweight/obese children aged 2 to 16 compared to their normal-weight peers (5.5% vs. 2.1%). This increased risk of IDA remained after adjustments for age, sex, race, and poverty status. Studies have found few differences in nutrient intake between overweight/obese children and their normal-weight peers with the current evidence, suggesting that dietary factors do not account for the majority of differences in IDA status between these two groups. Factors including pro-inflammatory proteins and the effects of fat mass on iron absorption are under review as likely mechanisms (17). The proposed mechanism is related to the chronic inflammatory state resulting from metabolic disturbances in overweight/obesity. Serum ferritin is an acute-phase protein and is elevated during states of inflammation. This inflammation can affect overall iron homeostasis by disrupting the regulation and synthesis of other acute-phase proteins, including transferrin, haptoglobin (a protein produced by the liver that clears free hemoglobin found outside of red blood cells from circulation), and hepcidin (an important peptide hormone produced by the liver that binds and limits iron's gut absorption and inhibits irons release from macrophages, thereby causing systemic regulation of iron). This may affect the distribution of iron to cells throughout the entire body (18,19). Lastly, the type of iron in the diet greatly influences the absorption in the gut. Heme iron, mostly found in meats, is more efficiently absorbed (15% to 40%) and less influenced by modifiers, while nonheme iron, the predominant form in iron-containing plant foods and meats, is less well absorbed (1% to 15%) and very influenced by enhancers and inhibitors in the diet (20,21). While heme iron is better absorbed, reducing or eliminating meat in the diet can be done with minimal impact on total dietary iron content. In Western societies, vegetarians and nonvegetarians have a similar prevalence of true IDA, which is attributed to the iron fortification of many grain products. Nonheme iron is also affected by enhancers and inhibitors in the diet; phytic acids (found in legumes and lentils) and tannic acids (found in tea and coffee) can inhibit absorption of nonheme iron, while foods containing ascorbic acid (vitamin C) can enhance absorption (21). Although vegetarian women, in particular, do tend to have lower iron stores (i.e., low serum ferritin levels) and lower but normal hemoglobin and hematocrit levels, there is no resulting associated morbidity or mortality described in the literature (20,22).

Anemia of chronic disease is the second-most prevalent anemia worldwide and is often coexistent with IDA. Its diagnosis is usually associated with acute/chronic inflammation, cancer, or chronic infection. Treatment of underlying disease is the mainstay of therapy; however, when this is not feasible, there are alternate strategies that may be assisted with the use of micronutrient therapy (23).

Patients with anemia of chronic disease often receive treatment to optimize their hemoglobin level as this is associated with improved survival and treatment outcomes. However, iron treatment is used with caution as iron can be utilized by bacteria and tumor cells as well as cause free radicals that can lead to tissue damage (24). In many cases, treatment may also include red cell transfusion, parenteral (IV) iron, or erythropoiesis-stimulating agents (25).

The most recent dietary reference intake for iron is 8 mg/day for healthy, non-menstruating adults, 18

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mg/day for menstruating women, and 16 mg/day for vegetarians (26). As previously mentioned, dietary iron consists of meat-derived heme iron, and nonheme iron, occurring in meats, plants, and supplemented in foods. Nonheme iron constitutes the majority of the daily iron intake, and its absorption is dependent on other dietary factors. It requires acid digestion, and bioavailability may be enhanced by vitamin C (ascorbic acid) or meat, while it is inhibited by calcium (and therefore dairy products), fiber, tea, coffee, wine, and any medicine that reduces stomach acidity (H_2 blockers, proton pump inhibitors, and antacids).

In adults, dietary sources of iron provide only 5% of total daily iron needs; in infants and children, this proportion is approximately 30%, due to increased needs for growth and development. Eighty percent of the iron present in a newborn term infant is accrued during the third trimester of pregnancy. Infants born prematurely or infants born to mothers with certain conditions (anemia, hypertension, diabetes) can be born with low iron stores. At birth there is a rapid transfusion of fetoplacental blood to the newborn, and studies have shown that delaying the time the umbilical cord is clamped from 1 minute after birth to 3 minutes after birth can increase the infant's blood volume by 30–40% and decrease the risk of anemia. In healthy term infants, very little iron is needed in the first 6 months of life due to these stores, after this a significant amount of nutritional iron is required. Children and adolescents are therefore at increased risk for iron deficiency due to inadequate dietary iron intake (27). Studies have shown that further delay in cord clamping to beyond 3 minutes, particularly in resource-poor settings with high rates of nutritional deficiency, can further decrease rates of iron-deficiency anemia up to 12 months of life (28). Clinical consequences of iron deficiency (iron depletion in itself even before anemia ensues) in infants and children include impairment of psychomotor development (29), cognitive function, and reduced leukocyte and lymphocyte function (30). One cross-sectional study of school-aged children and adolescents found lower standardized math scores among those who were iron deficient, even after controlling for possible confounders (31). Pica or pagophagia may be observed in severe cases (32). Rapid growth during adolescence predisposes this demographic to iron deficiency; even higher risk is seen in menstruating or pregnant adolescent girls (33). Strenuous athletic training among both girls and boys may lead to *sports anemia* due to increased iron demands (34).

While iron deficiency is the major cause of nutritional anemia, several vitamins appear to play an important role in determining its development and severity. For example, riboflavin and vitamin A have been shown to enhance the response of supplemental iron and folic acid (35). Vitamin C and copper enhance the absorption of iron, while copper also assists with its utilization.

Vitamin B_{12} (cobalamin) deficiency is another common cause of nutritional anemia, especially in older adults. Approximately 20% of older adults have some form of cobalamin deficiency (36,37), most commonly caused by absorption difficulties due to either pernicious anemia or the food-cobalamin malabsorption syndrome, characterized by an inability to release B_{12} from food (38). Food-cobalamin malabsorption is thought to stem from atrophic gastritis and long-term use of antacids or biguanides (39). However, it is important to note that in all of these cases, B_{12} deficiency may not always become full-blown anemia. Other groups at risk for vitamin B_{12} deficiency are strict vegetarians and vegans, individuals with gastrointestinal surgery limiting absorption, and pregnant and lactating women following strict vegetarian diets along with their infants. Vitamin B_{12} is synthesized by microorganisms and is not produced by plants; therefore, humans must absorb it in food. This may be in a naturally existing form in animal products or through fortified foods and supplements, which also have good bioavailability. Infants are at the greatest risk for deficiency when their mothers do not consume enough vitamin B_{12} because during periods of pregnancy and lactation, the maternal intake through gastric absorption has a more

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potent influence in transmission than the maternal stores. These children become symptomatic within months of birth (2 to 10 months), with symptoms including failure to thrive, anorexia, and developmental regression (40,41). Pregnant or lactating women who are vegans or lacto-ovo vegetarians are recommended to have vitamin B_{12} supplementation throughout pregnancy and lactation to provide adequate nutritional support to the infant (42).

The Department of Agriculture (USDA) recommends dietary intake of vitamin B_{12} for most adults around 2.4 mcg/day, with slight increases required for pregnancy and lactating women. The average US diet consumes approximately 5 mcg/day (43). Body stores of vitamin B_{12} are 2 to 5 mg, enough to support a person for up to 5 years after dietary B_{12} is no longer present. Insufficiency due to diet alone is therefore unusual, though it is possible in cases of severe dietary restriction. Red meat and dairy products offer advantages for absorption of iron and vitamin B_{12}; however, a diverse and balanced vegan diet with the addition of fortified foods and supplements can ensure adequate intake of both micronutrients. This is particularly important for children and adolescents following a vegan diet as B_{12} is not available from plant-based diets and must be provided in the form of fortified foods, such as soy products and cereals or supplements with a dose of 0.5 mcg for infants and 1.2 mcg for school-age children. Useful guides have been published (44), and this issue is addressed in more detail in Chapter 43.

In contrast, the most common cause of folate deficiency is nutritional, due to poor diet, increased requirements, as in pregnancy, and alcoholism (see Chapter 40). Pregnancy and lactation increase daily folate requirements from 400 to 800 mcg; prophylactic supplementation is therefore recommended for all pregnant and lactating women and may be advisable in all women of reproductive age who might become pregnant (see Chapter 27).

When the cause of anemia has been established as being a nutritional deficiency, most cases can be easily treated with oral supplementation. Iron deficiency is easily treated with oral iron supplements if dietary modification is unattainable. The initiation of folic acid food supplementation has led to a documented decline in the prevalence of folate deficiency, as well as a significant reduction in the number of babies born with neural tube defects (45). A dose of 1 to 5 mg/day is usually sufficient to treat folate deficiency.

Although vitamin B_{12} deficiency has conventionally been treated with monthly intramuscular cobalamin injections, increasing evidence suggests that as long as pernicious anemia is not the cause, high-dose oral supplementation is equally effective (46), better tolerated, feasible in a community setting (47), and more cost-efficient (48).

NUTRIENTS, NUTRICEUTICALS, AND FUNCTIONAL FOODS

Folate

Natural dietary sources of folate include citrus and other fruits, dark green leafy vegetables, and legumes. Since 1996, all flour and uncooked cereal grains have been supplemented with 140 mcg of folate/100 g of flour or grain, making fortified breakfast cereals and other grain products an important dietary source of folate in the United States (see Chapter 4). As discussed in Chapter 27, this practice has reduced the prevalence of pregnancy-induced folate deficiency and megaloblastic anemia, as well as occurrence and recurrence of neural tube defects associated with folate deficiency (49).

In addition, it is important to mention the methylenetetrahydrofolate reductase (MTHFR) enzyme, which is important for folate metabolism. A common mutation of this gene reduces the function of this enzyme,

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which can lead to hyperhomocysteinemia and a functional folate deficiency. This is an emerging risk factor for cardiovascular disease, as well as having associations with various disease states, including recurrent pregnancy loss, neural tube defects, cancers, and neurodevelopmental disorders (50).

Iron

The best dietary sources of iron include beef and other meats, beans, lentils, iron-fortified cereals, dark green leafy vegetables, dried fruits, nuts, and seeds (see Chapter 4). Iron is best absorbed as the ferrous (Fe_2^+) salt in a mildly acidic medium; taking 250 mg vitamin C or eating citrus fruits along with iron supplements or iron-rich foods is therefore recommended to optimize absorption. Calcium is a potent inhibitor of iron absorption, so patients should be told not to take iron supplements with milk and to take them 2 hours before or 4 hours after ingestion of antacids. Other dietary factors that can inhibit absorption of iron salts include intake of certain antibiotics as well as simultaneous consumption of coffee, tea, eggs, dietary fiber, or cereals. Enteric-coated or sustained-release capsules are largely unnecessary as iron is best absorbed from the duodenum and proximal jejunum. Iron supplements come in two forms: Ferrous (Fe_2^+) and ferric (Fe_3^+). Ferrous is better absorbed, whereas the ferric forms tend to be better tolerated with less GI complaints (nausea, constipation, abdominal pain, diarrhea). These side effects can also be limited by slowly titrating the dose and temporarily dose with food (14,51).

Traditionally, the recommended treatment for iron deficiency in adults used daily dosing in the range of 150 to 200 mg of elemental iron/day, which correlates to one 325 mg ferrous sulfate tablet (containing 65 mg of elemental iron) given three times/day. Increasing evidence now suggests that alternate-day dosing appears to result in better iron absorption than daily dosing. In recent studies, there is evidence that circulating levels of hepcidin reduced iron absorption such that lower doses with less frequent administration, 40 to 80 mg of iron once every other day, were better absorbed. Every other day dosing also reduces GI side effects (48). Patients who are unable to tolerate oral supplementation, undergoing dialysis, or with increased need of iron supplementation may be given parenteral forms of iron. IV iron was previously considered dangerous and for use only in extreme situations when oral iron was not tolerated. This was primarily due to concern over anaphylactoid-like reactions, which were rare but showed serious adverse effects. With the improved understanding of hepcidin and regular use of recombinant erythropoietin for patients with anemia of chronic disease states, IV iron is known to improve erythropoietic response and is now routinely used. A number of formulations are available for IV treatment of iron deficiency, with major differences including number of visits and time required to administer the full dose and cost; all products are equally effective in treating iron deficiency. Low molecular weight iron dextran is most commonly used as it can be administered as a single dose (52–54). IM iron is still available but is painful, has variable absorption, is associated with gluteal sarcomas, and has not been shown to be less toxic than IV iron. Therefore, IM iron is no longer routinely recommended in clinical practice (52).

Vitamin B_{12}

As noted previously, Vitamin B_{12} is found naturally occurring as a byproduct of microorganisms in meat and dairy products, as well as in fortified plant-based products. A 2018 Cochrane review showed both oral and intramuscular (IM) B_{12} to be equally effective at normalizing serum vitamin B_{12} levels for those who are deficient. Though these were small studies in clinical practice, oral dosing is felt to be equally effective (55). A review of vitamin B_{12} disorders by Solomon notes that the available intervention trials

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have used immediate-release tablets or liquid suspensions, while most over-the-counter supplements are formulated for timed release and may not have the same efficacy (56). A newer intranasal formulation is available; however, this has not been thoroughly studied and tends to be rather expensive. Sublingual forms are considered to be just as efficacious as oral forms (57,58). In patients with pernicious anemia (due to autoantibodies in the GI tract that inhibit absorption of B_{12}) or altered GI anatomy that affects the ileum, treatment with parenteral vitamin B_{12} is necessary. This is most commonly given IM but can also be given subcutaneously. It is available in three forms: cyanocobalamin, hydroxocobalamin, and methylcobalamin. In the United States, cyanocobalamin is the most commonly used form; however, it does require conversion into methylcobalamin before use in the body. Methylcobalamin is the form most commonly used in Japan. Proponents of methylcobalamin claim that it is more potent and effective; however, this light-sensitive form has no clear increased superiority in the literature (59,60).

RELEVANT NUTRIGENOMIC CONSIDERATIONS

As previously described, the MTHFR enzyme is important for folate metabolism. The utilization of folic acid may be influenced by polymorphisms on the MTHFR gene. These changes result in changes in gene expression and in some cases can ultimately lead to folate deficiency. A polymorphism is a variant within a gene, and unlike a pathogenic mutation a polymorphism does not always affect function. The MTHFR enzyme plays a role in the conversion of the amino acid homocysteine to methionine, so genetic variations of this gene can lead to impaired function of this enzyme, which results in elevated levels of homocysteine. This effect is exacerbated in individuals who are also nutritionally deficient in folate as folate itself provides a key step in the re-methylation and utilization of homocysteine. The most common genetic variant in the MTHFR gene is known as 677C>T, where the DNA base T is substituted for C, which causes a mild hyperhomocysteinemia (61). Elevated homocysteine levels increase the risk of cardiovascular disease and neural tube defects. It has been hypothesized that additional folate supplementation can compensate for this potential genetic risk. Folic acid supplementation is recommended for all pregnant women to help reduce the risk of neural tube defects. In terms of cardiovascular disease and many other conditions that have associations with MTHFR polymorphisms, such as neuropsychiatric disorders and certain forms of cancer, the clinical impact of folic acid supplementation is less clear. Importantly, these polymorphisms do not change the recommended dietary allowance for folate or the type of folate, such as folic acid, that the body can safely and effectively process. Studies of these MTHFR gene variants have shown mixed results, and the role of these variations and differences in homocysteine levels in clinical disorders remains unclear. The area of nutritional genomics provides exciting opportunities to explore more personalized medicine, but as the ongoing research into the MFHFR gene has shown, there is still much to learn about the clinical implications of genetic variations in micronutrient metabolism.

CLINICAL HIGHLIGHTS

Nutritional anemias constitute one of the most common preventable conditions in both the developing world and industrialized countries. Iron deficiency is a public health problem in all countries but particularly among children in developing countries. Most cases of IDA and other nutritional anemias can be avoided by consuming a healthful, varied diet rich in dietary sources of iron, folate, and vitamin B_{12}. Heme iron is best absorbed, but adequate iron may be obtained from a vegetarian diet under most conditions. A diet rich in iron-containing foods should be particularly encouraged for those with high iron

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requirements, such as infants, children, and pregnant and menstruating women; when lean meat is not a part of the diet in these populations, supplementation may be warranted. In addition, during times where oral supplementation may not suffice, it is perfectly appropriate to consider the newer and safer intravenous iron formulations for better treatment of severe IDA. Particular attention to micronutrient intake is recommended for all vegans and strict vegetarians, as well as long-distance athletes. Pregnant and lactating women should be counseled to take prenatal vitamins containing extra folic acid, B_{12}, and iron.

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Chapter 14

Diet, Bone Metabolism, and Osteoporosis

Alexis Tingan

INTRODUCTION

The hydroxyapatite crystals of bone are made up predominantly of calcium and phosphorus. Osteoporosis is the demineralization of bone due to a net movement of calcium from bone to serum, mediated by a predominance of osteoclast over osteoblast activity. Osteoporosis is to be distinguished from osteomalacia, a different pattern of demineralization resulting from vitamin D deficiency.

Osteoporosis likely affects more than 20 million adults in the United States. Risk factors include gender (female), early menopause, ethnicity (white or Asian), thin bone structure, low body mass index, smoking, heavy consumption of alcohol, sedentary lifestyle, and family history.

Dietary pattern, use of supplements, physical activity, and sunlight exposure at various periods of life have the potential to affect peak bone density, the rate of bone mineral losses, and the propensity to bone injuries, such as traumatic and pathologic/fragility fractures. The principal dietary consideration in the prevention and management of osteoporosis has long been lifetime calcium intake, although understanding of this association continues to evolve. In addition to lifestyle interventions, various pharmacologic interventions may be indicated in efforts to prevent disability from skeletal demineralization.

OVERVIEW

Bone metabolism is influenced by a variety of hormone actions. The serum calcium level is a stimulus to both parathyroid hormone (PTH) and calcitonin. PTH varies inversely, and calcitonin directly, with circulating calcium; PTH mobilizes calcium from bone, whereas calcitonin enhances skeletal deposition of calcium. PTH also increases activation of vitamin D, enhancing intestinal calcium absorption, and reduces urinary calcium excretion.

Peak bone mass is reached in the third to fourth decade of life, with gradual demineralization thereafter. Relatively rapid bone loss occurs in women during the 5 years following cessation of menses, and spine density diminishes by 3% to 6% annually. Bone loss in men apparently occurs at a fairly constant rate of 0.5% to 2% annually, depending on site, after peak bone mass is achieved. The clinical sequelae of osteoporosis result from fracture, most commonly at the wrist, hip, and spine. More than 50% of women past the age of 80 have experienced compression fracture of the spine.

Diet

Definitive evidence that increasing dietary intake of calcium increases peak bone density is lacking. However, suggestive evidence is available. A National Institutes of Health (NIH) consensus panel convened in 1994 concluded that average calcium intake in the United States is too low to support optimal bone health, and it revised recommended intake ranges upward (1). The NIH currently recommends a daily calcium intake of 1,000 mg in men aged 51 to 70 and 1,200 mg in men over 70 and women over 50 (2). The basis for the NIH-recommended intake levels is the evidence of threshold doses above which

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further incorporation of calcium into bone does not occur. Optimal calcium intake over time is the level that allows bone density to reach the maximum genetically "encoded" for a given individual. Paleolithic intake of calcium is estimated in the range of 2 g/day for adults (3) (see Appendix E). Relative inefficiency in the absorption of ingested calcium is protection against calcium excess under the conditions prevailing during our evolutionary history.

Although supplements may be useful in achieving the recommended intake of calcium, food sources offer the benefits of other nutrients known or thought to confer benefits on the skeleton, including vitamin D and trace minerals. A diet rich in dairy products and a variety of vegetables and grains will provide all of the nutrients thought to optimize bone health and may be recommended on other grounds as well. Calcium intake up to 2,500 mg/day is generally safe, although extreme intake may contribute to the formation of renal calculi (see Chapter 16) and interfere with the absorption of iron, zinc, and other minerals. Physical activity, particularly repetitive weight-bearing activities and resistance training, confer benefit to bone mass and strength, in addition to that attainable by nutritional means (4). In addition, fitness reduces the risk of injurious falls (5,6).

Calcium requirements are lower when sodium and protein intake is low, as both of these increase urinary losses of calcium (7). The reduced calcium requirements associated with non-Western diets may partly explain the inability to demonstrate a transcultural dietary calcium gradient that corresponds with osteoporosis or fracture risk. A comparison of the characteristics of matched samples of older vegetarians and nonvegetarians demonstrated similar calcium profiles (8). Vegetarianism (see Chapter 43) need not, therefore, have adverse effects on calcium nutriture, unless the diet followed is one that is low in calcium and high in sodium. There is longitudinal evidence from the Framingham cohort that diets high in alkaline-producing components, specifically fruits, vegetables, potassium, and magnesium, are associated with preservation of bone mass in both men and women (9,10). A study of participants following the Dietary Approaches to Stop Hypertension (DASH) diet, which emphasizes fruits, vegetables, and whole foods, along with varying levels of sodium intake, found significantly reduced bone turnover in subjects who consumed the lowest-sodium DASH diet (11).

Controversy persists regarding the significance to bone mass of protein intake, both in intake amount and protein source (12). Protein, and therefore nitrogen, intake results in increased urinary calcium losses. The mobilization of mineral from bone induced by protein intake is thought to be due to the buffering of acid generated during protein metabolism. Most dietary sources of protein are also sources of phosphorus, which, as noted, reduces urinary calcium. To the extent that protein ingestion contributes to calcium loss in urine, it is the result of the sulfur load imposed from sulfur-containing amino acids. This load causes the consequent acidification of serum and urine.

Previous hypotheses have suggested that since the sulfur content of vegetable proteins is less than that of animal proteins, sulfuric acid production would be less with vegetable protein intake (12–14). However, differences in sulfuric acid production between animal and vegetable protein are negligible (12,15). In addition, negative effects to bone health from urinary calcium losses from increased protein intake are offset by increased calcium resorption. Further, there is evidence that increasing protein intake can promote bone formation via insulin-like growth factor 1 (IGF-1) (16,17).

There appears to be little net effect of moderate protein intake (approximately 100% to 150% of the recommended dietary allowance [RDA], or 1.0 to 1.5 g protein/kg) on bone density (15); however, only approximately 30% to 50% of US adults have been estimated to consume moderate levels of daily protein (18). Recent evidence suggests that low protein intake, as often occurs among older adults, reduces intestinal calcium absorption and stimulates PTH, which may lead to increased bone loss (19,20). Postmenopausal women with hip fractures have been shown to have low protein intake (<0.8 g/kg body

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weight/day), and protein supplementation has been shown to decrease postfracture bone loss, medical complications, and length of rehabilitation hospital stays (21,22). A recent meta-analysis showed that higher protein intakes are associated with higher femoral neck and total hip bone mineral density (23). Protein may therefore be beneficial to bone when habitual intake is low or in the context of malnutrition (24–26).

In contrast, high protein intake from omnivorous sources, as is characteristic of the typical Western diet, has been shown to produce sustained hypercalciuria (15), though long-term sequelae of this are not fully understood. A review by Calvez et al. (27) demonstrated that the increased calcium excretion in high-protein diets was not associated with bone loss, and data suggest that the hypercalciuria may be due to increased intestinal calcium absorption induced by the high-protein diet.

Evidence from the National Health and Nutrition Examination Survey III suggests that a diet high in saturated fat may have deleterious effects on the mineral content of cancellous bone (28). A review of 40 women with high bone mineral density demonstrated that lower fat intake, body fat levels, and Low density lipoproteins (LDL) were strongly correlated with higher bone mineral density (adjusted R^2 = 0.347; $p < 0.001$) (29). It is hypothesized that a high-fat diet may decrease absorption of calcium, negatively affect osteoclastogenesis, and increase overall oxidative stress.

Dietary factors thought to influence the incorporation of calcium into bone include vitamin D, copper, zinc, manganese, fluorine, silicon, and boron (30). The predominant effects of protein and phosphorus on bone metabolism are mediated by the fractional reabsorption of calcium in the renal tubule. Protein decreases and phosphorus increases calcium reabsorption. The concomitant ingestion of protein and phosphorus in meat and dairy products has little net effect on calcium loss.

The recommended intakes of calcium at different stages of life (see Appendix E) are based on what is known about obligate daily calcium losses in stool and urine (200 to 250 mg/day in adults), an absorption rate of 30% to 40%, and the rate of calcium incorporation into bone during the growth phase (140 to 500 mg/day during various stages).

Calcium needs in adolescence have been studied by examining variation in dietary intake and associated variation in bone density in populations, by calcium balance studies, and by the provision of supplements in controlled trials (31). Bone density in adolescence is consistently influenced by age, weight, height, and pubertal status (32). Recent studies suggest that regular exercise is an important determinant of bone strength in young women (33–35), although excessive exercising in girls may lead to the female athlete triad, characterized by disordered eating, amenorrhea, and osteoporosis (36) (see Chapter 25). There is increasing evidence that this syndrome involves endothelial dysfunction and can be more accurately described as a tetrad (36). Evidence indicating a role for dietary calcium supplementation is less consistent, though observational studies have found that high intake of carbonated soft drinks among adolescents is associated with lower bone mineral density, particularly in girls (37–39); whether due to direct effects of the soft drinks or displacement of milk from the diet (40), this is a concerning finding as soft drink consumption continues to rise among this age group. To some degree, inconsistency in the results with dietary supplementation may be due to limited sample sizes, variation in the calcium preparations used, habitual calcium intake, or the predominant effects of physical activity, weight, and hormonal status. Despite the inconsistency in research findings to date, the possible benefits and lack of potential harm in raising calcium intake during adolescence have resulted in recommendations from the NIH to increase the recommended calcium intake for adolescents to 1,200 to 1,300 mg/day (2).

Pregnancy (see Chapter 27) is associated with the diversion of approximately 30 g of calcium from the maternal circulation to the fetal skeleton during the course of gestation. The effects of this process on the maternal skeleton remain uncertain. Were maternal calcium absorption or ingestion not to increase or

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excretion not to decrease, the formation of the fetal skeleton would consume 3% of maternal bone calcium. However, the increased levels of estrogen in pregnancy, resulting from placental estradiol production, favor osteoblast action and calcium deposition in bone. Exercise may help reduce the physiologic decrease in bone mineral density that occurs in pregnancy. In comparison to nonexercising low-risk women, very active women who performed over 10 hours of weight-bearing exercises/week experienced less of reduction in bone density during pregnancy (41).

Despite this so-called transient osteoporosis of pregnancy, most women undergo complete recovery of bone marrow density, and the risk of postmenopausal bone fractures appears to be inversely associated with parity (42,43). The effect of multiparity on bone density may be independent of body mass index (44,45). Interestingly, the fracture protective effects of pregnancy may be due to the geometric remodeling of bone following pregnancy. Pregnancy is associated with increased levels of circulating active vitamin D (1,25-dihydroxy vitamin D) and consequently with enhanced intestinal absorption of calcium. The effects of adolescent pregnancy on bone mass and postmenopausal fracture are uncertain, with some studies showing no effects with adolescent pregnancy and others showing negative effects (46–48).

Lactation (see Chapter 27) is associated with an initial loss of bone mineral, with subsequent compensation when menses is restored. Approximately 150 to 200 mg/day of calcium is diverted to breast milk at 3 months postpartum, and nearly 300 mg is diverted at 6 months. A total of 6 months of breastfeeding would require 4% to 6% of the maternal skeletal calcium without compensation.

High levels of prolactin and reduced levels of estrogen are associated with reductions in bone mass. While lactation appears to reduce bone mineral density the first 6 months of lactation, bone mineral density loss begins to reverse after 6 months and after the cessation of breastfeeding (49). Further, weight-bearing and resistance exercise may slow bone loss during lactation (50). With restoration of menses, bone density is restored, provided that dietary intake is adequate; neither pregnancy nor lactation has been found to be associated with increased risk of osteoporotic fracture (51). Case reports have shown that pregnancy and lactation-associated vertebral fractures treated with active vitamin D supplementation resulted in long-term improvement in bone mineral density and bone turnover markers (52). As with pregnancy, the effects of lactation on bone density in adolescents are less certain and of potentially greater concern. The net effect of lactation on the skeleton when vitamin D or calcium intake is deficient has not been adequately addressed.

Celiac disease has significant effects on skeletal health, and low bone mineral density is commonly found in patients with celiac disease. Initially, it was thought that the low bone mineral density was directly related to intestinal malabsorption (53). Patients with active celiac disease undergo significant histological changes that alter their ability to absorb nutrients. One such change is the loss of villi from the proximal gut, where calcium is actively absorbed. Additionally, unabsorbed fatty acids can bind up calcium in the intestinal lumen and further contribute to the malabsorption. This malabsorption leads to hyperparathyroidism, which causes loss of bone mass (54). A gluten-free diet has been shown to reverse the histological, calcium malabsorption, and bone mineral density effects of celiac disease. However, the reversal of the histological and calcium malabsorption effect with changes in bone mineral density do not appear to occur in tandem (55), suggesting other factors that affect bone mineral density in celiac disease. The chronic inflammatory state of patients with celiac disease likely plays an important role in their bone health. The upregulation of pro-inflammatory cytokines, coupled with the downregulation of anti-inflammatory cytokines, is thought to be one possible mechanism of decreased bone mineral density in patients with celiac disease (56). Studies have shown that a gluten-free diet is often nutritionally deficient in calcium and vitamin D and has a higher percentage of fat relative to carbohydrates than a typical diet (57,58). Some studies have shown improvement in bone mineral density after calcium and vitamin D

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supplementation (59), while others did not show any improvement with supplementation (60–62). Although evidence suggests a positive relationship between bone mineral density and exercise in individuals with celiac disease who develop osteoporosis, a 2- and 5-year follow-up studies did not find any benefit to bone mineral density with exercise, in addition to a gluten-free diet (63).

Senescence (see Chapter 31) in both men and women is associated with progressive demineralization of bone and increasing fracture risk. In women, the rapid phase of bone demineralization following menopause results in the loss of approximately 15% of skeletal calcium before a new steady state is reached. This loss is approximately equal to one standard deviation of bone density; thus, greater-than-average bone density during premenopause can result in ostensibly "normal" bone density even after rapid postmenopausal bone loss. Conversely, failure to optimize bone density before menopause renders a woman much more susceptible to clinical sequelae of the bone loss induced by menopause. Based on currently available evidence, a total daily intake of 1,500 mg of calcium is appropriate for both older men and women, with supplementation indicated to compensate for lesser dietary intake. Vitamin D supplementation is also reasonable; the 400 IU contained in a typical multivitamin is likely sufficient, although more may be needed for fracture prevention among those without adequate sun exposure or dietary intake.

There is some evidence that calcium supplementation may retard bone loss in postmenopausal women with habitually low calcium intake (less than 400 mg/day). Epidemiological data suggest that hip fracture rates are lower in populations with high habitual intake of dietary calcium, and preliminary evidence from randomized trials suggests that supplementation can be effective (64). Calcium supplementation does not appear to have significant effects on bone mineral density and fracture risk when dietary intake is greater than the typical Western diet of 700 mg daily (65,66). There is also evidence that high calcium intake may have adverse effects on health (67). Particular benefits have been demonstrated when calcium supplementation has been combined with vitamin D supplementation; increased bone density and reduced fracture rate in older women have been reported (68). Some controversy exists regarding the intake of cow's milk and the reduction of fracture risk. Cow's milk is known to have positive effects on bone metabolism (69). However, some epidemiologic studies have shown that increasing intake of cow's milk may actually increase the risk of fracture, possibly through increasing oxidative stress and inflammation (69,70). While they are intriguing, these epidemiologic studies are hindered by biases and confounders. These studies ultimately do not provide adequate data to advocate for significant reduction of cow's milk intake in the typical diet.

Whereas the rapid phase of postmenopausal bone loss is highly dependent on estrogen, and therefore relatively unaffected by supplemental calcium, more than 5 years after menopause, when the rate of bone loss slows, responsiveness to supplementation increases, particularly in women with relatively low dietary intake. Although evidence has been gathered demonstrating a reduction in the fracture rate with calcium supplementation, particularly when combined with vitamin D, the benefit would likely be much greater were calcium intake to be adequate throughout life. Thus, it is probable that the fracture rates in the treatment groups of even the most successful trials are higher than they would have to be if lifelong calcium intake were optimized.

Although the focus in older adults was until recently on calcium intake, interest has shifted somewhat to stores of vitamin D. Vitamin D intake among adults in the United States is generally about 100 IU/day; the most recent RDA is 600 IU/day for people 51 to 70 years old and at least 800/per day for people older than 70 (71). Circulating levels of vitamin D tend to be lower during the winter in higher latitudes; effects on bone metabolism have not been established with certainty. Epidemiological data support an association between osteoporosis and low serum vitamin D and reduced rates of intestinal calcium

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absorption. There is no consensus regarding circulating serum 25-hydroxy vitamin D levels and bone mineral density in both younger and older adults (72–74). Vitamin D levels in older adults are generally lower than in younger adults, with actual deficiency not uncommon in institutionalized older adults not exposed to natural light (75). Because of reduced sunlight exposure among older adults in general, dietary intake of vitamin D appears to be an important determinant of circulating levels. The principal source of dietary vitamin D is fortified milk. There is evidence to suggest that total serum vitamin D has a racial variance, with black Americans having lower total vitamin D levels than white Americans (76). The significance of this variance is unclear as white Americans have higher levels of vitamin D binding protein (VDBP) compared to black Americans (76). In one study comparing community-dwelling white Americans to black Americans, there was a difference in total vitamin D and VDBP but no difference in bioavailable vitamin D (76).

Vitamin D supplementation as an isolated intervention has not shown consistent utility in preventing fractures in older adults. A recent meta-analysis found no significant association between vitamin D and risk of hip fracture in community-dwelling adults older than 50 (RR, 1.21 [95% CI, 0.99 to 1.47]) (77). Meanwhile, another recent meta-analysis showed that high vitamin D levels did not reduce total fracture risk but did reduce hip fracture risk (RR, 1.1 [95% CI, 0.99, 1.24] for total fractures and RR, 0.89 [95% CI, 0.8, 0.98] for hip fractures) (78). There is evidence, however, that suggests that high-dose oral vitamin D supplementation (700 to 800 IU) given to older men and women can increase bone density and decrease the fracture rate, especially in those with documented vitamin D deficiency (79,80). One randomized trial of the effect of vitamin D supplementation on calcium absorption in postmenopausal women observed that vitamin D supplementation did not significantly improve calcium absorption except when serum 25-hydroxyvitamin D levels were below 10 ng/mL (81). The potential benefits of vitamin D supplementation are most likely to be realized in subjects with low habitual vitamin D intake or limited sun exposure and if coadministered with supplemental calcium (82).

Phosphorus, the other main mineral in bone, is abundantly available in the typical Western diet. Phosphorous is modulated by PTH, vitamin D, and fibroblast growth factor 23 (FGF23) (83). Excess intake of phosphorus increases PTH synthesis and upregulates FGF23 expression with the net effect of increasing calcium reabsorption (83). Therefore, there appears to be minimal net effect of increased phosphorous intake on bone health. Diets high in processed foods with phosphate additives, meat, and soda may contain an excess of phosphorus that can detrimental to bone mass (84). However, if calcium and phosphorus in the diet remain proportional, high phosphorus intake does not appear to be harmful (84).

Once osteoporosis has developed, dietary manipulations are relatively, if not completely, ineffective at restoring bone density. Pharmacotherapy is required for this effect; a recent review of treatment options is available (85). Hormone replacement with estrogen directly stimulates osteoblasts and enhances production of active vitamin D, and estrogen supplementation effectively prevents the rapid bone loss that occurs at menopause. However, use of hormone replacement has not been considered first-line treatment due to its potential harms such as stroke, venous thromboembolism, and invasive breast cancer (86). The selective estrogen receptor modulators (SERMs), tamoxifen and raloxifene, appear to have comparable effects on bone as estrogen, decreasing risk of nonvertebral and vertebral fracture, respectively (87). SERMs are not without risks as both increase risk of thromboembolic events and tamoxifen increases risk of endometrial cancer (87). Bisphosphonates, such as alendronate, etidronate, and risedronate, inhibit osteoclast activity. Alendronate has been shown to increase bone density in osteoporosis and to reduce the fracture rate (88–91). Calcitonin reduces osteoclast activity and bone resorption. Salmon calcitonin, which is available as a nasal spray, offers analgesic action helpful for patients with acute osteoporotic

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fracture (92). It reduces osteoclast activity and bone resorption. Teriparatide, a recombinant form of PTH, can help stimulate new bone formation. Phytoestrogens (see Chapter 33) have estrogen-like properties, and limited evidence suggests that high intake of foods or supplements containing isoflavone phytoestrogens may help reduce bone turnover rates and increase bone mineral density (93,94).

The role of pharmacotherapeutics warrants mention in defining the limitations of dietary management of osteoporosis. Malnutrition contributes importantly to adverse outcomes following hospitalization of older patients for hip fracture. Sequelae are partly preventable with a vigorous program of nutritional support, which should be a part of the management plan for every such patient (see Chapter 26).

NUTRIENTS, NUTRICEUTICALS, AND FUNCTIONAL FOODS

Calcium

Calcium intake is essential to bone health and the prevention of osteoporosis, as discussed earlier. More detail regarding calcium intake is provided in the Nutrient Reference Data Table in Appendix E. Good sources include dairy products, mustard greens, almonds, tofu, and sardines. Other seafood is a moderately good source. High-oxalate vegetables, such as spinach, provide little calcium that is bioavailable. There is evidence to suggest that calcium may have more favorable effects than calcium supplements on estrogen metabolism and bone mineral density in postmenopausal women (95).

The association between calcium supplements and cardiovascular events is unclear. A meta-analysis by Bolland et al. (96) reviewed over 12,000 participants from 15 placebo-controlled double-blind randomized trials and demonstrated that a 31% increase in the relative risk of myocardial infarction in the individuals taking ≥500 mg of daily calcium supplementation (HR, 1.31, 95% CI, 1.02 to 1.67). It is thought that perhaps calcium supplements result in an acute increase in calcium levels that may result in vascular calcification. However, the meta-analysis did not observe any increase in any vascular-associated endpoints, such as the incidence of stroke or death. Other studies have shown that overall increased calcium intake may be protective against cardiovascular events. The Iowa Women's Health Study of 34,486 postmenopausal women aged 55 to 69 years demonstrated that women who had the highest quartile of calcium intake had a 33% reduction in deaths from ischemic heart disease (RR, 0.67; 95% CI, 0.47 to 0.94) (97). A more recent meta-analysis showed that upper intake levels of calcium was not associated with Cardiovascular disease (CVD) in healthy adults. However, vascular-associated endpoints of cardiovascular disease were not the primary outcomes examined (98).

There is also continued debate regarding the association between calcium and cancer risk. A Cochran review of two Randomized controlled trial (RCT) demonstrated that calcium supplementation may help prevent the development of adenomatous polyps in the colon, but there is not enough evidence to recommend the use of calcium supplementation to prevent colorectal cancer (99). A recent 4-year, double-blind, placebo-controlled, population-based randomized trial comparing calcium and vitamin D supplementation versus placebo did not find any significant reduction of cancer risk in the treatment group (100).

There are a variety of calcium preparations available. The two most widely available supplements are calcium carbonate and calcium citrate. Calcium carbonate is considered the first line in supplementation since it is generally less expensive than calcium citrate and is well absorbed when taken with a meal (101). However, calcium citrate appears to be more available than calcium carbonate when taken with a meal (102). In addition, calcium citrate is absorbed well in a fasting state, in individuals with achlorhydria and in those taking proteinpump inhibitors and H2 blockers (103,104). Its absorption is

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enhanced if the tablet is chewed or disintegrates readily. Although some controversy exists regarding the optimal dose of calcium for prevention of osteoporosis, a teleologic view would favor fairly high intake. Our paleolithic ancestors apparently consumed considerably more calcium than we do (3,105).

Magnesium

Although the average intake in the United States is below the RDA, the effects of magnesium deficiency on bone health are unclear (106,107). Magnesium is essential for the secretion and action of PTH, but supplementation of magnesium has not shown clear benefit bone metabolism. Fruit and vegetable consumption has been linked to bone health, and one mechanism for this association is thought to be their high magnesium content (108). Since magnesium is a known calcium antagonist, magnesium supplementation should be approached with a goal of achieving optimal magnesium-calcium homeostasis (109,110).

Approximately 60% of the body's magnesium stores are in bone: one-third on the bone surface and two-thirds incorporated into hydroxyapatite (111). Under conditions of calcium deficiency, magnesium may displace calcium in bone mineral. The exact influences of magnesium nutriture on osteoporosis or fracture risk are uncertain (112,113)

Vitamin K

Vitamin K functions in the γ-carboxylation of glutamic acid, contributing to the production of a variety of physiologically important proteins. The most prominent products of vitamin K metabolism participate in coagulation (see Chapters 4 and 9). Several protein products that are dependent on vitamin K are incorporated into bone. One such product, osteocalcin, can be measured in serum as a marker of bone turnover. Circulating osteocalcin is low in low vitamin K states, such as use of warfarin (114). In vitro, vitamin K has been shown to inhibit osteoclastogenesis, promote osteoblastogenesis, and regulate the extracellular matrix mineralization of bone (115,116). Further, signs of impaired vitamin K metabolism are common in patients with osteoporosis (114).

Evidence is conflicting regarding vitamin K supplementation decreasing fracture risk (117–120). One randomized trial reported that vitamin K supplementation did not prevent age-related declines in bone mineral density but did reduce fracture risk (118). In transplant patients, postoperative vitamin K supplementation was demonstrated to have a positive effect on lumbar spine bone mineral density (120). A meta-analysis of observational and experimental trials concluded that supplementation with oral vitamin K (phytonadione and menaquinone) reduces bone loss and prevents fractures (114). However, a recent update to this meta-analysis did not find statistically significant evidence for vitamin K supplementation affecting bone mineral density or vertebral fracture (121). The investigators found reduced risks of any clinical fracture, but there was insufficient evidence to confirm this finding (OR, 0.72, 95% CI, 0.55 to 0.95) (121).

Iron

Iron plays a role in bone health by participating in the synthesis of collagen from procollagen as well as in vitamin D metabolism via the cytochrome P450 superfamily (122–124). Although there are no well-established guidelines regarding iron supplementation and bone health, iron overload and iron deficiency have been found to negatively affect bone health. Therefore, maintaining a balanced level of iron intake is optimal for maximizing bone homeostasis (125).

Phosphorus

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Phosphorus is stored in bone at a ratio of 1:2 with calcium, based on mass. Although 85% of body phosphorus is stored in the skeleton, it contributes to a wide range of physiologic functions, including the storage and generation of energy in the phosphate bonds of Adenosine triphosphate (ATP). Phosphorus is widely distributed in the diet; a typical American diet provides approximately 1 g/day for adult women and 1.5 g for adult men. The major sources are dairy, meat, poultry, and fish; cereals contribute approximately 12% of the total. Phosphorus is abundant in food additives; a highly processed diet may provide as much as 30% of intake in the form of additives. Of note, the ratio of calcium to phosphorus in human milk is nearly twice as high as that in bovine milk.

Phosphorus deficiency does not occur under normal dietary conditions. It may be induced by protracted use of aluminum bases, which bind phosphorus. Some studies show that intake of carbonated soft drinks, which contain phosphoric acid, is associated with reduced bone mineral density in women and adolescent boys and girls (126–128). Other studies show no link between carbonated drink intake and decreased bone density (40,129). Since milk itself has a high phosphorous content relative to carbonated beverages, it is thought that any decrease in bone density as a result of carbonated drink intake is due to these drinks substituting for milk in the diet rather than an increased phosphorous load (84). Bone loss results when phosphorus deficiency occurs, though the ratio of phosphorus to calcium appears to be more important than the absolute intake (130). Recommended intake of phosphorus is based on the maintenance of a 1:1 ratio with calcium.

Vitamin D

Vitamin D is essential in the intestinal absorption of calcium and may be derived from food sources or synthesized in skin with exposure to sunlight. The RDA for vitamin D is based on age, as follows: for those 1 to 70 years of age, the RDA is 600 IU daily, 15 mg of cholecalciferol activity; for those 71 years and older, 800 IU daily; and for pregnant and lactating women, 600 IU daily (131). Although the evidence base is limited, an intake of 400 IU/day is recommended for children 0 to 12 months. These RDAs are based on minimal sun exposure. The principal dietary source of vitamin D in the United States is fortified milk, which contains 400 IU/quart. The vitamin is stable with regard to processing, storage, and cooking.

Vitamin E

Vitamin E is an antioxidant that has been shown to promote trabecular bone formation and prevent bone calcium loss in rodent models, decrease cartilage resorption, and improve bone structure in animal models (132,133). It is hypothesized that vitamin E counteracts the increased bone resorption resulting from oxidative stress. In human studies, vitamin E supplementation has been associated with a decreased risk of hip fracture in smokers only (134,135).

Phytoestrogens

Phytoestrogens are a group of plant-based compounds that exert estrogen-like effects on the body. Although there is considerable interest in the potential of phytoestrogens to ameliorate the impact of ovarian endocrine failure at menopause on bone density, there is not consistent animal and human data to suggest that phytoestrogens help protect postmenopausal bone loss (136,137). Further, the benefits of phytoestrogens are likely stage of life dependent (137). Isoflavones, a group of phytoestrogens, are particularly abundant in soy products. Diets rich in soy have been associated with low rates of osteoporotic fracture (138,139) (see Chapter 33). The Shanghai Women's Health Study, a population-based prospective cohort study of 75,000 Chinese women aged 40 to 70 years, found that higher soy intake was associated with a lower risk of fracture (140). Despite their potential benefits, phytoestrogens

are endocrine disruptors, and their long-term effects on growth and reproductive health are unknown (141).

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Boron

Boron appears to influence calcium balance, reducing urinary losses. The mechanisms of boron's action on calcium metabolism are uncertain. Postulated effects include hydroxylation of vitamin D and stimulation of increased estradiol production (142). Boron may enhance the effects of estrogen on bone (143). Excess from diet is unlikely, and doses up to 10 mg/day are nontoxic. Doses exceeding 50 mg/day in the form of supplements have induced gastrointestinal discomfort and possibly seizures. Estimated intake in the United States ranges from 0.5 to just over 3 mg/day; 1 mg/day is believed to be sufficient. Boron is found in beans, beer, nuts, legumes, wine, and green leafy vegetables (see Appendix E).

Fluoride

Fluoride is nearly ubiquitous in soil and water but in small and variable amounts. The incorporation of fluoride into bone is proportional to intake. Food sources of fluoride in the United States contribute an estimated 0.3 to 0.6 mg/day, with the distribution of foods obscuring differences in the regional fluoride contents of soil.

The principal determinant of variation in fluoride intake is water and beverages. An intake of 1.5 to 4.0 mg/day is recommended for adults; average intake is in this range. Intake of 0.1 to 1 mg daily during the first year of life, and up to 1.5 mg for the next 2 years, is recommended. Mottling of teeth occurs in children with a fluoride intake above 2 mg/day. Chronic intake of more than 20 mg/day induces toxicity in adults, leading to disruption of bone architecture and adverse effects on kidney, muscle, and nerve.

Fluoride is incorporated into hydroxyapatite and stimulates the action of osteoblasts. Studies have shown that fluoride can increase bone density and strength, but because of reduced elasticity, the resistance of bone to fracture is not necessarily enhanced by fluoride supplementation (144–146). High-dose fluoride (greater than 50 mg/day) has been shown to increase bone density in osteoporosis and to reduce the rate of vertebral fracture (147–149). However, one study showed an increase in nonvertebral fractures with supplementation with sodium fluoride 75 mg daily and calcium carbonate 1500 mg daily (147). For benefits to occur with fluoride supplementation, sufficient calcium must be provided concomitantly; fluoride induces osteogenesis and especially consequent "bone hunger" in the spine. If calcium is unavailable from the diet, it may be leached from other skeletal sites (150).

Variation in doses and regimens used in clinical trials has perpetuated controversy regarding the role of fluoride in the treatment and prevention of osteoporosis (150–152). Evidence from recent randomized trials suggests that a low-dose fluoride regimen (approximately 11.2 mg/day) may be more effective at preventing fractures, even though higher doses (20 mg/day) have been associated with greater increases in bone density (153,154). Although supplementation at 20 mg/day can decrease the incidence of vertebral fractures, this should be weighed against evidence that supplementation at 20 mg has been found to increase the incidence of nonvertebral fractures (154).

Caffeine

Caffeine apparently reduces active transport of calcium in the intestine, thereby reducing absorption and inducing a slight negative shift in calcium balance. The effect is modest and completely compensated by the addition of milk to coffee (see Chapter 41).

Sodium

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Sodium and calcium share a transport system in the kidney, and filtered sodium is accompanied by calcium. For every 2.3 g of sodium excreted in urine, 20 to 60 mg of calcium is lost (106,155). High-sodium diets therefore increase calcium requirements (156).

Omega-3 Fatty Acids

Since increased expression of inflammatory cytokines with aging is thought to be one mechanism contributing to osteoporosis, anti-inflammatory nutrients such as omega-3 fatty acids are hypothesized to be beneficial for bone health. Abundant in oily fish such as salmon, tuna, and trout, omega-3 fatty acids, may be beneficial for bone metabolism. The United States Food and Drug Administration recommends 8 or more ounces of oily fish/week, which translates to 250 mg/day of omega-3 fatty acids (157). One review of 10 randomized trials investigating skeletal outcomes in individuals with omega-3 fatty acid supplementation versus placebo demonstrated that 4 of the 10 studies reported improvements in bone mineral density or bone turnover markers (158). However, given that three of these studies combined high calcium supplementation with omega-3 fatty acid supplementation and the limited number of trials, there is insufficient evidence to draw conclusions regarding the effect of omega-3 supplementation on skeletal health. A recent meta-analysis of 8 randomized control trials studied the effect of omega-3 fatty acid supplementation on bone turnover markers in postmenopausal women. The investigators found a slight decreasing effect of omega-3 fatty acids on bone turnover markers, but one study combined omega-3 fatty acids with fortified milk and another combined omega-3 fatty acids with omega-6 fatty acids (159).

Other Nutrient Effects

Phytate and oxalate in food complex with calcium. They are abundant in cruciferous vegetables and limit the bioavailability of calcium from such sources. Although phytate and oxalate levels are high in beans, calcium from beans is relatively bioavailable. Fiber can interfere with calcium absorption, and wheat bran seems to have a particularly strong influence.

Unlike with phytate and oxalate, the effects of concomitantly ingested fiber generalize to calcium from other foods. In the average US diet, the effects of fiber intake on calcium absorption are negligible (106,160).

A role for zinc, manganese, and copper as cofactors in enzymatic processes germane to bone metabolism has stimulated interest in the influence that dietary levels of these trace minerals may have on bone. To date, there is minimal evidence in humans that these trace minerals exacerbate osteoporosis when intake is low or ameliorate it when intake is raised (161,162).

Elevated serum homocysteine levels have been associated with osteoporosis, as well as vascular disease, raising the possibility that vitamins B_{12}, B_6, and folate may affect bone metabolism (163,164). In particular, these nutrients tend to be deficient in the diets of older people (165). A recent cross-sectional study in Shanghai, China, of men ≥ 50 years and women ≥45 years did not show evidence of increased osteoporosis associated with decreased B_6 when calcium, vitamin D, and PTH were controlled (166). There is some evidence of an association between vitamin B_{12} status and bone mineral density, particularly in frail older women (167,168); however, evidence that B vitamin supplementation may play a role in the prevention of osteoporosis is not yet available (169).

Evidence suggests that antioxidant intake may protect against osteoporotic hip fracture; however, this effect may be significantly reduced in patients who smoke (134). Conversely, high intake of vitamin C, E, or both, may protect against the adverse effects of smoking on bone, presumably because oxidation plays a role in the acceleration of osteoporosis in smokers (170).

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There is increasing evidence that chronic proton-pump inhibitor (PPI) use or high-dose PPI treatment is associated with increased risk of bone fractures. A meta-analysis demonstrated that PPI use was associated with increased risk of hip (RR, 1.30; 95% CI, 1.19 to 1.43), spine (RR, 1.56; 95% CI, 1.31 to 1.85), and any-site fractures (RR, 1.16; 95% CI, 1.04 to 1.30) (171). This was corroborated by a subsequent meta-analysis of 12 studies covering 1,521,062 patients (172). Further, a recent meta-analysis of 32 studies involving 2,181,546 individuals suggested that PPI use may moderately increase the risk of any-site, hip, or spine fracture (173). The mechanism underlying this relationship between PPI and bone fractures is unclear. One hypothesis is that the hypochlorhydria induced by the PPI results in decreased absorption of important vitamins and nutrients, including calcium, magnesium, and vitamin B_{12} (174). PPIs have been shown to increase gastric pH to 5.5, and in vitro studies have reported that calcium dissociation decreases from 96% at pH 1 to 23% at pH 6.1 (175). PPIs have also been shown to induce hypomagnesemia (176) and cause malabsorption of vitamin B_{12} (177).

CLINICAL HIGHLIGHTS

Dietary management is fundamental to the primary and secondary prevention of osteoporosis, and it plays an important role in tertiary prevention. The origins of osteoporosis are in childhood and adolescence, during which time adequate physical activity, vitamin D, and dietary calcium are particularly important. Peak bone density is reached by around the end of the third decade. Calcium intake of about 1,300 mg/day is advisable during adolescence, along with moderate sun exposure and/or at least 600 IU of vitamin D. To achieve these thresholds and to optimize bone metabolism, the diet should be rich in fortified nonfat dairy products and a variety of vegetables, fruits, and grains. Moderation in protein and sodium intake is advisable.

These recommendations are compatible with the dietary pattern advisable on other grounds (see Chapter 45). Hormone replacement therapy is no longer recommended as first-line treatment for postmenopausal women; instead, the use of SERMs, calcium and fluoride supplementation, calcitonin, or alendronate might be considered. These options have not been studied for primary prevention, but evidence supports consideration of their use for secondary prevention (178).

In older adults, vitamin D supplementation to achieve an intake of at least 800 IU/day is indicated; such an intake can be achieved with use of a multivitamin. As calorie intake declines, the need to supplement calcium to achieve recommended intake levels is more probable. Calcium carbonate is readily available and inexpensive. Any calcium preparation should be given in divided doses to optimize absorption (57).

A diet in compliance with overall recommendations for fruit, vegetable, grain, meat, and dairy intake will provide various nutrients—including magnesium, zinc, boron, and vitamin K—in amounts adequate to contribute to the health of bone. Brief recommendations in office practice should focus on consuming a diverse diet, consuming nonfat dairy products, avoiding or quitting smoking, limiting alcohol intake, and engaging in consistent weight-bearing physical activity, at least some of which should be outdoors in sunlight (35).

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Chapter 15

Diet and Respiratory Disease

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INTRODUCTION

Nutritional and respiratory status are related in a variety of ways. Malnutrition, either in isolation or as the result of acute or chronic illness, impairs respiratory function directly by weakening diaphragmatic contractions and overall diaphragmatic strength, making it more difficult to expel mucus (see Chapter 26). Malnutrition impacts the respiratory system indirectly by causing relative immunosuppression (see Chapter 11). As pneumonia is a leading cause of hospitalization due to infectious disease and is a leading nosocomial infection, the relationship among nutritional status, immune function, and the respiratory system is of particular importance.

The link between diet and the pulmonary system is especially clear in patients with limited respiratory reserve and CO_2 retention. The respiratory quotient of carbohydrate is higher than that of either fat or protein, justifying the restriction of carbohydrate in certain patients. Evidence supports the manipulation of diet to reduce the respiratory quotient for modification of long-term outcomes in patients with chronic obstructive pulmonary disease (COPD) (1,2).

Dietary triggers of asthma and exacerbations of COPD are under investigation. Dietary intake may influence the production of surfactant. Whereas conclusive evidence supports a role for adequate nutritional status in obstructive pulmonary disease, evidence for a protective or provocative role of specific micronutrients is mostly preliminary to date. Generally, obesity and asthma have been closely linked, and a diet high in fiber and low in fat has been linked with improved respiratory function in asthmatics. The antiinflammatory properties of n-3 fatty acids, described in other chapters (See Chapters 2, 6, 7, 9, and 45) pertain to airway inflammation as well and may prove to be of benefit in obstructive disease, such as asthma and chronic bronchitis.

OVERVIEW

Diet

Malnutrition has been shown to be common among patients with clinically significant obstructive airway disease, ranging from 17% to 28% (2–4). Mortality rates among patients with COPD rise substantially with the advent of malnutrition. Airway obstruction increases the metabolic costs of breathing, as does the need for higher respiratory rates to compensate for a reduction in the proportion of tidal volume effective in gas exchange. In addition, malnourished patients with COPD have decreased diffusion capacity and increased CO_2 retention.

Macronutrient intake patterns may directly influence the adequacy of gas exchange by leading to variable CO_2 production. Every molecule of carbohydrate ingested results in a molecule of CO_2 produced; therefore, the respiratory quotient of carbohydrate has a value of 1. The respiratory quotient of

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protein is 0.8, whereas that of fat is 0.7. Protein supplementation may increase oxygen consumption due to its relatively high thermic effect. Protein consumption also tends to increase ventilation, potentially leading to dyspnea in patients with limited reserve. Thus, based on metabolic effects, a relatively high-fat, carbohydrate-restricted diet is indicated for patients with CO_2 retention. Although the capacity of such diets to reduce CO_2 production has been shown, the capacity of such diets to modify clinical outcomes has not been demonstrated conclusively to date.

Weight loss in chronic pulmonary disease, such as COPD and cystic fibrosis, has been attributed to increased resting energy expenditure, although evidence in support of this is inconsistent. An increased work of breathing (WOB) may contribute to an elevation of resting energy expenditure, but inefficiency in oxygen metabolism with exertion may contribute more. Cytokines associated with the disease state may contribute to catabolism and attenuate appetite. Negative energy balance during acute exacerbations of COPD is apparently due to both reduced energy intake relative to baseline and an increase in resting energy expenditure (5,6). Elevated levels of tumor necrosis factor-alpha (TNF-alpha), and other acute-phase-reactant proteins, have been reported in patients with COPD and weight loss, although causality has not been adequately studied to date (7,8).

A review of nutritional support for severe pulmonary disease of diverse etiologies suggests that weight loss, particularly loss of fat-free mass, is a poor prognostic sign and an independent risk factor for mortality. Preliminary evidence suggests there is some benefit to nutritional support, combined with an anabolic stimulus such as exercise, in order to avoid adipose weight gain from supplemental calories (9–11). A recent study examining the clinical outcomes in patients with COPD who received comprehensive pulmonary rehabilitation and nutritional support showed that oral nutritional supplements could improve functional status, upper-extremity muscle strength, and quality of life in patients with COPD (12). Further investigation of effective means of suppressing inflammatory mediator activity and preferentially restoring lean body mass is indicated. The use of nutrients to help preserve or increase lean body mass is addressed more thoroughly in Chapter 32.

In COPD, energy intake of 1.4 to 1.6 times the resting energy expenditure is indicated during periods when lean body mass is being recovered; energy then should be maintained at 1 to 1.2 times the resting energy expenditure to avoid increased CO_2 generation (13,14). Protein supplementation at approximately 1.5 g/kg/day is advocated by some in the aftermath of COPD exacerbation to facilitate the reconstitution of lean body mass (7). Ingestion and postprandial gastric distension may impair gas exchange slightly, leading to reduced calorie consumption as a means to avoid dyspnea.

The energy requirements of patients with COPD and malnutrition are estimated at 45 kcal/kg/day, approximately 80% to 90% higher than predicted resting energy expenditure (see Nutrition Formulas in Appendix A). In such patients, expert opinion favors a diet relatively high in total fat (45% to 55% of total calories), with low intake of saturated fat to avoid cardiovascular sequelae (15). Population-based survey data suggest an association between an overall healthy dietary pattern, which includes fish, and lower risk of developing smoking-related COPD (16).

Nutritional support with high-fat rather than high-carbohydrate preparations, in addition to increasing energy density to meet sufficient needs, offers the theoretical advantage of a lower respiratory quotient (14,15). Cai et al. demonstrated improvement in lung function measurements and other clinical parameters with this approach as compared to the traditional high-carbohydrate diet (15).

Reduction in the mass and contractility of the diaphragm has been observed in both animals and humans subject to malnutrition. Muscle wasting of the diaphragm results in decreased ability to expel mucus, as well as the patient's ability to exercise. Nutritional support may reverse this effect (17,18). Growth

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hormone and anabolic steroids have been used with some success, but their roles in clinical management are uncertain (19). Muscle wasting is characteristic during exacerbations of COPD and is compounded by the administration of corticosteroids. Tashkin and Strange (20) showed enhanced effects when inhaled corticosteroids were combined with long-acting beta-2-agonists (LABAs). Androgenic anabolic steroids and creatine supplementation have also shown promise in COPD individuals with muscle wasting (19,21). Dietary supplementation has been shown to attenuate, but not reverse, this tendency (22).

One study comparing patients with COPD with healthy smokers without a diagnosis of COPD found that 61% of patients with COPD had muscle protein and fat depletion compared to 16% of healthy smoker controls. The study found that body mass index distribution, body weight, body fat, serum albumin, pre-albumin, and transferrin levels were similar in COPD patients compared to healthy smokers (23).

Difficulty in achieving measurable improvements in anthropometry or pulmonary function with energy-supplemented diets has been reported (9). Therefore, current interest has largely shifted from isolated dietary intervention to diet, combined with exercise and/or anabolic agents (19,24).

Oxidative injury by free radicals is thought to be a key factor in acute lung injury. Preliminary evidence suggests that antioxidant supplementation in the form of vitamin E and C, retinol, and beta-carotene may have protective effects. Beta-hydroxybutyrate supplementation was shown to have antiinflammatory effects in intensive care unit patients with COPD (25). Dietary supplementation of n-3, gamma-linoleic acid, and antioxidants has not been shown to benefit patients with acute lung injury (26).

An area of active investigation is the potential associations between both dietary antioxidants (including vitamins) and n-3 fatty acids and the rising incidence of asthma. Although epidemiological and observational studies suggest benefits from higher intake of these nutrients, as well as methyl donors like vitamin B_{12} (27), clinical intervention trials have, for the most part, been less encouraging (28).

Data from the Nurses' Health Study suggest that vitamin E intake may be inversely associated with the risk of asthma development, although the association was relatively weak; other antioxidants did not reveal significant effects (29). Evidence that a variety of dietary antioxidants may protect against COPD is preliminary but provocative (30). The evidence and biologic plausibility of antioxidant benefits in asthma are less robust, although vitamins E and C and selenium appear to be protective, based on available evidence.

There is increasing work focusing on pregnancy and early childhood periods as potentially crucial times for dietary intervention to influence respiratory health (31). Early breastfeeding has been shown to reduce the risk of asthma (32,33). A meta-analysis of dietary intake during pregnancy found that infants born to mothers who had consumed the highest amounts of vitamin D, vitamin E, and zinc during pregnancy were less likely to develop a recurrent wheeze during childhood (34).

The generation of lactic acid, and resultant cellular acidosis, is thought to contribute to muscle fatigue by a variety of mechanisms, including interference with calcium release, glycolytic enzyme activity, and neural impulse propagation (35). The retention of CO_2 and the resultant systemic acidosis imposes a respiratory workload on patients with COPD, limiting exercise capacity. Sodium bicarbonate has been studied as an ergogenic aid in healthy subjects with mixed results; approximately half of the published trials show benefit (see Chapter 32). In a small study, Coppoolse et al. (36) demonstrated no increase in exercise capacity in COPD subjects given an acute oral bicarbonate load. Potential benefits of chronic bicarbonate supplementation remain speculative.

Folklore has long suggested that dairy product consumption increases the production of respiratory tract mucus and exacerbates asthma. A double-blind, placebo-controlled crossover trial in 20 subjects showed no effect of acute milk consumption on symptoms or pulmonary function (37). A review article

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further solidified this point; even in patients with upper respiratory infections, milk consumption did not change the amount of mucus production (38).

In a survey of readers of a peer-reviewed journal of alternative and complementary medical practices, nutritional therapy for asthma was the most frequently cited practice among physicians and other medical providers testifying to widespread interest in the topic (39,40). Recent studies have shown some effects on asthma outcomes with traditional Chinese medicine (41–43) and Ayurvedic methods (44). Use of nutrition and other alternative medical practices has been reported by approximately 50% of patients with asthma in both the adult and pediatric populations (45).

A link between asthma and obesity has been widely reported in the medical literature. Most cross-sectional and prospective studies have demonstrated obesity as a risk factor for developing asthma. Hypothesized mechanisms for this association include change in lung physiology, increase in inflammatory mediators, and modification of hormonal factors. Changes in lung physiology of obese patients involve decreased pulmonary compliance secondary to increased blood volume and fatty infiltration of the lung (46). Inflammatory mediators, such as Interleukin-6 (IL-6), have been shown to be increased in obesity and correlate with the severity of asthma (47). Furthermore, the link between obesity and asthma has been found to be greater in women. This is thought to be secondary to elevated estrogen levels linked to increased adipose tissue (48). The mechanism is still unclear but may be related to estrogen-mediated effects on mast cells and eosinophils (49). A systematic review evaluated weight-loss interventions on asthma severity. Four randomized controlled trials with a total of 246 children and 6 randomized controlled trials with 502 adults were evaluated in this review. The study showed that there may be improvement in asthma-related quality of life, TNF-alpha, interleukin-8 (IL-8), c-reactive protein, and to some degree in asthma control in patients who were successful with weight loss (50). In children, weight gain has also been linked to an increased risk of developing asthma. Infants with rapid increase in body mass index during the first 2 years of life have been shown to be at increased risk of childhood asthma between the ages of 2 and 16 years (51).

Dietary intake can modify the severity of asthma in patients. One study showed through food questionnaires and spirometry that patients who consumed a low-fiber and high-fat diet were more likely to have severe persistent asthma and lower forced expiratory volume (FEV1) (52). In addition, patients who consume a high-antioxidant diet and adequate vitamin D have been shown to have better FEV1 than patients who consume less (28).

Respiratory Infections

Respiratory infections pose a great burden on the healthcare system. Pulmonary infections from *S. pneumoniae* are still a major source of morbidity and mortality in children of developing countries. Recent literature suggests probiotics may be helpful not only in intestinal flora but also in respiratory pathogenesis (53). The World Health Organization defines *probiotics* as “a live micro-organism which confers a health benefit to the host and are generally regarded as safe in humans” (54). Probiotics have been shown to change the microflora in the nasopharynx and to help maintain the integrity of the epithelial layer in the nasopharynx. As a result, probiotics containing *Lactobacillus* and *Bifidobacterium* can be helpful even in the pediatric population in decreasing the infection rate of respiratory pathogens like *Streptococcus pneumoniae* (55).

In 2020, COVID-19, an infection caused by the SARS-COV-2 virus, became a global pandemic. While commonly asymptomatic, patients with COVID-19 infection had flulike symptoms, such as cough, shortness of breath, fever, chills, muscle pain, sore throat, and loss of sense of taste and smell. The immunocompromised, older adults, and those with diet-related chronic disease, obesity, diabetes,

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hypertension, and cardiovascular disease were at greater risk of severe complications and death (56–60). Severe cases experienced COVID-19-related acute respiratory distress syndrome and were placed on ventilators, often for prolonged periods of time, necessitating enteral nutrition. Preliminary evidence suggested that vitamin D deficiency may contribute to COVID-19 severity and prognosis (61).

NUTRIENTS, NUTRICEUTICALS, AND FUNCTIONAL FOODS

Phosphorus

Hypophosphatemia is known to impair diaphragmatic contractility and exacerbate CO_2 retention. Phosphorus depletion commonly occurs due to intracellular shifts following the correction of respiratory acidosis (35).

Impaired skeletal muscle function, attributable to loss of lean body mass, is associated with functional deterioration in COPD (62). Weight loss generally correlates with loss of respiratory muscle strength, which in turn is predictive of CO_2 retention. Nonetheless, patients not demonstrably underweight may be impaired due to losses of fat-free mass.

Monosodium Glutamate

The perception among asthma sufferers that the condition is exacerbated by food additives is widespread (see Chapter 15). A Cochrane review included two randomized controlled trials with a total of 24 subjects comparing monosodium glutamate challenge to placebo. There were no statistically significant differences between the monosodium glutamate and placebo groups when evaluating FEV1 fall of 15% or 200 mL (63).

Antioxidants

Inverse associations between dietary antioxidants and both asthma and COPD have been reported in epidemiological and observational studies. A randomized controlled trial demonstrated that modifying dietary intake of carotenoids from actual food sources improved clinical asthma outcomes (64). Theoretical support is strongest for vitamin C, which is found abundantly in pulmonary secretions; however, interventional studies have not shown significant clinical benefit (65). One recent randomized trial found that supplementation with vitamin C or magnesium over a period of 16 weeks, as compared to placebo, led to significant reduction in required corticosteroid dosage in adult asthmatics (66). In addition, a cross-sectional study including 452 Japanese children who were 3 to 6 years old evaluated the diet of asthmatic and non-asthmatic subjects. The study supported an inverse relationship between asthma and vitamins E and C intake. They found no relationship between asthma and fatty acid intake (67). Nevertheless, a Cochrane systematic review of the effectiveness of vitamin C in children and adults with asthma concluded that studies were generally too small and findings inconsistent. There is currently no indication that vitamin C should be recommended as a therapeutic agent in asthma (65).

Magnesium

Magnesium relaxes bronchial and vascular smooth muscle through its calcium antagonist properties. It has been studied for the treatment of acute, reversible bronchoconstriction, and early studies have shown mixed results in mild to moderate asthma. One prospective study evaluated emergency room visits for acute asthma exacerbations in children and found that patients who received intravenous magnesium sulfate had fewer intubations (33% vs. 5% $p < 0.001$) (68). However, a recent systematic review and

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meta-analysis evaluated the effect of oral magnesium supplements in eight randomized controlled trials among adults and children with asthma. They found only a modest effect on FEV1 at week 8, and no effect at other follow-up points, no effect on forced vital capacity (FVC), Methacholine challenge test, the frequency of bronchodilator use, or symptoms score (69).

n-3 Fatty Acids

There is considerable interest in the potential benefits of n-3 fatty acid supplementation on inflammatory conditions in general and pulmonary diseases in particular. n-3 fatty acids are found in abundance in mucosal tissue. They are thought to undergo enzymatic transformation into substances that assist in resolution of inflammation (70). Evidence in support of this interest is limited to date, and interventional trials thus far have yielded conflicting results (71,72). One study suggests that optimal n-6/n-3 ratios may ameliorate the inflammation-enhancing effects of n-3 eicosapentaenoic acid (EPA) alone (73). Several small randomized controlled trials have found beneficial effects such as acute reductions in TNF-alpha (60) and suppression of exercise-induced bronchoconstriction (61). One systematic review found that fish oil supplementation may be beneficial for asthma prevention in children (74). Further research in this area is warranted.

Vitamin D

A positive association between serum vitamin D levels and pulmonary function indices, such as FEV1, has been observed (75). A recent cross-sectional study of 10,860 children showed low levels of 25-hydroxy vitamin D was associated with increased odds of having asthma (28). In another study among 2,607 adolescents, levels of 25-hydroxy vitamin D correlated with FEV1 and FEV1/FVC ratio (76). However, evidence is mixed, and further prospective trials are needed to elucidate the role vitamin D may play in treatment or prevention of respiratory diseases.

Other Nutrients

Indirect benefits of nutrients on lung function may derive from ergogenic effects (see Chapter 32), vascular effects (see Chapters 7 and 10), or influences on immune function (see Chapter 11).

Nutrigenomic Considerations

As discussed previously, there is an association between asthma and obesity. Questions of whether genetic variations play a role in this association have arisen. One biobank study identified shared genetic components between obesity and specific asthma subtypes, suggesting that obesity causally increases the risk of asthma and that specific pathways might underlie both obesity and asthma (77). Another study identified common single-nucleotide polymorphisms (SNPs) at 17q21.2 that were associated with increased body mass index (BMI) only among patients with asthma (78). Further research is required to elucidate any genetic mechanisms that may connect asthma and obesity.

Gene variations involved in developing cachexia in patients with COPD have been evaluated. Particularly, gene polymorphisms for interleukin-1-beta (IL-1-beta), IL-6 (79), TNF-alpha (8,79,80), and lymphotoxin-alpha have been researched for patients with COPD and cachexia. IL-6 polymorphisms are significantly different in patients with COPD cachexia compared with healthy controls, further strengthening the potential role of genetics in developing malnutrition in COPD (81,82).

Diet–Drug Interactions

Montelukast, a leukotriene inhibitor, often used as a second or third-line asthma therapy, is metabolized

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by the cytochrome P450 CYP3A4 enzyme in the liver. A potential dietary interaction of this medication is a potent P450 3A4 inhibitor, grapefruit juice. Therefore, the metabolism of montelukast would be decreased if one were to consume a large amount of grapefruit juice.

Hypokalemia after use of inhaled albuterol has been seen on rare occasions. The hypokalemia can require treatment and even cause electrocardiogram (EKG) changes with usual dosages of inhaled albuterol (83).

CLINICAL HIGHLIGHTS

Inflammation is important in the pathogenesis of chronic airway diseases. The inflammatory process leads to oxidative cell injury, implicating oxidation in chronic airway disease as well. Therefore, a theoretical basis exists for optimizing intake of antiinflammatory and antioxidant nutrients and possibly vitamin D. Although definitive evidence of benefit in airway disease has been reported for neither, both are supported by other lines of evidence and may be recommended on general principles (see Chapter 45). Minimally, a diet rich in fruits, vegetables, whole grains, and fish is advisable. Literature supports a link between obesity and asthma. A diet high in fiber and low in fat can be beneficial in improving FEV1 reading for asthmatic patients.

Supplementation with vitamin C 500 mg/day, vitamin E up to 200 IU/day, and fish oil or flaxseed oil (roughly 2 g/day of the former or one tablespoon/day of the latter) would appear to be reasonable components of an overall plan to ameliorate the course of chronic airway disease, despite the lack of conclusive outcome data. Vitamin C and E supplementations may also be an appropriate recommendation for asthmatic children. On general principles, a daily multivitamin/multimineral supplement is appropriate for all patients with chronic airway disease. A daily probiotic supplement may help to decrease respiratory infection and could be considered in patients with frequent infections.

Patients with more advanced airway disease are at risk of malnutrition and should be monitored closely for signs thereof. Nutritional consultation is indicated at the earliest emergence of such signs and, not unreasonably, even before. Both increased energy expenditure and decreased intake may contribute to catabolism, and the diet should be tailored to compensate. Relative restriction of carbohydrate may be indicated to limit CO_2 production in retainers, but conclusive evidence of benefit for this practice is lacking. More convincing is evidence of benefit of maintaining nutritional adequacy, with relatively high protein intake, in combination with a program of conditioning exercise.

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Diet and Kidney Disease

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INTRODUCTION

The development of chronic kidney disease (CKD) often occurs in the context of other chronic conditions, such as hypertension, diabetes, or atherosclerosis, for which dietary management is both essential and of proven benefit. Thus, there is a clear role for diet in the prevention and management of CKD. Despite an extensive literature on the role of dietary protein in the development and progression of kidney disease, clear support for a single management strategy is lacking. However, evidence that a range of dietary interventions may contribute to the preservation of kidney function at varying levels of compromise is increasingly abundant and compelling. The clinician managing patients with, or at risk for, CKD is obligated to attend to nutrition as well as pharmacotherapy.

OVERVIEW

Stages and Causes of Chronic Kidney Disease

CKD is defined by the estimated glomerular filtration rate (eGFR), the extent of the albuminuria defined as an albumin excretion rate of more than 30 mg/24 hours, and the presence of structural kidney damage (1). Table 16.1 provides an outline of the five stages of CKD using eGFR. CKD affects up to 16% of the worldwide population, with a greater prevalence in low- and middle-income countries (2–4).

TABLE 16.1

Stages of Chronic Kidney Disease

Stage	GFR (mL/min/1.73m2)	Description
1	≥90	Kidney damage with normal or increased GFR
2	60–89	Kidney damage with mild decrease in GFR
3a	45–59	Mild to moderate decrease in GFR
3b	30–44	Moderate to severe decrease in GFR
4	15–29	Severe decrease in GFR
5	<15 (or dialysis)	Kidney failure

CKD is defined as either kidney damage or GFR <60 mL/min/1.73 m^2 for ≥3 months.

CKD, Chronic kidney disease; GFR, glomerular filtration rate; KDIGO, kidney disease improving global outcomes.

Adapted from K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation,

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Classification and Stratification and Levey AS, Coresh J, Balk E, et al. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Ann Intern Med. 2003; 139:137–147

While the two leading causes of kidney disease in the United States are diabetes mellitus and hypertension (5), genetic factors may play a risk in development of CKD (2). There is decisive evidence that diet influences the course of diabetes (see Chapter 6) and accruing evidence that diet may enhance, and at times substitute for, pharmacotherapy in the management of hypertension (see Chapter 8). Both type 2 diabetes and hypertension may be preventable with appropriate dietary interventions (see Chapters 6 and 8). Blood pressure reduction appears to retard the progression of CKD in a dose-responsive manner (i.e., the lower the blood pressure, the slower disease progression) and can reduce the risk of developing cardiovascular disease (6). However, aggressive blood pressure reduction increases risk for side effects of therapy, which has been demonstrated in subgroup and secondary analyses of clinical trials (7). Target blood pressure is <130/80 mm Hg for the general population as well as CKD. Atherosclerosis contributes to the development of kidney dysfunction and may be retarded or prevented by dietary management (see Chapter 7). Kidney failure is a potential consequence of systemic atherosclerosis and of low cardiac output and thus may often compound the challenges of nutritional therapy in congestive heart failure (8). Dietary intervention to mitigate cardiovascular risk is often warranted in patients with CKD due to the common origins of the two conditions and the tendency of each to propagate the other (9) (see Chapters 7 and 8).

The prevention or treatment of risk factors for kidney disease may prevent CKD caused by these risk factors. As discussed in other chapters, the course and natural history of the leading causes of CKD are substantially modifiable by dietary means (see Chapters 6 and 8), which then may affect the development of CKD. Evidence for this comes from several studies like the Look AHEAD trial, which showed a 31% lower rate of incident CKD in those with type 2 diabetes undergoing intensive lifestyle interventions (10). Even more tellingly, a study by Fioretto et al. in patients with type 1 diabetes showed clinical and pathologic regression of diabetic nephropathy in patients attaining euglycemia after receiving a pancreas transplant, leaving open the question of whether such results are possible (11) through euglycemia attained with lifestyle changes in those with nephropathy from type 2 diabetes mellitus.

Consequently, the primary care practitioner in collaboration with a specialized dietitian may play a role in the prevention and treatment of CKD by achieving optimal dietary management of the principal risk factors. If early detection and treatment of CKD are not addressed, consequences of progressive CKD include further deterioration of the kidney leading to end-stage kidney disease (ESKD) requiring either dialysis treatment or a renal transplant to maintain life, cardiovascular disease and death (3).

Diet

CKD is associated with many metabolic derangements, including but not limited to abnormal and altered energy and protein homeostasis, acid–base balance and protein catabolism, and hormonal dysfunction (12). Further, patients with advanced CKD often experience altered taste (13) and appetite (14), making nutrition of the upmost importance. Once symptomatic or clinically overt CKD has developed, the generalist almost invariably will, and should, be guided by a nephrologist in tailoring both dietary therapy and pharmacotherapy. Such patients are at risk of azotemia (i.e., the accumulation of nitrogenous waste) as well as specific micronutrient abnormalities, including phosphorus retention; impaired absorption of calcium and iron; and deficiencies of thiamin, riboflavin, vitamin B_6, folate, vitamin C, zinc, selenium, manganese, and active vitamin D (15–17).

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While many nutrients, both macro- and micronutrients, have been studied in this patient population, much attention has been and continues to be given to protein intake throughout the various stages of CKD as the evidence for altering protein to preserve kidney function as it declines or to avoid protein energy wasting while receiving dialysis (18) remains strong (19). The subsequent sections of this chapter will explore each macronutrient and various micronutrients, focusing on the optimal intake for overall health. Kalantar-Zadeh and Fouque have published a comprehensive summary of the nutrient requirements for all stages of CKD (12); Table 16.2 provides this summary of dietary and nutrients requirements for all stages of CKD while Table 16.3 provides a summary for protein intake for the various stages of CKD. Table 16.4 provides a summary of biochemical goals for CKD patients including pertinent macronutrients and micronutrients. Reconciling the priorities of nutrition for kidney protection and for ensuring adequate overall nutritional status is a challenge best met through the application of general principles modified to suit each individual (20–22). It's important to reiterate the complexity of dietary management and medical nutrition therapy in kidney disease generally requires the input of the primary care provider, a specialized dietitian, and a nephrologist (23,24). Medical nutrition therapy should be tailored to each individual patient based on their current nutrition status, metabolic state, comorbid conditions, and needs (23).

TABLE 16.2

Recommended Dietary and Nutrient Intakes at Different Stages of Chronic Kidney Disease in Adults

	Normal kidney function (eGFR >60*) and no proteinuria, but at higher CKD risk, e.g. diabetes, hypertension, or solitary kidney†	Mild to moderate CKD (eGFR 30–<60*) without substantial proteinuria (<0.3 g/d) ¶	Advanced CKD (eGFR <30*) or any CKD with substantial proteinuria (>0.3 g/d) ¶	Transitioning to dialysis therapy with good RKF including incremental dialysis preparation¶	Prevalent dialysis therapy, or any CKD stage with existing or imminent PEW
Dietary Protein (g/kg/d)	<1.0 g/kg/d, increase proportion of plant food proteins.	<1.0 g/kg/d (consider 0.6–0.8 if eGFR <45 mL/min 1.73m2 and fast progression).	0.55–0.6 g/kg/d for nondiabetic patients and 0.6–0.8 g/kg/d for diabetic patients, including 50% plant foods, or <0.43 g/kg/d with addition of EAA/KA.	0.6–0.8 g/kg/d on non-dialysis days (e.g. incremental dialysis) and >1.0 g/kg/d on dialysis days.	1.2–1.4 g/kg/d, may require>1.5 g/kg/d if hypercatabolic.
Dietary Sodium (g/d)	<4 g/d (<3 g/d for HTN)‡	<4 g/d, avoid <1.5 g/d if hyponatremia likely.	<3 g/d, avoid <1.5 g/d given high likelihood of hyponatremia.	<3 g/d.	<3 g/d.

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Dietary Potassium (g/d)	Same as recommended for the general population (4.7 g/d).	Same as the general population unless frequent or severe hyperkalemia excursions likely.	<3 g/d if hyperkalemia occurs frequently while maintaining high fiber intake.	<3 g/d if hyperkalemia occurs frequently while maintaining high fiber intake.	<3 g/d, target high fiber intake (see under Fibers).
Dietary Phosphorus (mg/d)¥	<1,000, minimize added inorganic P in preservatives and processed foods.	<800, minimize added inorganic P, encourage more vegetarian food.	<800, minimize added inorganic P, more vegetarian food.	<800, minimize added inorganic P. Consider P binder therapy.	<800, minimize added inorganic P. Add P binders as needed.
Dietary Calcium (mg/d)	1,000–1,300 mg/d (to be adjusted for age).	800–1,000 mg/d.	800–1,000 mg/d.	800–1,000 mg/d or less.	<800 mg/d.
Fibers, Alkali and Vegetarian Foods	25–30 g/d, target higher proportion (>50%) of plant foods such as DASH diet.	25–30 g/d or more, higher proportion (>50%) of plant foods.	25–30 g/d or higher, consider >70% vegetarian foods.	25–30 g/d or higher.	25–30 g/d or higher, suggest avoiding strict vegan dieting.
Energy ‖ (Cal/kg/d)	30–35 Cal/kg/d**, adjust to target weight reduction if BMI >25 kg/m2.	30–35 Cal/kg/d, increase proportion with low-protein diet.	30–35 Cal/kg/d, increase proportion with low-protein diet.	30–35 Cal/kg/d.	30–35 Cal/kg/d, target higher if PEW exists or imminent.
Fats	Mostly mono- and polyunsaturated lipids including omega-3-fatty acids.	Mostly mono- and polyunsaturated lipids including omega-3-fatty acids, increase proportion with low-protein diet.	Mostly mono- and polyunsaturated lipid including omega-3-fatty acids, increase proportion with low-protein diet.	Mostly mono- and polyunsaturated lipid including omega-3-fatty acids.	Mostly mono- and polyunsaturated lipid including omega-3-fatty acids.
Vitamin D	Nutritional D (ergo- or cholecalciferol) as needed.	Nutritional D or calcifediol, consider adding 1α-OH D analogues in progressive sHPT.	Nutritional D or calcifediol, add 1α-OH D analogues in progressive or symptomatic sHPT.	1α-OH D analogues to control sHPT.	1α-OH D analogues to control sHPT, add calcimimetics as needed.
Other Vitamins and Trace Elements	Daily multivitamin intake especially if	Avoid aluminum-based medications,	Avoid aluminum, and magnesium based agents.	Avoid aluminum, and magnesium-based agents.	Avoid aluminum, and magnesium-based agents.

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	inadequate intake of fresh fruits and vegetables.	monitor iron indices and ensure iron therapy as needed.	Treat iron deficiency.	Treat iron deficiency.	Treat iron deficiency.
Management of Weight and Cardiovascular Risks	Lipid and weight reduction strategies target BMI in 18.5–25 kg/m2 range, recommend regular exercise training.	Avoid excessive weight loss. consider careful exercise training, follow conventional lipid targets.	Identify unintentional weight loss and intervene with higher energy and protein.	Identify unintentional weight loss and intervene with higher energy and protein.	Avoid weight loss or BMI <23 kg/m2 unless required for imminent kidney transplantation or other life-saving interventions.
Fluid Management	No fluid restriction, adequate hydration >1.5 L/d (if risk of hyponatremia is minimal).	<1.5 L/d if edematous state or hyponatremia, consider adding diuretics.	<1.5 L/d, consider loop diuretics and titrate the dose or sliding scale dosing.***	<1.5 L/d, consider more frequent high-dose loop diuretics.	<1 L/d, avoid excessive ultrafiltration on dialysis.

**The unit for eGFR is mL/min/1.73 m^2 body surface area (BSA).*

†Solitary kidney can be congenital, acquired, or surgical including status post donor or cancer nephrectomy.

¶Prevalent renal transplant recipients are often in the two categories of eGFR 30–<60 and >30 mL/min/1.73m^2, or transitioning to dialysis and can be approached similarly.

Certain conditions such as salt-losing nephropathies may not be subjected to sodium restriction.

Protein-energy wasting (PEW) according to the International Society of Renal Nutrition and Metabolism criteria (Fouque D, Kalantar-Zadeh K, Kopple J, et al. A proposed nomenclature and diagnostic criteria for protein-energy wasting in acute and chronic kidney disease. *Kidney Int*. 2008;73:391–398).

‡In patients with heart failure the recommendations of the American Heart Association (www.heart.org) can be considered. The American Heart Association recommends no more than 2.3 g/d (equivalent of a teaspoon salt) and suggests an ideal limit of no more than 1.5 g/d (source: https://sodiumbreakup.heart.org)

In hypokalemic peritoneal dialysis patients, higher potassium intake should be targeted.

¥Dietary phosphorus restriction is independent of hyperphosphatemia.

‖Carbohydrates provide 40% to 60% of the daily energy intake, and should be natural (non-

refined) and complex with high fiber content (see under Fibers).

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***In obese patients, lower energy ranges can be targeted.*

**** Sliding scale dosing of loop diuretics instructs upwards dosing for fluid retention and downward dosing for volume depletion based on daily weight and other parameters.*

In case of worsening edema, more stringent fluid restrictions may be necessary such as <1 L/d.

1*α-OH D*, 1-*alpha-hydroxylated vitamin D; BMI, body mass index; BSA, body surface area; Cal: kilocalorie; CKD, chronic kidney disease; d, day (such as in g/kg/d); D, vitamin D; DASH, Dietary Approaches to Stop Hypertension; see text, DPI, dietary protein intake; EAA, essential amino-acids; eGFR: estimated glomerular filtration rate in mL/min/1.73m^2 BSA; HTN, hypertension; KA, ketoacids (keto-analogues of amino-acids); LPD, low-protein diet; P, phosphorus; PD, peritoneal dialysis; RKF, residual kidney function; sHPT, secondary hyperparathyroidism.*

Adapted from Kalantar-Zadeh K, Fouque D. Nutritional management of chronic kidney disease. N Engl J Med. 2017;377(18):1765–1776

TABLE 16.3

Ranges of Dietary Protein Intake across Clinically Relevant Kidney Disease Stages and Conditions Including Recommending Target Ranges by the Kidney Disease Outcome Quality Initiative Clinical Practice Guidelines in Kidney Disease 2020

Dietary Protein Intake Range	Daily grams of protein intake per kilogram body weight (g/kg/d)*	Comment
Protein-free diet	<0.25 g/kg/d	Generally, not recommended for any person including CKD patients.
Very low-protein diet	0.25–0.55 g/kg/d	Usually supplemented with essential amino acids or their keto- or hydroxy-acids. KDOQI CPG recommends 0.28–0.43 g/kg/d with additional keto acid/amino acid analogs to meet protein requirements (0.55–0.60 g/kg body weight/d) for metabolically stable CKD patients without diabetes.
Low-protein diet for nondiabetic CKD**	0.55–0.6	Recommended by KDOQI 2020 for CKD patients without diabetes.
Low-protein diet (for DKD**)	0.6–0.8 g/kg/d	More consistently recommended for advanced CKD (eGFR<45 mL/min/1.73m2 or substantial proteinuria), ideally with >50% plant food sources of protein (plant-dominant low-protein diet). This range is recommended by KDOQI CPG for CKD patients with diabetes.

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Moderately low-protein intake	0.8–1.0 g/kg/d	Recommended range for adults without CKD but at high risk of CKD including those with a solitary kidney (following nephrectomy), diabetes mellitus, hypertension, and polycystic kidneys.
Moderate protein intake**	1–1.2 g/kg/d	Recommended by KDOQI CPG for metabolically stable patients on maintenance HD or PD.
Moderately high-protein diet	1.2–1.5 g/kg/d	Reported protein intake of average United States adult without CKD.
High- to very high-protein diet	>1.5 g/kg/d	Can be used over limited period of time for acute conditions such as hypercatabolic AKI, high-grade burns, and PEW.

**KDOQI CPG in Kidney Disease 2020 states it may be reasonable for a Registered Dietitian or Physician to use clinical judgment in determining the method to assess body weight.*

***Recommended by KDOQI CPG in Kidney Disease 2020.*

AKI, Acute kidney injury; CKD, chronic kidney disease; DKD, diabetic kidney disease; DPI, dietary protein intake; eGFR, estimated glomerular filtration rate; HD, hemodialysis; KA: ketoacids supplement; LPD, low-protein diet; PD, peritoneal dialysis; PEW: protein-energy wasting; sVLPD, supplemented very low-protein diet; VLPD, very low-protein diet.

dapted from Kistler BM, Moore LW, Benner D, et al. The International Society of Renal Nutrition and Metabolism Commentary on the National Kidney Foundation and Academy of Nutrition and Dietetics KDOQI Clinical Practice Guideline for Nutrition in Chronic Kidney Disease. J Ren Nutr. 2021 Mar;31(2):116–120.e1.

TABLE 16.4

Nutritional Biochemical Targets of Chronic Kidney Disease Specific Outcomes in Adults

Biochemical Test	Desired Range
Albumin (g/dL)	≥4.0
enPCR (g/kg/d)*	≥1.1
Potassium (mEq/L)	3.5–5.5
Phosphorus (mg/dL)	3.0–5.5
Calcium (mg/dL)	8.5–10.0
Intact Parathyroid Hormone (pg/mL)	150–600
Vitamin D (25–OH D3) (ng/mL)	≥20
Ferritin (ng/mL)	HD: 200–500 PD: ≥100
Transferrin Saturation (%)	≥30
Hemoglobin (g/dL)	9–11
Hemoglobin A1C (%)	≤7

Triglycerides (mg/dL)	</= to 150
Interdialytic Weight Gain	<1 kg/d

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**for dialysis patients only.*

HD, hemodialysis; PD, peritoneal dialysis.

NUTRIENTS, NUTRICEUTICALS, AND FUNCTIONAL FOODS

Protein

As CKD progresses, dietary protein restriction is common practice (25) and generally slows progressive deterioration of kidney function (26–29). It is important to highlight the difference in protein requirement for stages 3 to 5 CKD and the ESKD patient. Notably, stages 3 to 5 CKD including nondialysis patients generally require a diet restricted in protein, whereas patients undergoing hemodialysis or peritoneal dialysis generally require higher protein intakes to replace losses and maintain nutritional status.

Protein Intake in Chronic Kidney Disease

Persons with stages 3 to 5 CKD not receiving dialysis require a protein restriction to slow the progression of CKD. However, protein restriction may contribute to nutritional deficiencies, with net adverse effects in children (29,30). CKD in childhood in particular is associated with impairment of growth that can adversely affect quality of life and bone metabolism (31,32). Further, a limited number of studies to date have not found a significant impact of protein restriction on delaying progression to end-stage disease in children (33). Minimum protein intake equivalent to the Dietary Reference Intakes (DRI) for ideal body weight has therefore been recommended in pediatric CKD to prevent uremia and reduce dietary phosphorus intake (34).

The evidence supporting protein restriction in adult patients with established CKD to slow disease progression is convincing (27,35,36). The restriction of protein intake reduces glomerular flow and pressures. It also slows the accumulation of urea, creatinine, and other guanidine compounds in CKD. The benefits of protein restriction have been convincingly demonstrated for patients with stages 3 to 5 CKD. The standard diet for such patients restricts total protein to approximately 0.55 to 0.8 g/kg/d. More specifically, for patients with CKD who are metabolically stable without diabetes, the suggested protein intake is 0.55 to 0.6 g/kg/d (24), whereas for diabetic patients the range of 0.6 to 0.8 g/kg/d has been suggested by the Kidney Disease Outcome Quality Initiative (KDOQI). However, as a streamlined approach, and given major benefits of diets consisting of predominantly plant foods in the management of CKD, a so-called Plant-Dominant Low-Protein Diet (PLADO) with dietary protein intake of 0.6 to 0.8 g/kg/d and >50% plant sources of dietary protein has been recommended for all CKD patients regardless of CKD etiology (37) (see Figure 16.1); randomized controlled trials are needed to examine superiority of PLADO in improving CKD outcomes. Alternatively, if lower dietary protein intake is targeted, commercial supplements of amino acids, keto acids, and hydroxy acids, when coupled with a very low-protein diet (defined as 0.28 to 0.43 g/kg/d) have showed great promise in delaying the need for kidney replacement therapy (24,38). The putative benefit of keto or hydroxy acid supplements is that the amino group, which contributes to the body's nitrogen load, is eliminated, thereby avoiding hyperfiltration in the kidney, which may contribute to CKD progression. Keto and hydroxy acids can be converted into their respective amino acids endogenously thereby reducing nitrogenous waste that would otherwise be processed and excreted by the kidney (38). There is evidence to date that such diets confer greater

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benefits than standard protein-restricted diets in nondialyzed patients. The addition of keto acids to the diet may allow for the preservation of adequate nutriture with a lower intake of protein than could otherwise be achieved and beneficial effects on kidney function (39–42). Such a diet has been shown to reduce blood pressure as well (42,43), offering another mechanism by which kidney function may be preserved. For stage 3 to 5 CKD patients with diabetes, the suggested protein intake is 0.6 to 0.8 g/kg/d (24).

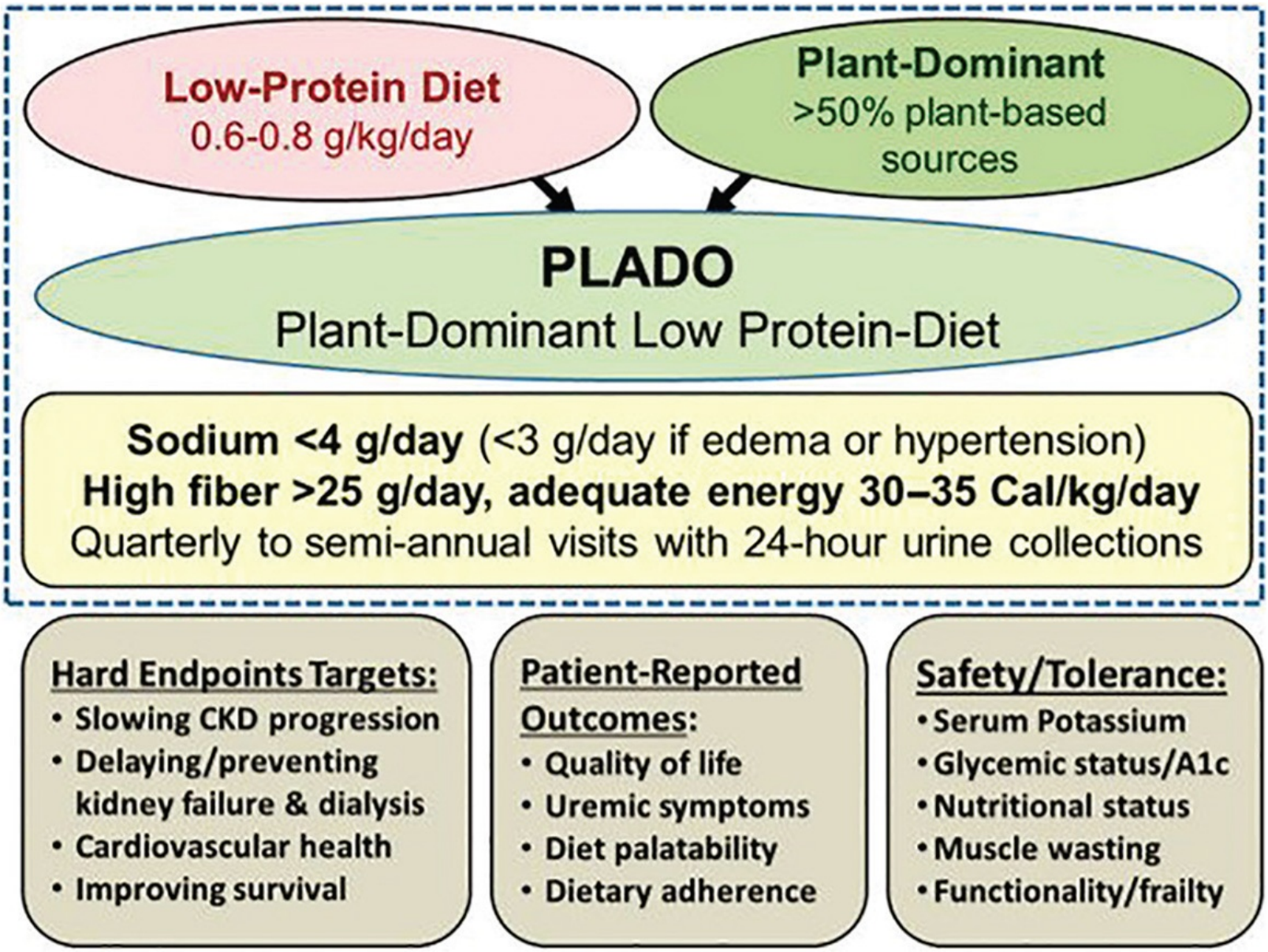

FIGURE 16.1 Summary of the plant-dominant low-protein diet (PLADO) for the nutrition-based management of kidney disease. These recommendations are based on a total dietary intake of 0.6 to 0.8 g/kg/d of protein of which >50% come from plant-based sources. This dietary pattern also recommends to limit dietary sodium intake to <4 g/d (<3 g/d if edema or hypertension are present), to consume at least 25 g/d of dietary fiber, and to ensure an adequate energy intake of 30 to 35 kcal/kg/d. Weight is based on the ideal body weight and vitamin B_{12} supplementation should be encouraged.(Reprinted from Kalantar-Zadeh K, Joshi S, Schlueter R, et al. Plant-Dominant Low-Protein Diet for Conservative Management of Chronic Kidney Disease. *Nutrients*. 2020 Jun 29;12(7):1931.)

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There is animal evidence that dietary supplementation with L-arginine may prevent age-related decline in kidney function and protects against acute kidney injury (44–46). The mechanism for this effect is unclear and may be independent of nitric oxide (44). Implications for humans are as yet uncertain.

Whereas protein restriction is a mainstay in the dietary management of CKD, declining protein intake as eGFR declines may independently predict incipient malnutrition (47). Malnutrition of multifactorial origin often develops in patients with advanced CKD (48–50), and the primary care provider should play a role in ensuring nutritional adequacy. Just as CKD may contribute to malnutrition, malnutrition, particularly protein deficiency, tends to lower eGFR and impair the concentrating ability of the kidney. These effects are reversible in healthy individuals with the restitution of adequate protein intake. With the help of a specialized dietitian, creative dietary strategies to maximize dietary choices within the context of a protein-restricted diet may enhance compliance and nutritional status (51).

Protein Intake in End-Stage Kidney Disease

Most patients with end-stage kidney disease experience some catabolism while on dialysis (18). Malnutrition, or at least the risk of it, is considered common in this population. Wasting is due both to increased metabolic demand, perhaps due to dialysis, and poor intake due to malaise, anorexia, and the unpalatability of a therapeutic diet. Poor nutritional status in dialysis patients appears, not surprisingly, to be a poor prognostic sign. Therefore, patients on hemodialysis tend to lose protein and would benefit from minimum protein intake in the range of 1.0 to 1.2 g/kg/d (24). In peritoneal dialysis, protein losses are particularly high, and intakes of up to 1.3 g/kg/d are recommended (52).

Types of Protein

Historically, high biological value proteins, like meat, eggs, and dairy, have been recommended to patients with kidney disease given their perceived superiority over protein from plant foods, which have been viewed as being of lesser quality. However, these views are being challenged for two important reasons (53,54). First, concepts of protein superiority were based on varying definitions of nitrogen absorption or amino acid digestibility. Research now suggests food quality should refer to the food and its overall effects on health, rather than just to amino acid distribution (55). In addition, with an abundant food supply, issues of protein deficiency have become less important in the Westernized world. Secondly, it is becoming increasingly recognized that animal-based proteins tend to have more bioavailable phosphate and a higher potential acid load, both of which are problematic to an ailing kidney that would be responsible for excreting these substances. The accumulation of dietary acids and phosphates requires treatment, usually with additional medications that add to an already large pill burden (56,57). Further, undertreated metabolic acidosis or hyperphosphatemia can lead to even further complications (see in the following section). Because of these issues and others, plant proteins are increasingly being adopted for the mainstay of proteins to be consumed by patients with kidney disease (58). Protein from plant foods have a lower bioavailability of phosphate, natural alkali that is useful in treating CKD-related metabolic acidosis, and have not been shown to consistently raise serum potassium levels. Further, the emphasis of foods like fruits, nuts, vegetables, whole grains, and legumes has been associated with numerous positive health markers, like improvements in insulin sensitivity and reductions in cardiovascular disease and cancer risk (59).

Protein Alteration in Healthy Adults

Evidence for a protein restrictive diet in the primary prevention of kidney disease and the age-related decline in GFR is inconclusive (36,60). There is less convincing evidence that protein restriction can

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prevent the onset of CKD in healthy individuals. The average protein intake in the United States exceeds recommendations and may contribute to the age-related decline in GFR. In a review of Paleolithic nutrition, Eaton et al. (61) suggest that our ancestors adapted to high protein intake and that such a diet is unlikely to be harmful in the context of healthy activity levels and overall dietary pattern. However, extrapolation from the prehistoric diet may not be appropriate in this instance, given a markedly shorter life expectancy until, in evolutionary context, quite recently. In general, it is difficult to demonstrate the efficacy of preventive measures when disease is not common, does not develop rapidly, or lacks good surrogate markers. Perhaps for these reasons, or perhaps because healthy kidneys do not benefit from protein restriction, the benefits of protein restriction have only been convincingly demonstrated for an eGFR below 70 mL/1.73 m^2/min.

Energy

To maintain lean body mass and nutritional status, and to prevent protein energy wasting, patients with CKD, whether or not on dialysis, generally should receive an energy intake of approximately 30 to 35 kcal/kg/d (24). It is important to take into consideration other factors that may affect energy requirements in CKD patients, including but not limited to presence of wounds (62), health status, weight status, chronic inflammation, hyperglycemia, and hyperparathyroidism (24).

Peritoneal dialysis is conducive to weight gain and obesity in patients receiving adequate nutrition, due to the delivery of 400 to 700 kcal/d in dialysate glucose with most dialysis solutions (63). Obesity may contribute to the development and progression of CKD and should be prevented or treated due to its other associated hazards (see Chapter 5).

Dietary Fat

Atherosclerosis affects the renal arteries and is associated with CKD. The contribution of diabetes and hypertension to atherosclerotic disease of the kidney vasculature is one means by which these conditions lead to kidney failure. Consequently, dietary interventions to prevent or reverse atherosclerosis may be valuable in preventing or reversing renovascular disease (see Chapter 7). A high intake of dietary fat and cholesterol may contribute to high glomerular pressures. Observational evidence has associated the consumption of animal products and saturated fat intake with increased albuminuria (64,65). Filtration is impaired by the deposition of foam cells in the glomerular endothelium. Alternatively, polyunsaturated fats may indirectly improve glomerular pressures and function through their effects on eicosanoid and prostaglandin metabolism. Optimal dietary fat intake in the prevention of kidney disease is the same as for the prevention of other atherosclerotic conditions. There is evidence that while total, saturated, and trans fat intake should be restricted, intake of polyunsaturated fat, especially n-3 fatty acids, should be liberalized in all stages of CKD and for ESKD patients requiring dialysis treatment (12,66,67). Recent updated guidelines indicate the supplementation of approximately 2 g/d of long-chain n-3 fatty acids in stages 3 to 5 CKD could lower triglyceride levels while 1.3 to 4 g/d of long-chain n-3 fatty acids in adults receiving dialysis therapy, both peritoneal and hemodialysis, could be beneficial to improve lipid profile but may not reduce mortality risk or cardiovascular events (24).

Carbohydrates and Dietary Fiber

The benefit of dietary fiber consumption has been well established and known for quite a while, both in the adult population (see Chapter 1) and in the CKD population. In fact, dietary fiber was used as a treatment for ESKD over 30 years ago because of its ability to reduce plasma urea (68). Notably,

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insoluble fiber may lower serum nitrogen and other uremic toxins by enhancing fecal nitrogen excretion. In the CKD population, fiber supplementation has been shown to decrease serum urea and creatinine levels (69) and high fiber intake is associated with lower inflammation and mortality (70). More specifically, in a prospective cohort study of maintenance hemodialysis patients, Wang and colleagues found that for every 1 g increase in fiber consumed, the risk of major adverse cardiovascular events was reduced by 11% and this reduced risk was independent of other risk factors, including diabetes, albumin, and left ventricular mass index, among others (71). Therefore, fiber intake should be 25 to 30 g/d in all stages of CKD (12).

Sodium and Fluid

Sodium filtration and reabsorption are both reduced with CKD; therefore, restriction of sodium intake below levels recommended for the general population in early CKD is generally not necessary. As CKD becomes more severe, sodium restriction to between 1,000 and 2,400 mg/d is appropriate as the ability of the kidneys to excrete free water and sodium becomes diminished. In CKD, the reduced excretion of sodium and fluids leads to accumulation of these substances and the activation of the sympathetic nervous system, which ultimately leads to secondary hypertension. The accumulation of these substances may also lead to edema. Although hypertension is a cause of CKD, it is also a complication of it as well. The control of hypertension, especially with the use of loop diuretics in advanced CKD, is important for the primary, secondary, and tertiary prevention of CKD.

In general, thirst is a reliable indicator of appropriate fluid intake. Adequate intake of water is important in the preservation of kidney function over time and in the avoidance of nephrolithiasis. An intake of water equal to urine output plus 500 to 1,000 mL (to account for insensible losses) is an appropriate guideline as eGFR decreases and thirst becomes a less reliable index.

Potassium

Potassium is generally found in fruits, vegetables, some dairy (milk and yogurt), and some animal sources (organ meats and cattle) (72). It has been well established that a diet rich in potassium from healthy sources is generally considered beneficial and cardioprotective (see Chapter 7). However, tubular secretion of potassium tends to rise as eGFR falls, preserving the ability to excrete potassium in the urine. In later stages of CKD, potassium accumulation becomes a threat. In long-term hemodialysis patients, hyperkalemia is associated with an increased mortality risk (73–75). Interestingly, a few studies have also demonstrated those with an increased intake of potassium have little to no increase in serum potassium levels (73), questioning the true effect of dietary potassium intake on serum potassium levels. Recent evidence suggests that the bioavailability of potassium from plant foods may be no more than 60% due to the presence of cell walls (76). Further, plant foods have attributes to help mitigate hyperkalemia like natural alkali and fiber. Natural alkali facilitates the intracellular movement of potassium, lowering serum potassium levels, and fiber increases the excretion of potassium from the body, also lowering serum levels.

Nonetheless, in hemodialysis patients, the restriction of potassium intake to <3 g/d is recommended; however, the potassium restriction should focus on an individualized meal plan that continues to include fruits, vegetables, and fiber, as the health benefits of these foods is unequivocal (12). One way to preserve the inclusion of vegetables in the diet is to boil the vegetables, which reduces the potassium content by approximately 50% to 70%, but may not be universally necessary (77–79). Avoidance of foods excessively high in potassium (molasses, raw beans), dried fruit, fruit juices, and vegetables sauces is also recommend for patients with advanced kidney disease to prevent the ingestion of a large amount of

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potassium in a short period of time. For peritoneal dialysis patients and those with hypokalemia, potassium intake should be adjusted to account for losses and low levels, respectively (12). All patients undergoing dietary changes should be monitored with regular measurements of their serum potassium values as an additional safety measure.

Recently, new and novel potassium binders have recently been introduced and approved for use in the CKD population. More research is needed to determine if CKD patients could follow a more healthy, cardioprotective, and nutrient dense diet with or without the use of a potassium binder; however, strong arguments have been made advocating for a more liberalized and healthy diet overall (80).

Dietary Acids and Metabolic Acidosis

Acid–base balance is dependent on kidney function such that the kidney lowers acid levels. As expected, as kidney function declines, acid levels rise. Currently, CKD patients are often given sodium bicarbonate as a neutralizing agent as it has been shown to slow the decline in GFR (81–83).

Potential renal acid load (PRAL) is defined as the "contribution of food or dietary pattern to net endogenous acid production" (84). Acid generation from food, as indicated by PRAL (as mEq), shows animal sources of food are the most acid producing, with hard or processed cheeses and egg yolks with the highest PRAL. Alternatively, most fruits and vegetables are more basic, with raisins and spinach with the lowest PRAL (84). Consumption of more basic foods would, thus, result in less metabolic acidosis. Research has shown vegan diets to be considered nearly acid neutral, compared to their omnivore counterparts (85,86).

Several trials have demonstrated equal effectiveness in reducing metabolic acidosis when CKD patients consume sodium bicarbonate or two to four cups of fruits and vegetables daily (83,87–89). While both sodium bicarbonate and fruit and vegetable consumption improves metabolic acidosis, consuming fruits and vegetables has demonstrated superior effects on secondary outcomes, including weight loss, blood pressure and urine protein (87,88), systolic blood pressure, low-density lipoprotein (LDL) levels, body mass index, lipoprotein (a), and vitamin K1 levels (83). In addition, despite the higher potassium intake, participants did not experience an increase in serum potassium (87–89), although these trial did exclude those with higher serum potassium levels.

Phosphorus

Phosphorus is an essential mineral for various functions in the body including activation of enzymes through phosphorylation and dephosphorylation; a structural component of teeth, bones, DNA and RNA, and cell membranes; energy transfer and storage through ATP; and pH regulation, to name a few (90). Phosphorus in food can be found as organic or inorganic. Generally, organic phosphorus is found naturally in food sources and is 30% to 60% absorbed while inorganic phosphorus is found in processed food, particularly dark sodas, as a food additive to preserve shelf life, enhance flavor, and retain moisture, and is almost entirely (>90%) absorbed (91–93). Further, foods from plants, including fruits and vegetables, have a lower bioavailability (10%–30%) of phosphorus compared to animal-based foods (40%–60%) due to the presence of phytate in plant foods which binds to phosphorus, allowing it to pass unabsorbed as feces (93). Typically, a greater majority of phosphorus is excreted through the urine with a smaller percentage (10%–33%) excreted in the feces (90), but this can vary depending on the sources of food consumed. As CKD progresses and the eGFR becomes ≤ 45 mL/min/1.73 m^2, phosphorus excretion is reduced leading to phosphorus accumulation. Current guidelines recommend restricting dietary phosphorus when hyperphosphatemia develops; however, earlier restriction could help prevent secondary

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hyperparathyroidism (94). Phosphorus restriction, independent of protein restriction, appears to retard the progression of CKD (95–97). There is evidence that restriction of phosphorus is beneficial in CKD, particularly in the prevention of secondary hyperparathyroidism (35,95,96).

Phosphorus intake should be restricted to 800 to 1,000 mg/d in patients with stages 3 to 5 CKD and those receiving dialysis treatment. A majority of phosphorus should come from plant foods because of their lower bioavailability and many other benefits as previously described (37,98). As kidney function declines and patients transition to dialysis, phosphate binders may be necessary to control serum levels. It's important to note that calcium-based phosphorus binders have been shown to be effective in binding phosphorus in the gastrointestinal tract; however, their regular use may be associated with increased vascular calcifications and all-cause mortality (99).

Calcium and Vitamin D

As kidney function declines, there is a decreased activation of 25-hydroxycholecalciferol (25(OH)D) to 1,25-dihydroxycholecalciferol ($1,25(OH)_2D$) in the kidney, resulting in reduced calcium absorption from the gastrointestinal tract. Vitamin D supplementation is generally indicated in all stages of CKD and for dialysis patients as it's generally accepted that this patient population is vitamin D insufficient or deficient. Guidelines suggest supplementation be in the form of ergocalciferol (vitamin D_2) or cholecalciferol (vitamin D_3) to correct for vitamin D deficiency (24) as native vitamin D supplementation has not been shown to lead to hypercalcemia or hyperphosphatemia (100). In addition, since extrarenal organs are able to convert 25(OH)D to $1,25(OH)_2D$, native vitamin D supplementation is warranted (100,101) to restore serum 25(OH)D concentrations and reduce secondary hyperparathyroidism (SHPT) development in CKD or treat SHPT in dialysis patients (102). Finally, vitamin D is now known to have pleiotropic effects on other organs and functions in the body, including the neurological and immune system and on antineoplastic activity (100,101).

While the decrease in 1,25-dihydroxycholecalciferol will generally lead to hypocalcemia, treatment for low $1,25\ (OH)_2D$ can result in hypercalcemia as secondary hyperparathyroidism SHPT continues to develop, resulting in reduced urinary excretion of calcium and an increase in calcium released from bone, potentially leading to vascular calcification (12). Therefore, it is important to monitor serum calcium, phosphorus, and vitamin D levels regularly, avoiding high or low levels of each. Patients with stages 3 or 4 CKD and those transitioning to dialysis should restrict calcium intake to 800 to 1,000 mg/d while dialysis patients should restrict calcium intake to <800 mg/d.

Water-Soluble Vitamins

For a variety of reasons, including dietary restrictions, anorexia, diuretic use, and kidney replacement therapy losses, patients with chronic CKD and those on dialysis are at risk for deficiencies of B vitamins, folate, and vitamin C—all water-soluble vitamins (103,104). A kidney-friendly multivitamin providing the recommended dietary allowance/adequate intake (RDA/AI) of water-soluble vitamins is generally considered appropriate.

Other Minerals and Trace Elements

Iron

Iron deficiency is relatively common in chronic CKD and is generally multifactorial. The management of iron deficiency and iron-deficiency anemia in CKD is complicated and beyond the scope of this review.

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A multivitamin designed for use in CKD may be adequate, but often iron supplementation is needed. For those undergoing hemodialysis, intravenous iron is often required in the setting of elevated hepcidin levels that impair intestinal absorption. Provision of adequate iron is necessary for exogenous erythropoietin to be effective.

Zinc and Selenium

Both zinc and selenium levels are generally lower in CKD patients (105) and dialysis patients (17,106,107) compared to healthy adults. Despite the overwhelming amount of literature to show low levels of both of these trace elements and low selenium status being independently and strongly associated with death and all-cause hospitalization (17), supplementation in dialysis patients remains controversial and is not recommended (108) as supplementation has not been shown to improve nutritional status, markers of inflammation, or overall micronutrient status (24).

Aluminum

Patients with CKD are at risk of aluminum toxicity from aluminum-based phosphate binders and aluminum-containing antacids. Therefore, these types of products should be avoided. Aluminum-based phosphate binders should only be used in an emergency and are not to be used as a routine treatment for hyperphosphatemia. Finally, citrate, which is sometimes used to treat metabolic acidosis in CKD, enhances intestinal absorption of aluminum and can facilitate aluminum toxicity. As such, citrate-containing medications should not be combined with aluminum-based substances in patients with CKD.

Carnitine

Carnitine is a nitrogenous compound abundant in meat and dairy products. Carnitine serves as a cofactor in the mitochondrial oxidation of long-chain fatty acids and buffers the pool of coenzyme A by accepting an acyl group in transfer. Carnitine requirements are met by carnitine ingestion and by carnitine biosynthesis, which occurs in the liver and kidneys. CKD may lead to carnitine deficiency by several mechanisms, including reductions in both intake and manufacture. Hypertriglyceridemia is common in kidney failure and may be due in part to impairments in fatty acid oxidation resulting from carnitine deficiency. There is suggestive evidence that carnitine supplementation may be effective in the treatment of hypertriglyceridemia associated with CKD. A systematic review and meta-analysis by Chen et al. of 49 randomized controlled trials found L-carnitine supplementation in maintenance hemodialysis patients to lower serum LDL; however, the decrease was not clinically significant, whereas the decrease in C-reactive protein (CRP) was clinically and statistically significant.

To date, reliable data characterizing carnitine balance in uremic and dialysis patients are lacking (109). Carnitine has been used in attempts to lower triglycerides; enhance responsiveness to erythropoietin; and improve the following: exercise tolerance, cardiac function, insulin resistance, and quality of life, among others. The current evidence is inconclusive for any of the outcomes and more research is needed (110). The use of carnitine should be considered experimental until additional evidence becomes available.

TOPICS OF SPECIAL INTEREST

Nephrolithiasis

The incidence of nephrolithiasis has been increasing sharply over recent decades in affluent populations, such that over 10% of the US population experiences a kidney stone in their lifetime, with up to 75% of

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having recurrence after 20 years (111). The most common type of kidney stone is a calcium oxalate stone, which accounts for 70% to 80% of kidney stones formed (111). Contrary to popular belief, the dietary treatment of kidney stones is not calcium restriction, but the restriction of oxalate, sodium, and animal protein (112,113). Additional recommendations include increasing fluid intake to increase urine volume, thereby reducing the concentration of stone promoters (see in the following section).

Animal Protein Intake

The association of animal protein with nephrolithiasis dates back to the end of World War II when animal protein ingestion began to increase in the 20th century (114). Over the ensuing decades, some have postulated that those with recurrent calcium oxalate stones should consider becoming vegetarians due to their lower risk of kidney stones (115). Several large observational studies since then have documented that those eating dietary patterns emphasizing vegetarian food sources have a lower risk of having kidney stones (116). Recently, the Oxford Cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC) study showed that vegetarians were associated with a 31% reduced risk of having kidney stones whereas those in the top tertile of meat consumption were associated with a 64% increased risk compared to those in the lowest tertile (117). It is thought that animal protein increases the risk of kidney stones by increasing urinary levels of acid, calcium, and uric acid, all of which are favorable for stone formation. As such, research suggests that stone formers be advised to limit the intake of all animal proteins, including fish (118). In contrast to animal protein intake, which has an acidifying effect and diminishes urinary citrate excretion, and important inhibitor of stone formation in the urine, plant protein has an alkalinizing effect (119). Further, plant protein has natural citrate and other stone inhibitors, like calcium, potassium, and magnesium, all of which reduce the risk of stone formation. In fact, for those unable or unsuccessful in altering their urine composition through dietary means, potassium citrate, a medication, is often prescribed for treatment.

Fluid Intake

All patients affected by stones should be counseled to increase their fluid intake to at least 2 L to reduce the concentration of stone-forming substances, like calcium and oxalate. A meta-analysis of 15 studies has shown that each 500 mL increase in water intake was associated with a 7% reduction in relative risk of stone formation (120). It is estimated that perhaps up to 80% of kidney stones recurrences may attributable to inadequate water intake (118).

Sodium

Sodium ingestion results in sodium excretion, which ultimately leads to calcium excretion in the urine (120). The increased concentrations of calcium allow for binding with urinary oxalate, thus leading to a stone. As such, dietary sodium restriction is often recommended.

Calcium

Consuming adequate dietary calcium may be particularly useful to reduce intestinal oxalate absorption in calcium oxalate stone formers (121). However, the extent of calcium's benefit may be affected by dietary fat and oxalate consumption as well. The importance of calcium in the diet was demonstrated in a prominent RCT by Borghi et al. (119) that followed participants for 5 years. In that study, 120 people were randomized to one of two diets: a diet low in calcium or a diet low in sodium and animal protein. Those following the low sodium, low animal protein had a 51% lower relative risk of stone formation compared to those eating a calcium-restricted diet. Calcium in the gastrointestinal tract may complex with

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oxalate, reducing oxalate absorption and thereby oxalate in the urine. Thus, restriction of dietary calcium may "paradoxically" increase the risk of calcium stone formation and thus is to be discouraged. Evidence to date suggests that a high intake of dietary calcium from food sources may protect against stone formation, but this association may not pertain to calcium derived from supplements (122,123).

Oxalate

The precipitation of calcium oxalate from urine is much more sensitive to oxalate than to calcium. Although oxalate levels are influenced by dietary intake, the preponderance of urinary oxalate is derived from metabolism. The metabolism of several amino acids contributes to oxalate levels in blood and urine; therefore, oxaluria correlates directly with protein intake. Ascorbate can be converted to oxalate. Although this generally contributes minimally to oxalate levels, the ingestion of megadoses of vitamin C can lead to hyperoxaluria in susceptible individuals. Pyridoxine serves as a cofactor in glycine metabolism, and its deficiency leads to excess oxalate production.

As such, restricting oxalate-containing foods tends to result in a minimal reduction in urinary oxalate in those without significant hyperoxaluria (124). Emerging evidence from the human microbiome shows that bacteria like *Oxalobacter formigenes*, which exclusively depends on dietary oxalate for survival, may reduce intestinal absorption of dietary oxalate (125), suggesting a more complex relationship of dietary oxalate with urinary oxalate levels. However, the frequent consumption of certain high-oxalate-containing foods like rhubarb, spinach, Swiss-chard, beet greens, cashews, and starfruit should be avoided in individuals with hyperoxaluria. Non-dietary risk factors for hyperoxaluria include bowel disease, bowel surgery, antibiotic exposure, and vitamin C supplementation.

Ascorbate

The metabolic conversion of ascorbate to oxalate suggests that high levels of vitamin C intake might increase the risk of stone formation. Urinary oxalate has been shown to increase with high ascorbate intake, but the effects on actual stone formation have not been confirmed. Thus, the risk of nephrolithiasis with an intake of vitamin C above 1.5 g/d may be increased, and this should be considered by those favoring supplementation of this nutrient (126). However, no change in the risk of nephrolithiasis attributable to vitamin C was seen in the Health Professionals Follow-up Study (127). The risk of vitamin C and kidney stones should not translate into the avoidance of citrus-containing foods, which contain lower, and more physiologic, quantities of vitamin C. Further, these foods have an abundant supply of natural alkali which has been associated with a reduction in stone risk. However, grapefruit juice may need to be avoided in some as it has been associated with an increased risk of stone formation in epidemiologic studies but not in experimental studies (128).

Pyridoxine

Vitamin B_6 is a cofactor in the metabolism of glyoxalic acid. High levels of B_6 intake reduce the production of oxalate by shifting the pathway toward the production of glycine. Pyridoxine has been used to treat oxalate stones with limited anecdotal success for dietary causes. Pyridoxine plays a larger role in primary hyperoxaluria, a genetic disease resulting in abnormal glyoxalic acid metabolism and the accumulation of oxalate.

Uric Acid

Uric acid excretion in urine rises with the intake of dietary animal protein. The solubility of urate is reduced in an acidic environment, and ingestion of certain amino acids acidifies the urine. Thus, purine

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ingestion both increases urinary urate and reduces its solubility. Hyperuricosuria contributes to the development of calcium oxalate stones by saturating urine and reducing the threshold for solute precipitation. Animal protein restriction protects against urate and calcium oxalate stone formation by reducing urinary urate (129). In one study (129), vegetarian diets were associated with a 93% reduction in risk of urine uric acid crystallization. For those with disease refractory to dietary changes, urinary alkalization is preferred over allopurinol, a common medication used to treat chronic hyperuricemia.

Nephrotic Syndrome

Evidence suggests that the combination of dietary protein restriction and angiotensin-converting enzyme inhibitor or angiotensin receptor blocker therapy reduces protein loss in urine without contributing to declines in serum albumin levels. Evidence for protein restriction or supplementation in nephrotic syndrome is inconclusive, and modification of protein intake is not routinely recommended (130). Moderate sodium restriction may help to manage edema (130). Nephrotic patients generally require vitamin and mineral supplementation, as they are subject to vitamin D and trace element deficiencies. Hypoalbuminemia results from albumin losses in urine in the nephrotic syndrome, increased albumin catabolism in chronic ambulatory peritoneal dialysis, and reduced synthetic capacity in hemodialysis (44).

Acute Kidney Injury

The dietary management of acute kidney injury (AKI) is not well delineated in the literature and depends in part on the etiology. When AKI occurs in the context of shock, parenteral nutrition may be necessary. The composition of parenteral nutrition formulas should be developed with the input of a nephrologist and hospital-based dietitian.

AKI is characterized by a state of accelerated protein breakdown that is not suppressed by provision of exogenous protein. The causes of excessive protein catabolism are diverse, including uremic toxins, insulin resistance, metabolic acidosis, inflammatory mediators, and dialysis-related losses of nutrients, as well as declines in the multiple metabolic and endocrine functions of the kidney. Patient requirements for dietary protein vary and are influenced more by the illness causing kidney failure and by the extent of hypercatabolism, as well as by the type and frequency of kidney replacement therapy, than by the kidney function (45). Patients undergoing continuous kidney replacement therapy may need up to 1.8 to 2.5 g/kg protein/d; in hemodialysis, 1.5 g/kg/d is typically required (131). A dietitian should be involved in the management of all patients with AKI that persists for more than several days.

Nutritional management in the setting of AKI may influence prognosis; a potential benefit of essential amino acid supplementation is suggested in particular (132,133). The diet plan in such a setting should result from a collaborative effort involving, minimally, the nephrologist and specialized dietitian.

Endocrine Abnormalities

Although a variety of endocrine abnormalities are associated with kidney disease and uremia, most are beyond the scope of this discussion. Most relevant to dietary management is the development of both insulin resistance and elevations of glucagon, which contribute to impaired glucose metabolism. The dietary approach to impaired glucose metabolism and insulin resistance is discussed in Chapter 6. The basic approaches are unchanged in the setting of kidney failure, although medication doses may need adjustment.

Hyperlipidemia

Elevations of both LDL and very-low-density lipoprotein (VLDL) occur commonly in kidney disease. Management is as described in Chapter 7.

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CLINICAL HIGHLIGHTS

A growing body of evidence suggests that diet can alter the risk factors of CKD, like type 2 diabetes and hypertension, the progression of CKD, and the complications of CKD and ESKD, like metabolic acidosis and hyperphosphatemia. In CKD, judicious and tailored restriction of protein, sodium, dietary acid, and phosphorus is indicated, along with supplementation of vitamins and trace elements. Further, emphasis of plant food sources of protein has been shown to have multiple benefits, including those related to kidney disease.

The dietary management of patients with severe CKD should be a collaborative effort involving the patient and the patient's family, the primary care provider, the nephrologist, and a dietitian with expertise in kidney disease. An effort to delay dialysis in a patient with advanced CKD may involve complex dietary management, including the use of a low-protein diet from plant food sources and/or keto or hydroxy acids to minimize nitrogen load while preserving adequate nutriture.

The contribution of dietary pattern to the risk of kidney stone formation is increasingly recognized. The difference in rates of stone formation between developed and developing countries suggests that nephrolithiasis may be largely preventable through dietary modification. A diet rich in fruits and vegetables and restricted in animal protein and sodium is recommended. Fluid intake leading to a urine output of more than 2 L/d is likely protective. Avoidance of excessive dietary oxalate is a prudent precaution in patients with a history of hyperoxaluria. A generous intake of magnesium, potassium, and fiber may be beneficial and is indicated for purposes of health promotion (see Chapter 45). Dietary calcium should not be restricted and actually may be protective. Dietary measures to prevent kidney calculi are largely consistent with recommendations for health promotion and may be advocated to patients both with and without a history of nephrolithiasis.

Patients with recurrent stone disease despite prudent dietary interventions are candidates for pharmacotherapy and/or more tailored nutritional therapies. Potassium citrate and thiazide diuretics have also shown promise in the management of recurrent calcium stones. Tailored interventions to prevent recurrent nephrolithiasis should be predicated on chemical analysis of a 24-hour urine collection.

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Chapter 17

Diet and Respiratory Disease

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INTRODUCTION

The importance of the liver in the metabolism of ingested nutrients and drugs suggests that hepatic function can be influenced by dietary manipulations. Less obvious is the potential role of specific nutrients in ameliorating the natural history of various chronic liver diseases or toxic exposures. Preliminary evidence supports the use of several nutriceutical agents in the treatment of liver diseases for which conventional therapies are limited.

OVERVIEW

Diet in compensated chronic liver disease need not differ from that recommended for general health promotion (1,2). In uncompensated liver disease, malnutrition is a common sequela (1–3). Malnutrition in patients with chronic liver disease may develop despite near-normal dietary intake, even in mild disease, due to increased muscle protein breakdown and decreased synthesis (4).

Liver disease directly influences biomarkers of nutrient energy deficiency, such as albumin, prealbumin, transferrin, and retinol-binding protein, shifting their interpretation to a reflection of liver functionality rather than nutrition status (5). Upper body anthropometry, particularly triceps skin-fold thickness, may be necessary to assess body fat reserves, and mid-arm muscle circumference to assess protein reserves in a patient with ascites (6). Bioelectrical impedance analysis may also be useful, but it has limitations in patients with ascites (7). For bedside assessment, clinical parameters such as weight change, functional status, and visible muscle wasting are reliable indices of nutritional status, particularly when used in combination (2,7). Where available, indirect calorimetry should be used to determine energy needs in intensive care unit (ICU) patients with liver disease, as predictive equations do not correlate well with measured resting energy expenditure (3,8,9), particularly for those who do not have the expected response to nutritional therapies. In one meta-analysis, only 45% of predictive equations yielded estimates within 90–100% of resting energy expenditure measured by indirect calorimetry, mostly underestimating needs (9).

While cross-sectional imaging is considered the gold standard for assessment of muscle loss in liver disease, techniques usable at the bedside and without exposure to radiation seem more practical. A prospective study of 159 outpatients with cirrhosis compared identification of sarcopenia via cross-sectional imaging with results from subjective global assessment (SGA), serum albumin, mid-arm muscle circumference, hand-grip strength, and a combination of Body Mass Index (BMI) and thigh muscle thickness assessed by ultrasound. All were significantly associated with sarcopenia, and the combination of BMI and thigh muscle thickness showed reliable results for its identification. Interestingly, mid-arm circumference and mid-arm muscle circumference also predicted sarcopenia reliably in both men and women, while SGA was not very useful (10). A complete nutritional assessment should include evaluation of micronutrients at high risk of deficiency, including vitamins A, D, and E, folate, zinc, and

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iron, as well as thiamin in alcoholic liver disease (6). A dietary consultation is generally indicated for inpatients and outpatients alike, given the frequency of protein-energy malnutrition in patients with advanced liver disease and the complexity of evaluating the nutritional status of such patients.

Maintenance of adequate nutritional status should be a priority in patients with chronic liver disease and hepatic insufficiency, as malnutrition in this population is significantly correlated with poorer clinical outcome (3) (see Chapter 26). Particularly sarcopenia is well researched as predictor of morbidity and mortality in advanced liver disease (11). Ascites is associated with anorexia and has been shown to increase energy expenditure, to the point where it is suggested to use actual body weight for estimation of energy requirements (12). Nausea, which frequently accompanies liver disease, further reduces dietary intake. Malabsorption and poor dietary intake associated with alcoholism are other common reasons for malnutrition in chronic liver disease. A systematic review found a positive effect of nutrition support on clinical outcome of nutritionally at-risk patients with cirrhosis (13). Results vary though, possibly depending on length of intervention (15) or specific disease combination and severity (16). Reduction in the frequency of infectious complications, reduction in hospitalization, and improvement in hepatic function have also been seen in patients with liver disease in response to nutrition support (2). Additionally, in one prospective observational study on 65 patients evaluated for liver transplantation, an individualized nutrition care plan and personalized nutrition counseling improved nutrition status and significantly improved protein and energy intakes, compared to the same number of historic patients who underwent liver transplantation the year before implementation of the personalized care plan (14).

Protein restriction is no longer recommended for patients with mild to moderate hepatic encephalopathy (HE) and is now generally discouraged (2). A concern regarding protein provision has been that it may increase the risk of hepatic encephalopathy. Current recommendations hold that even provision of 1.8 g/kg body weight does not negatively affect HE for alcoholic cirrhosis (2,3). A small study investigated the serum amino acid response to a normal protein diet in patients with compensated liver cirrhosis, compared to healthy age-matched volunteers (20 g protein in one meal), and to a high protein meal in patients with decompensated liver cirrhosis (1 g/kg body weight in one meal). They found that the total of leucine, isoleucine, and tyrosine increased more in patients with compensated cirrhosis than in healthy subjects, and the branched-chain amino acid (BCAA) to aromatic amino acid (AAA) ratio decreased further from baseline. In the 1 g/kg body weight group of patients with unstable cirrhosis, the BCAA/AAA ratio decreased more significantly, mainly due to large increases in isoleucine and leucine. One of six patients in this group developed mild signs of HE via electroencephalogram. No clinical symptoms of HE were seen in any of the subjects (17). The increase in BCAA may be due to insulin resistance (17).

Alarmingly, minimal HE, the earliest form of encephalopathy, reportedly occurs in up to 80% of patients with cirrhosis but is rarely tested for (18). Lactulose, followed by a nonabsorbable antibiotic, such as rifaximin, is now considered the standard therapy for HE. This strategy facilitates clearance of nitrogenous waste while permitting protein intake adequate for metabolic needs (19).

Patients with cirrhosis should take between 30 and 40 kcal/kg/day (kcal/kg/d), along with 1.2 to 1.5 g/kg/d protein from various sources (20). Higher protein intake may be indicated during periods of physical stress or in the recovery phase from malnutrition. For maximal effect of caloric consumption, the evidence suggests greatest benefit from frequent feeding, with four to six smaller meals throughout the day and a late-night snack (21). Late-night, carbohydrate-rich snack interventions improve nitrogen balance and quality of life, and potentially reverse sarcopenia, by reducing time spent in the fasting state (22). Snacks include fruit and yogurt, blended smoothies or liquid nutritional supplements, and whole-grain crackers or cereal with milk. Additionally, when enteral tube feeding is required to maintain nutritional

adequacy in liver disease, esophageal varices are no longer considered a contraindication (2).

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Dietary fat should be restricted in patients with steatorrhea but otherwise should be unmodified. A reduction in dietary fat may be indicated on general principles if fat intake exceeds recommendations. In a malnourished patient, any reduction in dietary fat should be balanced by an increase in calories from other sources, preferably complex carbohydrates. Protein malnutrition is exacerbated whenever energy intake is insufficient, as amino acids are extracted from skeletal muscle to support gluconeogenesis (21,23).

In patients with portal hypertension and ascites, restriction of fluid and sodium intake is generally indicated. An unpalatable diet may exacerbate the tendency toward malnutrition common to patients with advanced liver disease (7) and, therefore, may be harmful even if the dietary restriction imposed would otherwise be judicious. Accordingly, the recommendation is to restrict sodium to 80–120 mmol/d (1.8–2.8 g/d), and not below 60 mmol/d, even for patients with ascites (2,21).

The prevalence of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) has risen in adults in the past few years (24–27). The rate in children is expected to increase (25), even though no change in the prevalence of NAFLD in children and adolescents was detected over 5 years in one meta-analysis (28). Because NASH and its precursor, NAFLD, are hepatic manifestations of the metabolic syndrome, nonpharmacologic treatment centers on diet and exercise to promote gradual weight loss and improve insulin resistance (see Chapters 5 and 6). A variety of approaches to low-calorie diets may be effective for weight loss. One way to achieve reduced energy intake is reducing consumption of sugar-sweetened beverages and excess fructose. At this point however, data is insufficient for a universal recommendation for a reduction specifically of fructose intake (3,21,30). The problem with studies investigating the relationship between fructose intake and liver diseases is that increased energy intake in the study arms that include fructose confounds the results (29, 31). The known metabolic effects of fructose include increased de novo lipogenesis, increased mitochondrial dysfunction, stimulation of inflammatory pathways, increased insulin resistance, likely impairment of copper status, and negative effect on the microbiota (32–35), and justify at least further research in the efficacy of reduced fructose intake. These effects, along with the easily increased energy intake, also justify limitation of sugar-sweetened beverages as approach to nutritional management (36).

The role of intestinal microbiota in the pathogenesis of NAFLD suggests potential utility of probiotics in the prevention and treatment of fatty liver disease, with increasing evidence for beneficial effects (37,38).

Nutritional management of liver disease in the pediatric patient varies with etiology. Given the importance of adequate nutrition in proper neurodevelopment and growth, nutritional assessment is a critical part of the management of children with chronic liver disease (39), and chronic liver disease is correlated with increased morbidity and mortality in this patient population (40). When liver disease is due to inborn errors of metabolism, such as galactosemia and Wilson's disease, specific dietary interventions are indicated. The management of such children generally should be overseen by a specialist.

NUTRIENTS, NUTRICEUTICALS, AND FUNCTIONAL FOODS

Silymarin

Silymarin is derived from the seeds of *Silybum marianum* (milk thistle). The extract contains a group of chemical compounds in the flavonoid family. There is a long history of its use in traditional medical systems for treatment of liver disease and manifestations of portal hypertension (41). It is well studied for

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its protective effect on the liver in patients with NAFLD, via multiple pathways. Silymarin improves liver enzymes, fasting glucose, insulin resistance, and mortality (41,42).

Its beneficial effect for NAFLD has been demonstrated in a number of small studies (42,43). Conversely, for alcoholic liver disease, results are conflicting, and the quality of the studies is not always convincing. It does not seem to be effective for viral hepatitis or hepatocellular carcinoma (42). The nutriceutical has been reported to be well tolerated and to have few interactions with drugs (41,42,44).

Vegetable Protein

Benefits from a diet deriving protein from plant sources have been reported to reduce the incidence of hepatic encephalopathy in patients with cirrhosis. Such diets often are poorly tolerated, however, because of their high fiber content and high total food volume. To the extent that protein derived from plant sources is tolerated by individual patients, its use is reasonable (19), though not supported without question (21). In addition to vegetable protein, dairy-based proteins may also be better tolerated than meats in patients with cirrhosis (2).

Branched-Chain Amino Acids

Impairment in amino acid metabolism in cirrhosis results in accumulation of aromatic-ring amino acids and depletion of BCAAs. An imbalance in the amino acid distribution has been implicated in the development of hepatic encephalopathy, and an association with sarcopenia has been found (18). The competitive action of BCAAs on amino acid transport across the blood–brain barrier may help alleviate this condition (45). Serum BCAA levels were reduced in patients with sarcopenia, a predictor of morbidity and mortality in patients with liver cirrhosis (18). Based on knowledge of physiologic processes, BCAA supplementation should promote detoxification of ammonia, reduce muscle catabolism, and prevent false neurotransmitter generation (46). In clinical trials, BCAA supplementation has been shown to improve hepatic encephalopathy and quality of life (2,19,21,46). Recent studies suggest that BCAAs may also be helpful in reducing morbidity in patients with hepatocellular carcinoma (47).

Branched-Chain Keto Acids

The keto acid analogs of BCAAs offer the putative advantage of providing a substrate for protein synthesis devoid of the amine group. Metabolic advantages of such preparations have been well described, but the evidence of clinical benefit in advanced liver disease is limited. Use of branched-chain keto acids in patients intolerant of standard protein may be appropriate; however, recent research in this area is limited (48).

S-Adenosyl-L-Methionine

S-adenosyl-L-methionine (SAMe) is a precursor of the essential amino acid methionine. The majority of SAMe is produced in the liver, and its metabolism is slowed down significantly in several types of liver disease (49,50). Studies in various animal models support supplementation of SAMe to ameliorate liver injury and NASH, and to reduce fibrosis (49). Several studies in humans show a beneficial effect of SAMe supplementation on chemotherapy-induced liver toxicity (46,47,49). Limited evidence suggests that SAMe is not an effective treatment for alcoholic liver disease (51) but may improve early response to treatment for hepatitis C and Primary Biliary Cholangitis (50,52,53). While trials are underway, reliable evidence is not sufficient at this time (54).

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Glutamine

Glutamine is a nonessential amino acid (see Chapter 3). Because of abnormal intestinal permeability, endotoxemia in cirrhosis accelerates turnover of skeletal muscle. Glutamine is the predominant amino acid in muscle, and its consumption in cirrhosis might suggest a need for dietary replacement. However, glutamine is metabolized into ammonia and may increase plasma ammonia levels. Clinicians should therefore advise patients with cirrhosis to avoid glutamine supplements (20).

Medium-Chain Triglycerides

Medium-chain triglycerides (MCTs), generally containing 8- to 10-carbon fatty acids, can be absorbed in the intestine without incorporation into chylomicrons and require minimal hepatic metabolism. MCTs are useful in malnourished patients after bariatric surgery (55). Preliminary evidence suggests survival benefit from enteral nutrition, with MCTs as therapy for acute alcoholic hepatitis, with the benefit depending on total energy intake (16). After liver transplantation, use of MCTs is recommended (2). Supplementation with essential fatty acids (see Chapter 2) is required if MCT supplementation is sustained and intake of fat from other sources is negligible.

In patients with cirrhosis, use of MCTs should be avoided. The ability of the liver to extract MCTs from circulation and metabolize them is impaired in cirrhosis. MCTs cross the blood–brain barrier and have been known to cause encephalopathy and coma when they accrue.

Minerals

Zinc deficiency has been reported in patients with various liver diseases, including NAFLD, NASH, chronic hepatitis, and liver cirrhosis. This deficiency is likely due to a combination of impaired intestinal absorption, excessive urinary loss, and reduced binding to albumin when albumin levels are low (19,56). Zinc deficiency may trigger oxidative stress, causing iron overload, insulin resistance, and hepatic steatosis. Additionally, it leads to increased ammonia levels. Zinc supplementation does not appear to have a beneficial effect on hepatic encephalopathy though (2,19).

Selenium deficiency may contribute to insulin resistance, particularly in patients with hepatitis C (2). Circulating levels of magnesium, iron, and calcium should be corrected. Conversely, manganese accrues and accumulates in the basal ganglia. Accordingly, supplements with manganese should be avoided (2).

Vitamins

Patients with chronic liver disease should take a multivitamin supplement. Thiamine supplementation is indicated in all alcoholic patients (2). Vitamin E supplementation of 800 IU daily in adults with NASH is recommended (3), as it improves liver enzymes, histological changes, steatosis, and inflammation (57).

Vitamin D deficiency is very common in patients with chronic liver disease, with a prevalence of 64–92%, and levels correlate with response to treatment in patients with various liver diseases (2). Supplementation is recommended particularly in patients with low bone mineral density (2); however, given its benefits, supplementation for all patients with NAFLD in general should be considered (41). This recommendation is more meaningful in view of data that supplementation improves response to treatment of hepatitis C infection and that low pre-transplant levels increase the likelihood of organ rejection (58). Similarly, vitamin D deficiency was a prognostic indicator of poor outcome in a study on patients with hepatocellular carcinoma (58). The impact of vitamin D on liver disease is complicated as its metabolism depends on the liver. Thus, vitamin D deficiency in liver cirrhosis would be an expected consequence rather than a cause or contributing factor. Some genetics studies suggest that at least with

respect to fibrosis, vitamin D levels may be involved in initiation of the process (58).

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Bioactive Components

Multiple mechanisms contribute to the pathogenesis of NAFLD and nonalcoholic steatohepatitis (NASH), and ultimately, cirrhosis. Accordingly, multiple bioactive components can be found to influence one or several of these mechanisms. Several of these components have been researched extensively and are currently in clinical trials. These include berberine, resveratrol, curcumin, and ginger (59). Berberine is an alkaloid found in the herb *Coptis chinensis* Franch (Chinese goldthread). It was used for treatment of diabetes in traditional medicine. Berberine lowers cholesterol (60) and may have therapeutic value for NAFLD (61). Studies in rodents and cell models have revealed details of the molecular pathways by which berberine reduces hepatic steatosis and inflammation in liver and adipose tissue (61). It decreases inflammatory cytokines and reduces oxidative stress, among other pathways it influences (62). A phase 4 trial with berberine is registered with the FDA (59).

Resveratrol, well known for its beneficial effects on cardiovascular health, decreases lipogenesis and increases fatty acid oxidation, among other mechanisms, thereby decreasing hepatic steatosis (63). However, a meta-analysis of four randomized control trials did not yield sufficient evidence of a benefit of resveratrol for treatment of NAFLD, relative to fibrosis, inflammation, or liver damage (64). Curcumin, another substance well known for its antioxidant properties, was shown to improve liver injury via the Nuclear Factor-kappa B pathway (63). A meta-analysis of four randomized control trials with a total of 228 participants showed that curcumin supplementation may lower levels of aspartate aminotransferase, an enzyme whose serum levels can indicate liver damage. Other parameters could not be analyzed based on available data (65).

Positive study results have also been reported for astaxanthin, an antioxidant, and coenzyme Q10 (41). Additionally, the impact of coffee on liver disease is found to be sufficiently positive to not discourage its consumption (30,66).

CLINICAL HIGHLIGHTS

Liver disease, whether cholestatic or noncholestatic, of alcoholic, viral, or other origin, imposes significant nutritional demands. Once severe, liver disease increases energy demands considerably. The sequelae of liver disease make malnutrition common.

Nutritional management should be directed toward preventing protein-energy malnutrition. Where available, indirect calorimetry should be used to determine energy needs in ICU patients with liver disease. Protein intake should be unrestricted unless severe encephalopathy is present in a patient without underlying malnutrition. In contrast to previously held clinical belief, recent studies suggest that restricting protein in patients with mild to moderate encephalopathy and malnutrition may actually impair recovery; lactulose and a nonabsorbable antibiotic, such as rifaximin, with adequate protein intake is now recommended in this situation. In patients intolerant of standard protein, BCAAs should be considered, although their benefit and particularly their cost-effectiveness are as yet uncertain. All patients should receive vitamin and mineral supplements.

In the case of NAFLD and NASH, nonpharmacologic treatment centers on diet and exercise to promote gradual weight loss and improve insulin resistance.

Patients with ascites should consume a salt-restricted and, if necessary, water-restricted diet. In the setting of malabsorption, MCTs may be advantageous. The possible benefits of silymarin and other nutriceuticals in the amelioration of hepatocyte function once cirrhosis has developed are intriguing, and

evidence is accruing for the beneficial effects of some of them, but such benefits are as yet inadequately demonstrated.

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Chapter 18

Diet and Common Gastrointestinal Disorders

Sheila Vance and and Jill Deutsch

INTRODUCTION

Normal functioning of the gastrointestinal (GI) tract is essential to normal digestion, nutrient absorption, and egestion. GI pathology can impair nutritional status in a variety of ways, depending on the site, nature, and extent of disease or injury. Conversely, nutritional status and specific exposures to ingested substances can significantly affect the health of the GI tract via both direct and systemic influences. Many GI diseases respond well to dietary interventions, either alone or integrated with conventional medical interventions.

OVERVIEW

Upper Gastrointestinal Disorders

Eosinophilic Esophagitis

Eosinophilic esophagitis (EoE) is a chronic, allergic, and inflammatory condition of the esophagus. EoE is relatively rare (1 per 2,000 people, with considerable regional variability), though the incidence of the disease is rising. EoE is marked by eosinophilic infiltration of the lining of the esophagus, which can lead to long-term damage, including scarring and strictures. Symptoms are generally marked by difficulty or pain with swallowing that may result in food impactions (food becomes stuck in the esophagus), feeding intolerance, and reflux. While the exact mechanism of inflammation in EoE is not understood, it is hypothesized that it is secondary to an immune response to food. To diagnose EoE, upper endoscopy esophagogastroduodenoscopy (EGD) with biopsies of the mid- and distal esophagus must be obtained to prove the presence of an abundance of eosinophils.

The mainstays of treatment to reduce the number of eosinophils in the esophagus are dietary modification and medications. The dietary modifications that have been most well studied in EoE management involve removing the six most common allergy-causing foods (six-food elimination diet, SFED); these include milk, wheat, eggs, soy, peanuts/tree nuts, and fish/shellfish. A systematic review published in 2017 suggests a histologic response (decrease in number of eosinophils on biopsy) rate of 69% (95% Prediction Limits (PL) 31.9–91.4%) and a symptom response rate of 87.3% (95% PL 64.5–96.3%) for the six-food elimination diet (N1). The magnitude of response to this exclusion diet is comparable to traditional medical therapies with topical steroids (N1). Another study in a mixed pediatric and adult population utilized a step-up elimination diet; 56 of 130 (43%) patients achieved reduction in eosinophils by eliminating only milk and wheat (N2). Remission rates increased to 60% with the additional elimination of eggs and legumes, and 79% achieved remission with the full six-food elimination diet (N2). The ability to limit a smaller number of foods limits diagnostic endoscopy between each phase and is more feasible for patients with limited financial resources, as dietary modifications can

prove to be expensive.

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The elemental diet, which consists of an amino acid formula, has also been studied as therapy for EoE. This diet is often a routine part of therapy in children with EoE. However, its use in adults is fraught by the need for a feeding tube to achieve adequate caloric intake. A group in the Netherlands published on the use of the elemental diet in a small population of adults with EoE and showed that 71% of those (12/17) who completed the diet achieved complete histologic response and 24% (4/17) had partial response (N3). Additionally, symptoms improved in all subjects, including 88% (15/17) who became asymptomatic (N3).

Gastroesophageal Reflux Disease

Gastroesophageal reflux (GER) is the preferred term for retrograde acid reflux into the esophagus, sometimes associated with pain typically referred to as heartburn. Getting acid reflux, or heartburn, is not unusual, but for the more than 10% of the population (N4) with frequent symptoms, referred to as gastroesophageal reflux disease (GERD), dietary and medical management may be necessary. Mechanistically, reflux occurs due to failure of the antireflux barrier to protect against frequent and abnormal amounts of refluxed material; relaxation of the lower esophageal sphincter (LES) or low LES pressure contributes to the impaired antireflux barrier (N4). A small amount of refluxate is physiologically normal, but when symptoms occur frequently, long-term damage to the esophagus may manifest as esophagitis and subsequent scarring, leading to peptic strictures or Barrett's metaplasia. While the diagnostic examination of upper endoscopy (EGD) and pH testing may be recommended in the evaluation of GERD, it is not necessary to make a diagnosis as reporting of typical symptoms is adequate.

Symptoms of GERD may occur postprandially, which is often the result of lifestyle factors, including weight gain and assuming an immediate recumbent posture postprandially. Dietary precipitants are thought to include large meals, fatty or fried foods, coffee, alcohol, and tobacco use (1). Additionally, acidic foods like tomato-based foods and citrus, chocolate, peppermint, and carbonated beverages may all exacerbate heartburn. Thus, dietary interventions to control GERD include eating small, regularly spaced meals and/or snacks, avoiding food within several hours of sleep, avoiding meals with high fat content, avoiding carbonated beverages and excess caffeine, and controlling weight (see Chapters 5 and 25). There are additionally some home diet remedies for heartburn that may neutralize the burning pain associated with atypical esophageal acid exposure; these include milk and ginger. Dietary interventions may serve to control GER symptoms entirely, but severe cases often require adjunctive pharmacotherapy.

Gastroparesis

Gastroparesis refers to "paralysis" of the stomach marked by delayed emptying of the stomach of a standard test meal in the absence of mechanical obstruction. Multiple-disease processes contribute to gastroparesis, including diabetes, postsurgical changes (i.e., vagotomy), and postinfection states, as well as chronic mesenteric ischemia, prescription medications such as opiates, and idiopathic causes. Diabetic gastroparesis may become apparent only after living many years with diabetes, especially with erratic glucose control, with an incidence of 1% in type 2 and nearly 5% in people with type 1 diabetes (N5). The most severe clinical symptoms of gastroparesis include nausea and vomiting, which may lead to dehydration and electrolyte derangements. Unfortunately, as there are few pharmacotherapeutic options, hospitalizations related to gastroparesis have increased since 2000, suggesting that adherence to dietary recommendations for management of disease is imperative.

The three-phased gastroparesis diet consists of liquid and solid foods that are easy for the stomach to mix and empty, thus limiting the work of the neuromuscular function of the stomach that is often impaired

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in gastroparesis (N6). In the first phase, patients are encouraged to consume sports drinks and bouillon sufficient to avoid volume depletion, typically1,000–1,500 mL/day. The goal of this short phase is to avoid citrus and highly sweetened beverages to overcome the nausea and vomiting that often accompany severe gastroparesis. In the second phase, soups, smoothies, peanut butter, cheese, and caramels are recommended to a total of 1,500 kcal/day while avoiding creamy and milk-based liquids. The third phase steps up to noodles, pasta, potatoes, rice, baked chicken breast, and fish, if tolerated. Fatty foods that delay gastric emptying, as well as red meats and vegetables, are to be avoided as they require significant mixing (fibrous foods also tend to promote formation of bezoars) from the stomach.

Parkman and colleagues reported a list of foods that provoke symptoms of gastroparesis, including orange juice, fried chicken, cabbage, oranges, sausage, pizza, peppers, onions, tomato juice, lettuce, coffee, salsa, broccoli, bacon, roast beef, and generally fatty, acidic, spicy, and roughage-based foods (N7). Saltine crackers, graham crackers, and Jell-O modestly improved symptoms (N7). Additional foods that did not worsen symptoms and were tolerated included ginger ale, gluten-free foods, tea, sweet potatoes, pretzels, white fish, clear soup, salmon, potatoes, white rice, popsicles, and applesauce (N7). A small randomized controlled trial (RCT) additionally demonstrated that a small particle size diet is preferred in patients with gastroparesis to overcome symptoms of nausea and vomiting, among others (N8).

Celiac Disease (Gluten Enteropathy)

Celiac disease (see Chapter 24) is a chronic cell-mediated hypersensitivity reaction to dietary gluten in susceptible individuals. After removing starch, gluten is the leftover water-insoluble protein found predominantly not only in wheat but also in barley, rye, and to a limited extent in oats (2). When severe, celiac disease can lead to near-complete villous atrophy of the small intestinal mucosa and thus malabsorption of key nutrients. Diagnosis is made by upper endoscopy (EGD) to obtain small bowel biopsies; however, immunoglobulin A (IgA) and IgG tissue transglutaminase (anti-tTG), IgA or IgG endomysium antibodies, and IgA or IgG deaminated gliadin peptide antibodies can aid in the diagnosis of celiac disease. Celiac disease is associated with several systemic diseases and particularly autoimmune conditions, such as type 1 diabetes (2).

The overall prevalence of celiac disease in Europe and the United States is estimated at 1% (N9). The prevalence, however, appears to be increasing; tTG seropositivity was estimated at 0.2% among 9,133 subjects whose blood samples were stored circa 1950 compared with 0.9% of modern-day blood samples (N10). The spectrum of disease manifestations is the result of the complex interplay of familial/genetic, immune-related, and environmental triggers. Nearly all patients with celiac disease test positive for HLA-DQ2 or DQ8 haplotypes, but only a fraction of those with these haplotypes actually manifest signs and symptoms of celiac disease. Thus environmental triggers have been proposed. Adenovirus infection, interferon alfa treatment, and intestinal infections have all been shown to increase the risk of celiac disease development in these genetically predisposed individuals. Breastfed babies and those with delayed exposure to wheat have reduced risk of the condition (2). Appropriate treatment for celiac disease requires the strict elimination of all sources of gluten, which is therapeutic but often difficult to accomplish. Gluten can be found in many products that do not even seem related to wheat, barley, or rye, such as ice creams, soups, sauces, and in many medications and cosmetics. Therefore, great care must be taken when making dietary changes. Furthermore, caution should be exercised among those with celiac disease when eating out at restaurants or traveling. Unfortunately, the acquisition of gluten-free products can be time consuming and costly. It is important to note that the gluten-free diet may be deficient in fiber and other key nutrients, such as iron, calcium, magnesium, zinc, folate, vitamin D, and

B vitamins; thus, patients may require supplementation (N11). Patients should be encouraged to join celiac disease support groups as support group members are generally better at managing their diet than those not participating in support groups (2). Print and online information is available to assist a patient in efforts to adhere to a gluten-free diet (see Appendix J). Consultation with a dietitian is always indicated.

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Lower Gastrointestinal Disorders

Constipation

The American Neurogastroenterology and Motility Society (ANMS) defines constipation as a symptom-based disorder characterized by one or more bowel symptoms that include infrequent stools, hard stools, and/or difficult stool passage (3). Constipation can be associated with hemorrhoids and diverticulosis, as well as anal fissures and incontinence. In the absence of alarm symptoms (such as rectal bleeding), constipation should be managed with diet whenever possible, as laxatives generally fail to address the problem at its source and may cause worsening of bowel function over time.

Dietary management consists principally of increasing fiber intake, with an emphasis on fruit and vegetable fibers and on maintaining good hydration. Fruits and vegetables provide soluble and insoluble fiber in combination, and their consumption should be encouraged for the prevention and management of constipation. There have been recent reports of the use of kiwi fruits to aid with constipation. Prunes (dried plums) are safer and generally more effective than psyllium in treating constipation (1). Dried fruits are an excellent source of fiber and should be incorporated into the diet in an effort to prevent constipation and on general principles, as they are nutrient dense. Although other dried fruits provide more fiber, prunes also provide phenolphthalein, which is used in commercial laxatives. Therefore, regular consumption of prunes may be particularly helpful. It is important to note that some people can be sensitive to dried fruits, which are associated with increased gas production and bloating. This can be problematic in patients with irritable bowel syndrome (IBS) (discussed later). A diet rich in fruits and vegetables, both fresh and frozen, is also recommended in patients with constipation. Additionally, dietary fiber can be increased using supplements such as psyllium, methylcellulose, and calcium polycarbophil, but response to these supplements is variable and patient dependent. Side effects of gas, bloating, flatulence, and abdominal pain are also very common (3).

Even with adequate fiber intake (30 g/day is recommended), hard stools and constipation are likely if hydration status is poor. Fiber increases stool bulk by absorbing water. A glass of water with every meal (and in between) should be encouraged. Anti et al. (4) reported results of a randomized trial in adults that demonstrated a significant benefit in the treatment of constipation of fiber intake and 1.5 to 2.0 L of fluid/day. Physical activity may stimulate GI peristalsis and contribute to the prevention of constipation. There is little evidence to support the use of probiotics to help improve bowel transit time and reduce symptoms of constipation (5) and constipation-associated IBS (see IBS discussed later); however other supplements and adjunctive therapies, including aloe vera, have been shown to improve constipation.

Diarrhea

Diarrhea generally is due to a specific perturbation of GI homeostasis, often infectious, and treatment should be directed at the underlying cause, as indicated. The World Health Organization defines diarrhea as three or more loose, watery stools per day (6). Dietary considerations should be directed based on evaluation of cause and determination of acute versus chronic diarrhea. Generally, diarrhea for greater than 4 weeks is considered chronic in nature. But there is variability in duration of diarrhea while determining acute versus chronic. For acute diarrhea, the most important dietary recommendation is

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adequate hydration. Maintaining hydration with oral intake of electrolyte-rich fluids is key to preventing hospitalization due to dehydration (7). The BRAT (bread, rice, apple sauce, and toast) diet is also often recommended as these are foods that are easier to digest, are less acidic, and result in fewer bowel movements. The BRAT diet consists of bread, rice, apple sauce, and toast. The addition of the Y (yogurt) recommendation stems from evidence that diarrhea can result from dysbiosis of the gut microbiome (8). Addition of yogurt to the diet during acute episodes of diarrhea can help by introducing both prebiotics found in the nutrient-rich yogurt and probiotics from the live active cultures contained in the yogurt. The yogurt should contain >6 live active cultures without added sugars or artificial sweeteners as these can result in worsening diarrhea. It is important to note that this should not be used as a long-term diet as it could result in nutritional deficiencies if used for an extended time.

Probiotics are recommended in a select group of patients who are taking antibiotics to prevent the occurrence of infectious diarrhea such as *Clostridium difficile* (N12).

Different dietary considerations need to be made for chronic diarrhea. Causes of chronic diarrhea are extensive, and diagnosis may be difficult. Common causes of chronic diarrhea include microscopic colitis, lactose intolerance, pancreatic insufficiency and malabsorption, parasitic infections, celiac disease, and inflammatory bowel disease (IBD). When an extensive workup without a clear culprit for diarrheal symptoms, the low FODMAP diet may be a good initial approach to help patients determine their specific dietary triggers. The theory behind the low-FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) diet is that certain carbohydrates can produce GI symptoms of gas, bloating and abdominal pain, and altered bowel habits because they are poorly absorbed by the GI tract (9). Eliminating these from the diet can improve symptoms and has also been found to be effective in improving diarrhea (10). Examples of high-FODMAP foods include apples, avocados, dried fruit, broccoli, brussels sprouts, garlic, onions, wheat, and artificial sweeteners. It is important that the elimination phase of the diet only be temporary as long-term restriction is associated with nutrient deficiencies. Polyols or sugar alcohols are often used as nonnutritive sweeteners and are well-known causes of diarrhea; however, patients are often not aware of this (10). Avoidance of artificial sweeteners in a patient with chronic diarrhea should be encouraged. The use of food and symptom diaries is also effective in determining specific food triggers that may be unique to each patient.

Irritable Bowel Syndrome

Irritable bowel syndrome (IBS) affects up to 25% of the population and is responsible for up to 50% of referrals to gastroenterologists. The mechanisms of development of symptoms in IBS are not well understood. The syndrome is characterized by crampy, abdominal pain and diarrhea, constipation, or cycles of both. The Rome IV diagnostic criteria define irritable bowel syndrome as recurrent abdominal pain or discomfort at least 1 day/month in the past 3 months, associated with two or more of the following: related to defecation, associated with a change in frequency of stool, and/or associated with the change in form (appearance) of stool (11). The Rome IV criteria also include four subtypes of IBS: IBS with predominant constipation (IBS-C), IBS with predominant diarrhea (IBS-D), IBS with mixed bowel habits (IBS-M), and IBS unclassified (IBS-U)(11). Treatment of IBS is multifactorial as the causes for each patient can vary. Stress and anxiety may be linked with exacerbations (see Chapter 32). First-line treatment of IBS often is dietary management as many patients with IBS report an association of food with their symptoms. The low-FODMAP diet has proven to be an effective treatment for IBS symptoms (12). A study by Zahedi et al. found that a low FODMAP diet significantly improved symptoms of abdominal pain, gas, bloating, and diarrhea compared to dietary recommendations from the British Dietetic Association (11). A systematic review by Rao and colleagues found that both fiber and a low-FODMAP

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diet were beneficial in treating symptoms of chronic constipation and IBS-C (13). Fiber should be increased gradually as side effects of gas and bloating are very common but can be mitigated when titrating the fiber slowly over time (13).

The treatment approach for IBS is best when individualized for each patient as the pathophysiology causing IBS symptoms is complex and still not well understood. Growing research supports that causes are multifactorial. (14). Research suggests that irritable bowel syndrome symptoms may be related to visceral hypersensitivity and alterations in the neuroendocrine system, with similarity to other chronic pain conditions that often occur together, such as fibromyalgia, temporomandibular joint disorder, and chronic regional pain disorder (15). Thus, similar clinical approaches may be relevant to all of these conditions.

Several randomized trials using peppermint oil as treatment for IBS symptoms have been conducted and summarized by meta-analysis (16,17). Peppermint oil can be a safe and effective therapy for patients with IBS; however, it is important to note that side effects include worsening reflux and therefore may not be beneficial for all patients (18). Fecal microflora has been shown to be altered in irritable bowel syndrome, suggesting a potential therapeutic role for probiotics (19), in particular *Bifidobacterium infantis* 35624 and VSL#3 (a high-dose combination of eight different strains of bacteria) (20). There have been newer guidelines, though, which do not routinely support the use of probiotics for treatment of IBS (N12).

Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) is a term for a family of idiopathic chronic disease that includes ulcerative colitis and Crohn's disease. Ulcerative colitis affects the colon, while Crohn's disease can affect the entire digestive system from the mouth to the anus. Pathophysiology of IBD is complex and still not well understood. Genetic and environmental factors are believed to play a role (21). IBD is more common in industrialized than developing nations, and dietary factors are thought to influence the natural history of the disease. A systematic review by Ng et al. found that the incidence of Crohn's disease and ulcerative colitis is stabilizing or decreasing in North America, Europe, and Australia. The prevalence, however, is still high at 0.3%. In newly industrialized countries such as Africa, Asia, and South America, the incidence is increasing (22). Pharmacological therapies are the primary treatment and are very effective in both adult and pediatric patients. Because medications are well studied and well established in treating IBD, not many studies on diet in the adult population are available. Studies on dietary intervention in the pediatric population are more readily available, given the significant long-term side effects of the medications used to treat IBD on children. New studies have determined an association between changes in the microbiome and IBD. The microbiome is affected by dietary changes, and studies involving dietary interventions for the treatment of IBD are becoming more prominent (21).

Both ulcerative colitis and Crohn's disease can lead to malabsorption and malnutrition. In adults, weight loss is common; in children, growth failure may occur. The adequacy of the diet is threatened not only by malabsorption due to mucosal injury or surgery but also by anorexia, diarrhea, increased metabolic demand, and medication effects. Nutritional management principles of the two variants overlap but are in some ways distinct. The evidence for nutritional management of IBD is stronger in pediatric population compared to adults. Overall the nutritional data is stronger for IBD symptom control compared to those on induction and maintenance of remission. Highlights of nutritional management have been summarized (23–25).

Nutritional therapy can be used to influence the course of IBD. Parenteral nutrition and bowel rest are no longer the mainstays of therapy during acute flares, but in some instances may contribute to

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improvement in symptoms while preventing malnutrition. As enteral feeding can often accomplish the same outcome with lower cost and risk, it is preferred unless clearly contraindicated (see Chapter 26). Elemental diets have been shown to induce remission in up to two-thirds of patients, but they are costly and generally unpalatable, especially for the adult population. Meta-analysis indicates that polymeric enteral feeds are as effective as elemental diets at lower cost and with improved palatability (26). However, steroids are more effective at inducing remission than enteral formulae of either variety (27). The nutritional risk index, based on serum albumin and weight loss, can be used to gauge the need for and urgency of nutritional support (28).

Dietary fats and their metabolites are involved in inflammation in the intestine as well as immune responses in IBD. A higher ratio of n-6/n-3 polyunsaturated fatty acids (PUFAs) and diets low in n-3 PUFAs (as well as low in fish, fruit, and dietary fiber) are associated with the risk of IBD (25). Higher amounts of protein and carbohydrate intake were also associated with IBD patients compared to healthy controls in a case-control study (29).

Nutritional deficiencies common in IBD, including both Crohn's and ulcerative colitis, include protein/energy, zinc, magnesium, selenium, iron, vitamin A, vitamin E, vitamin B_6, thiamine, riboflavin, and niacin (30,31). Zinc deficiency impairs wound healing (see Chapter 23), as well as taste sensation, potentially compounding anorexia. The most reliable measure of zinc status is 24-hour urinary zinc excretion. Magnesium deficiency can similarly impair wound healing and is best gauged via 24-hour urine collection. Serum levels of magnesium and zinc may be altered by globulin status and, therefore, are potentially unreliable in states of generalized malnutrition. Selenium deficiency can be assessed by measurement of serum level, erythrocyte level, or erythrocyte glutathione peroxidase. Routine selenium supplementation in IBD may thus be warranted.

Patients treated with corticosteroids for periods longer than 2 months should be supplemented with vitamin D and calcium (25). There is interest in supplementing with glutamine, believed to reduce intestinal damage in IBD patients (25). The related compound n-acetyl glucosamine was shown to provide benefit in 8 of 12 children with treatment-resistant IBD (32).

There is some emerging support for the Specific Carbohydrate Diet (SCD) and the low-FODMAP diet for the treatment of Crohn's disease and ulcerative colitis. The SCD is a diet that focuses on eliminating complex carbohydrates found in grains, starches, and sugars from the diet. The theory behind this elimination diet is that these complex carbohydrates result in inflammation in the mucosa of the small bowel and colon. Emerging studies show promise that the SCD is effective in increasing biodiversity of the microbiome, as well as in reducing inflammatory markers like C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and fecal calprotectin but more research is needed (33). The low FODMAP diet is becoming more widely recommended for IBD patients due to the overlap of IBS symptoms (34). A systematic review and meta-analysis by Halpin and Ford found that the prevalence of IBS symptoms in IBD patients was 39% (35).

Ulcerative Colitis

Two probiotic preparations (*Escherichia coli* Nissle and VSL#3) have been shown to induce remission and support maintenance in patients with ulcerative colitis (20). Because ulcerative colitis involves only the large bowel, it is potentially curable with total colectomy. After colectomy, dietary interventions pertain to the avoidance of dehydration and electrolyte imbalance and the management of an ileostomy (see Ostomies discussed later). A probiotic formula (VSL#3) can prevent pouchitis in post-colectomy patients (20). Other than the dietary interventions indicated with colectomy, to date there is little to suggest that diet influences the course of ulcerative colitis. An RCT found improvement in clinical

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response of patients, given an oral supplement enriched with fish oil, soluble fiber, and antioxidants (36). Dietary consultation is indicated to support efforts to maintain a diet adequate in energy and all essential nutrients.

Crohn's Disease

In general, a balanced diet should be maintained during periods of remission in Crohn's disease. Dietary consultation is indicated to help ensure the adequacy of energy and nutrient intake. Avoidance of excessive fiber is generally indicated to prevent the dilution of nutrient energy and to reduce the risk of obstruction. Restriction of lactose or use of supplemental lactase is often indicated. Restriction of dietary fat intake is useful in the prevention of steatorrhea. Supplementation with n-3 fatty acids may be useful in maintaining remission (37).

Evidence derived from studies subject to methodologic limitations suggests a possible role for corn, wheat, eggs, potatoes, tea, coffee, apples, mushrooms, oats, chocolate, dairy products, and yeast in the induction of flares of Crohn's disease. Evidence is stronger that elemental diets based on oligopeptides or amino acids are of potential benefit. A semi-vegetarian diet was shown to prevent relapse in Crohn's patients in remission (38). A randomized trial in 40 patients with Crohn's disease demonstrated symptomatic improvement and reductions in ESR when selected foods were eliminated based on IgG4 antibody reactivity (39). Another pilot study found changes in stool frequency in patients, given dietary recommendations based on IgG antibody responses (40). There is concern that elimination or restricted diets pose the threat of worsening nutrient deficiencies if they are found to be unpalatable by patients often already experiencing anorexia.

Diverticulosis/Diverticulitis

Diverticulosis is the development of a sac-like protrusion of the colonic wall. Increased prevalence of diverticulosis is associated with the Western lifestyle and diet. Outpouchings most commonly occur in the sigmoid colon but can be found throughout the colon. The prevalence of diverticular disease increases with age, with the incidence among patients over 60 years is 50% (41). Risk factors for diverticular disease and the development of diverticulitis include obesity, low-fiber diet, and physical inactivity. It is hypothesized that long GI transit time and increased pressure play a role in the development of diverticulosis. However, the actual cause of diverticular disease is still not clear (41). Diverticulitis occurs when bacteria are trapped within a diverticulum, leading to infection. Dietary interventions to prevent diverticulosis are aimed at preventing constipation and the attendant elevations of intraluminal pressure (see Constipation, discussed earlier). Historically, low residue diets minimizing food remnants in the intestinal tract (i.e., foods such as nuts, seeds, corn, and popcorn) were recommended to prevent diverticulosis, though no evidence supports this approach and it is no longer recommended (42). The principal strategy is to achieve and maintain a high intake of dietary fiber and water, indicated on general principles of health promotion as well. However, a large cross-sectional study done by Peery et al. found no association between dietary fiber and the development of diverticulosis (43). This data contradicts previous studies on diverticular disease, emphasizing our lack of understanding of the underlying pathophysiology of the disease.

Pediatric Considerations

Infant Colic

The incidence of colic in pediatric patients reported among caregivers is 20% (44). *Colic* refers to

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periods of nearly inconsolable crying in infants between the ages of 2 weeks and 4 months, apparently induced by abdominal distention and pain. Rome IV criteria define infant colic as an infant who is <5 months when symptoms start and stop. Infants present with recurrent and prolonged periods of infant crying, fussing, or irritability reported by caregivers without obvious cause and cannot be prevented or resolved by caregivers. Finally, there is no evidence of infant failure to thrive, fever, or illness (44). The etiology of the condition and its pathophysiology are uncertain. Colic occurs more commonly in bottle-fed than in breastfed infants. Breastfed infants with colic may benefit from modification of maternal diet, with avoidance of bovine milk, peanuts, eggs, seafood, or wheat, or several of these items. Temporary elimination of bovine milk protein from the diet of a colicky infant with appropriate substitution of soy protein is reasonable, although not certain to alleviate the condition. Bovine milk may be reintroduced after resolution of symptoms; it is then generally well tolerated. An RCT demonstrated marked reduction in infants' duration of crying when fed a whey hydrolysate formula compared to conventional formula (45). Probiotics are emerging as a potential treatment for colic (46,47). Treatment of GERD in infants with colic has become more widespread. However, all aforementioned treatments remain controversial because data are very limited, and effectiveness of dietary interventions and treatment of GERD have been found to have little benefit in reducing crying (44).

Functional Constipation in Children

Functional Constipation is defined by Rome IV Criteria as 1 month of at least 2 of the following in infants up to 4 years of age: two or fewer defecations per week, history of excessive stool retention, history of painful or hard bowel movements, history of large-diameter stools, and/or the presence of large fecal mass in rectum. In toilet-trained children, additional criteria may be used: at least 1 episode/week of incontinence after the acquisition of toileting skills, and/or a history of large-diameter stools that may obstruct the toilet (44). Functional constipation in children is likely to be related to dietary fiber intake (48). A case-control study of more than 100 Brazilian children found low intake of fiber, particularly insoluble fiber, to be a risk factor for constipation (48). Similar results were obtained from a larger case-control study in Greece (49). A double-blind cross-over study examining the effects of soluble fiber in constipated children demonstrated more frequent, softer stools (50). Goat milk yogurt, with and without *Bifidobacterium longum* probiotics, demonstrated improvement in stool frequency and abdominal pain in a randomized trial in children with constipation, with greater effects seen in the probiotic-containing yogurt (51). Constipation in infants can be treated with increased juice intake but data is limited on the effectiveness. The effectiveness of fruit juice in treating constipation in infants and children may be related to osmotic diarrhea resulting from carbohydrate malabsorption (52).

Diarrhea in Children

Viral gastroenteritis is among the most common conditions affecting healthy children. The mainstay of management is repletion of lost fluid and electrolytes. Most children do not need intravenous hydration; oral rehydration therapy has been proven just as effective and is the preferred treatment for moderate dehydration (53). Children under 2 years should be given a commercially prepared solution with balanced electrolytes (see Chapter 29). Older children may replenish fluid and electrolyte loss with clear liquids, broth, or commercial drinks. Highly sweetened drinks of any kind may worsen diarrhea and should be avoided.

Gastroenteritis in children may result in a state of temporary lactose intolerance. During and immediately after (up to 1 week) an acute diarrheal illness, milk and milk products should be avoided if there is evidence of lactose intolerance; lactose-free or lactose-reduced products may be substituted. A

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meta-analysis suggests that most children continue to tolerate nonhuman milk during the period of acute diarrheal illness (54).

Breastfed infants should continue to be breastfed, and older children generally should continue to receive their normal diet whenever possible (55). The so-called BRAT diet (bananas, rice, apples, toast) is no longer recommended for children, although these foods may be included as part of a more balanced diet during the illness. The CRAM diet (cereal, rice, applesauce, and milk) is an alternative to the BRAT diet and has a more complete protein and fat profile compared to the BRAT diet. Other foods rich in soluble fiber, such as oatmeal, have a binding effect and can be helpful. Foods high in insoluble fiber, such as wheat bran, should be avoided during the illness. Excessive fruit juice consumption in toddlers can induce an osmotic diarrhea; fruit juice intake is best limited to 4 oz/day until after age 1 (52). It is also recommended that juice consists of 100% fruit juice.

Postsurgical Dietary Interventions

Roux-en-Y Bypass and Gastrectomy

Dietary interventions after surgical gastrectomy are aimed at mitigating the symptoms of dumping syndrome (56). Dumping syndrome, as a result of rapid entry of a nutrient load into the jejunum, is characterized by tachycardia, nausea, and even hypotension. Rapid insulin release can result in hypoglycemia. Dietary interventions include at least six small meals daily with a high protein and fat content, avoiding combining liquids and solids, avoidance of meals with a high content of sugar or processed carbohydrate, use of nutrient-dense foods or supplements to prevent malnutrition due to early satiety, iron supplementation as indicated, and parenteral B_{12} due to loss of intrinsic factor (56). Postgastrectomy patients should be monitored for nutritional deficiencies. If nutritional deficits are noted, prompt repletion of nutrients and an evaluation by a registered dietician are recommended (56).

Short Bowel Syndrome

Short bowel syndrome, in which resection or loss of major lengths of the small bowel for any reason leads to impaired nutrient absorption, is associated with diarrhea, weight loss, and malnutrition. The incidence and prevalence are estimated at 0.3 and 0.5/100,000, respectively, estimated from home parenteral nutrition use (57). Resection of the small bowel impairs absorption of salt, water, various nutrients, and bile salts. Loss of bile salts in stool due to short bowel syndrome is associated with impaired fat absorption. Delivery of salt, water, and bile salts to the large bowel induces an osmotic diarrhea. Malabsorption tends to occur when more than 75% of the total small bowel length is lost; parenteral nutrition support generally is required. With lesser degrees of resection, oral intake can be maintained. Vitamin B_{12} generally needs to be supplemented parenterally, and oral calcium supplementation is indicated.

Short bowel syndrome generally is consequent to severe Crohn’s disease, radiation enteritis, neoplastic disease, infarction, or trauma. The condition occurs in infants due to congenital malformations or necrotizing enterocolitis. When bowel resections occur at specific sites, there is some adaptation over remaining lengths of bowel to develop compensatory absorptive capacity. Nonetheless, some degree of site specificity persists, so that nutrient deficiencies are characteristic to sites of resection.

The colon principally reabsorbs water and electrolytes. The duodenum absorbs iron, folate, and calcium preferentially. Water-soluble vitamins, proteins, electrolytes, and minerals (particularly trace elements) are well absorbed in the jejunum and ileum. Glucose uptake is coupled to active sodium absorption in the jejunum. Reduced secretion of cholecystokinin-pancreozymin after jejunal resection is

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associated with cholestasis and cholelithiasis, whereas loss of various hormones from the jejunum can lead to gastric hypersecretion as a result of unregulated release of gastrin. The distal ileum absorbs fat-soluble vitamins and vitamin B_{12}. Loss of the ileum results in bile salt malabsorption, bile acid delivery to the colon, and diarrhea accompanied by loss of fat-soluble nutrients. Loss of the ileocecal valve can allow colonic bacteria to migrate into the small bowel, a phenomenon called small intestinal bacterial overgrowth (SIBO).

Bacterial metabolism in the small bowel can generate nonmetabolizable D-lactic acid, resulting in acidosis. The condition may manifest with slurred speech and ataxia, mimicking intoxication with ethanol. Treatment of acidosis may require supplemental base, such as bicarbonate or citrate, and reduced carbohydrate to limit the generation of acid. Bile salt malabsorption results in binding of calcium to fatty acids in the gut, which in turn leads to absorption of free oxalate, normally bound by calcium. Oxalate excretion in urine can lead to formation of oxalate stones. Reduction of dietary oxalate may be indicated when significant portions of the ileum are missing. Also of use in preventing formation of renal oxalate stones is the binding of bile salts with cholestyramine, increased calcium intake, increased fluid intake, and alkalinization of urine with citrate to prevent crystallization.

Villous height and crypt depth both increase in response to small bowel resections, facilitating nutritional support with enteral preparations. Adaptation apparently can be expected to continue as long as 2 years after surgery. Enteral feeding stimulates continued adaptation, whereas exclusive parenteral nutrition induces atrophy. Immediately after small bowel resection, total parenteral nutrition is required; careful monitoring of electrolytes is necessary during this period. Enteral feeding should be initiated as soon as feasible (see Chapter 26). Pharmacotherapy likely will be needed to slow motility and reduce gastric acid secretion and more recently has been shown to increase villous architecture to improve vitamin and nutrient absorption. Cholestyramine may help control diarrhea induced by malabsorption of bile acids. A period of overlapping enteral and parenteral nutrition is commonly indicated.

Energy requirements are increased by malabsorption, and in short bowel syndrome it may be twice normal. Supplements of folate, iron, and fat-soluble vitamins generally are indicated; B_{12} injection is indicated after loss of the terminal ileum. Preliminary evidence and data from animal studies suggest that glutamine and pectin may stimulate enhanced intestinal adaptation.

Specific nutritional strategies may be tailored to the site and extent of small bowel resection. When only the jejunum has been resected, a near-normal diet can be maintained. When less than 100 cm of ileum is resected, cholestyramine and parenteral B_{12} are generally indicated. When more than 100 cm of ileum is resected, parenteral B_{12} is required, cholestyramine is not indicated (due to depletion of bile salts), and fat restriction is necessary to limit steatorrhea. Massive bowel resection (less than 60 cm of intact small bowel) requires home parenteral nutrition, although even in this group, gut adaptation may permit restoration of at least partial enteral nutrition in time. Nutritional management of the short bowel syndrome has been reviewed (58–60).

Studies of enteral solutions in malabsorption and the short bowel syndrome have largely failed to demonstrate the superiority of hydrolyzed protein or free amino acids, apparently because of the absorptive capacity of the intestine even when impaired. The higher costs of solutions containing free amino acids or peptides suggest that they be used only when absorption is severely impaired and other solutions are not tolerated.

Ostomies

An ostomy is a surgical anastomosis between a segment of the GI tract and the skin. Ileostomies are

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associated with the passage of rather liquid stool, raising the risk of dehydration and electrolyte imbalance. Patients should be advised to remain well hydrated at all times and to keep handy oral rehydration formula. Diarrhea may be associated with consumption of raw fruit and vegetables, beer, and spicy foods. These reactions are somewhat idiosyncratic, and diet should be adjusted individually, as indicated. Fiber intake should be moderate, as very high fiber intake may lead to stomal blockage.

Colostomies are associated with a risk of constipation, and thus good hydration is important in conjunction with adequate fiber consumption. Flatus may be a problem and is associated particularly with onions, leeks, and garlic, cruciferous vegetables, beans, resistant starches, cucumbers, and yeast. Again, dietary adjustment should be guided by general principles but individualized.

General recommendations in stomal management include chewing food well and maintaining good hydration status at all times. Stomal blockage is associated with very fibrous vegetables such as celery and asparagus, citrus fruits, nuts, cabbage, and the skins of apples, tomatoes, and potatoes. Individual, empiric dietary adjustments are indicated rather than blanket dietary exclusions. Foods particularly associated with stool odor include fish, eggs, cabbage, onion, garlic, and leeks. Stool odor may be reduced in some individuals by consumption of parsley or yogurt. Diarrhea may be induced by raw fruit, highly fibrous vegetables, and beer.

Intestinal Barrier Function, Permeability, and “Leaky Gut Syndrome”

The GI tract houses $1 \times 10^{13–14}$ resident bacteria (“the microbiome”) that modulates the normal function and development of the GI tract. The intestinal epithelial barrier is responsible for the equilibrium between tolerance and immunity to non-self antigens. Emerging translational research is determining the roles of the microbiome (and other antigens present in the GI tract) in autoimmune diseases, especially in the context of compromised intestinal permeability (61). This concept, colloquially referred to as “leaky gut syndrome,” attributes the development of a variety of chronic conditions to the displacement of antigens into the body’s bloodstream and the subsequent immunologic activation (62–70).

A common therapeutic approach follows, that is, to “treat the gut” by restoring compromised intestinal permeability through oral administration of nutrients and probiotics. A number of health claims exist purporting to treat intestinal hyperpermeability with various nutrients and natural products, including L-glutamine, n-acetyl glucosamine, digestive enzymes, and probiotics. The strongest evidence exists for glutamine supplementation, with mixed results with various probiotic formulations. It should be noted that the pathophysiology behind “leaky gut” is not entirely understood, though it is suspected to be a contributor to some of the disease processes discussed earlier, including celiac disease, Crohn’s disease, and IBS; thus, none of these supplements are routinely recommended.

Small Intestinal Bacterial Overgrowth

SIBO is defined as the presence of excessive numbers of bacteria in the small intestine (that may otherwise normally reside in the colon), which may lead to such symptoms as abdominal pain, bloating, gas, distension, flatulence, and diarrhea (or less commonly constipation) (N13). Severe SIBO may lead to nutritional deficiencies in fat-soluble vitamins, iron, vitamin B_{12}, and hypoproteinemia. Folate levels are frequently elevated in SIBO. There are multiple mechanisms by which SIBO might develop, including concurrently with other disease processes such as IBS and IBD, systemic sclerosis, motility disorders of the gut, and in many postsurgical states. The presence of SIBO as a pervasive diagnosis, even among those who might consider themselves otherwise healthy, highlights the importance of the balance of the gut microbiome. For this reason, the recommended diagnostic testing is hydrogen breath testing; the premise

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of this test is that human cells are incapable of producing hydrogen and methane gas; thus, if these gases are detected in breath samples, it signifies the presence of fermentation of carbohydrates by microbes in the gut (N13). The next rational presumption then, in patients with SIBO, is that the microbiome, especially within the small bowel must be altered. Often this is achieved by prescribing a short course of antibiotics targeted at the most frequent hydrogen and methane-producing microbes. However, dietary changes, including the low FODMAP diet to avoid the ingestion of highly fermentable carbohydrates, may be indicated. It may seem counterintuitive to add probiotics to an environment that is already colonized by a number of bacteria, but a meta-analysis recently found that probiotics appeared to reduce hydrogen breath production with an odds ratio (OR) or 1.61 (CI = 1.19–2.17), though it should be noted that the included studies were small and of poor quality (N14). Finally, it is worth noting that fecal microbiota transplantation (FMT) may be an option for patients with an altered gut microbiome, but there is no sufficient data to support its routine use at this time. In patients with presumed SIBO or IBS-D who do not respond to usual pharmacologic treatments of dietary interventions aimed at addressing the gut microbiome, the diagnosis of sucrase-isomaltase deficiency (SID) should be entertained. This is a rare enzyme deficiency of the brush border in the small intestine, which is diagnosed by upper endoscopy with small bowel biopsies or via breath testing. Children are more commonly affected than adults. In one study, SID was found in 35% of patients with presumed IBS-D or IBS-M (N15). The treatment modality for SID is akin to that of lactase deficiency, avoidance of sucrose-containing foods or use of sacrosidase (Sucraid) enzyme replacement.

NUTRIENTS, NUTRICEUTICALS, AND FUNCTIONAL FOODS

Prebiotics and Probiotics

There is rapidly proliferating evidence that manipulation of the intestinal microflora can influence health and alter outcomes of clinical importance (70–72). Probiotics refer generically to commensal organisms (live bacteria) associated with putative health benefits (73). Among the most commonly used species of probiotics are *Lactobacillus*, *Bifidobacterium, and Saccharomyces* fungi. The intestines are predominantly populated by *Bacteroides*, *Porphyromonas*, *Bifidobacterium*, *Lactobacillus*, and *Clostridium* species (74). *Prebiotics* refer to food high in nondigestible dietary fiber that promotes the growth of beneficial gut bacteria. Probiotics are extensively marketed outside of the United States, especially Japan. Fructo-oligosaccharides are found naturally in onions, garlic, asparagus, and artichokes.

Both *Lactobacillus acidophilus* and *Bifidobacterium bifidum* colonize the intestinal tract after birth; *L. acidophilus* is introduced from foods, whereas *B. bifidum* is introduced through breastfeeding. The concentration of *Lactobacilli* in the GI tract can be increased by ingestion of fermented dairy products, such as yogurt, or certain nondigestible substances, such as oligofructose or other short-chain polysaccharides (75). *Bifidobacteria* growth can be stimulated by introduction of fructo-oligosaccharides, which are components of prebiotics. Many probiotic strains have been studied in rigorous clinical trials to assess effects on alimentary tract health.

Probiotic supplementation has been advocated after, or during, use of broad-spectrum antibiotics for reconstitution of flora (76,77) (N12).

There is promising data regarding clinical benefits of probiotics in IBD. There is some evidence that VSL#3 could be used to treat pouchitis as well as prevent remission, though there is not enough evidence to currently recommend as monotherapy to induce remission (20).

In the past, *Lactobacilli* in foods and commercial supplements were generally categorized as GRAS

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("generally recognized as safe") by the Food and Drug Administration (FDA) (78,79), though recent considerations may result in probiotics being categorized as biologic products, with more rigorous safety requirements (80). The incorporation of nutrients such as oligosaccharides in the diet may alter more sustainably intestinal flora than the ingestion of probiotic organisms per se; such substances have been characterized as prebiotics, as noted (81–83). As with all supplements, quality control varies by manufacturer; the website www.consumerlab.com is a very useful resource for assessment and verification of product quality.

Probiotic supplements, in particular, have demonstrated poor quality control with some over-the-counter products even containing pathogenic bacteria (84). Thus, products made consistent with FDA Current Good Manufacturing Practices (cGMPs) are recommended (85). The website www.consumerlab.com also provides data about over-the-counter natural products regarding purity and constancy. A number of specialty laboratories offer assays of intestinal microbiota, often with concurrent therapeutic recommendations. Though the potential benefits of this type of testing are rational and reasonable, to date, none of the commercial tests have been independently studied for validity and clinical utility.

Other Natural Products

A variety of herbal (plant-based) remedies, digestive enzymes, and other natural products are widely used in GI conditions. Safety and evidence levels vary based on the intervention and condition. A detailed discussion of these products is beyond the scope of this chapter. High-quality information on natural products can be found Natural Medicines Database (https://naturalmedicines.therapeuticresearch.com/) website.

CLINICAL HIGHLIGHTS

That impaired GI function would adversely affect nutritional status and that nutrition would influence GI function and health are rather self-evident. Thus, nutritional management and dietary patterns are of considerable importance in GI disorders. The details of management vary with the specific effort to prevent or ameliorate a particular disorder. In general, when seeking guidance on use of dietary modifications for prevention of or treatment for GI disorders, it is imperative to seek the recommendations of a gastroenterologist and consider referral to an allied health professional with training and suitable experience in nutrition and GI disorders. Meal planning and the application of specialized diets are cumbersome and are safest and most effective when guided by an expert.

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Chapter 19

Diet, Dyspepsia, and Peptic Ulcer Disease

Amanda Velazquez

INTRODUCTION

Dyspepsia, gastroesophageal reflux disease (GERD), peptic ulcer disease (PUD), and other pathologies of the upper gastrointestinal (GI) tract are very common. Dyspepsia is a symptom rather than a diagnosis, defined by the Rome IV Criteria as any upper GI tract-related symptom outside of heartburn and regurgitation. Patients presenting with dyspepsia may undergo an investigation with an upper endoscopy where pathological findings, such as PUD, could be encountered. If found, PUD would serve as the organic cause for dyspepsia. For those without a detectable cause, functional dyspepsia can be returned as the diagnosis. First-line treatments for these upper GI conditions include acid-suppressing medications, such as proton-pump inhibitors, as well as lifestyle modifications. For more severe refractory diseases, surgical interventions are available (1).

It seems intuitive that that diet should play a role in the course of symptoms related to irritation of the upper GI tract. Adjustments in diet, including restrictions of spicy food, acidic food (e.g., citrus, tomatoes), alcohol, and caffeine, are common practices, by both clinicians and patients, in efforts to control symptoms of dyspepsia, GERD, and PUD. Lifestyle interventions include weight loss, smoking cessation, avoiding alcohol, and even elevating the head while sleeping (2). Evidence in support of these intuitive practices is slowly increasing, especially with a growing interest in dietary remedies as an alternative to medical management (3).

OVERVIEW

There is widespread belief that diet influences the development of upper GI tract pathology. Some foods and/or food groups are triggers of dyspepsia symptoms, while others are thought to serve as protection.

The most current systematic review in 2016, by Ness-Jensen, N et al. (2), substantiates associations between GERD and dietary and lifestyle interventions. This systematic review included meta-analyses, randomized clinical trials (RCTs), and prospective observational studies from PubMed (from 1946), Excerpta Medica dataBASE (EMBASE) (from 1980), and the Cochrane Library (no start date) through October 2014. Evidence was graded based on the American Heart Association's guidelines. Several small sample size RCTs demonstrated improvement in GERD through weight loss for individuals with obesity, smoking cessation for those who used tobacco products, increased dietary fiber intake, head of bed elevation, and avoidance of meals 2–3 hours prior to bedtime (2).

In 2019, Yuan et al. published a national multicenter survey study evaluating lifestyle factor effects on GERD for 1,518 participants in China. A univariate analysis determined 21 factors associated with GERD ($p < 0.05$), including but not limited to Body Mass Index (BMI) in the overweight or obese range, smoking, consuming alcohol, eating fast, eating beyond fullness, lying down shortly after eating, eating hot foods, and showing preference for spicy and high-fat foods. Logistic multivariate regression analysis found risk factors for GERD [with odds ratios (ORs)] to include high BMI (1.805), smoking (1.521),

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eating quickly (4.058), eating beyond fullness (2.849), lying down soon after eating (1.544), eating very hot foods (1.811), and wearing girdles or corsets (2.187). Notably, this study also found that lifestyle interventions in combination with medication improved outcomes over medication alone ($z = –8.578$, $p < 0.001$). Overall, this study illustrated the complexity of GERD being multifactorial in origin, while also reinforcing numerous dietary and lifestyle factors supported by the literature. More data are needed to fully understand the role and impact of eating pace, quantity of food eaten, and temperature of food on the development of dyspepsia and GERD (4).

While evidence is mounting to support the aforementioned specific dietary and lifestyle interventions for dyspepsia, GERD, and PUD, data about other dietary and nutrient interventions (described later) have otherwise been fairly heterogeneous.

Simple Carbohydrates

In general, simple carbohydrates, such as low-fiber monosaccharides and starches, have been found to increase GERD symptoms. Several studies have investigated the relationship between carbohydrate consumption and GERD; however, most of these studies have been small in size (5). A 2018 study that monitored 130 participants with GERD asked to follow a low-glycemic diet for 2 weeks. The results demonstrated statistically significant improvements in GERD symptoms. However, the resulting weight loss for patients attributed to a change in diet could have confounded the findings (5). Further studies are needed.

Fiber

In the late 1990s, results from the prospective Health Professionals Follow-up Study, based on observations of more than 47,000 male health professionals in the United States, found dietary fiber reduces the risk of duodenal ulcer (DU)—perhaps by half—comparing the highest to the lowest quintile of intake. The protective effect of soluble fiber appeared particularly strong (relative risk [RR] 0.4 for the highest quintile) (6).

More recently, in 2017, Kim, J et al. found high-fiber diets were inversely related to the prevalence of PUD in women, and the results were significant. Data were collected from a nationally representative sample of South Korean population using the Korea National Health and Nutrition Examination Survey (KNHANES I), a prospective cross-sectional survey issued by the Korea Center for Disease Control and Prevention (KCDC) in 1998, to assess health and nutrition. This included over 39,000 participants, ages ranging 30–70, who were diagnosed by a physician with PUD (defined in the study as gastritis, gastric ulcer, or DU) (7).

The literature also suggests that GERD may improve with high-fiber intake, and several small, prospective trials have already demonstrated the inverse relationship of fiber intake with heartburn symptoms (8). Also, Nissan et al. performed a large, case-control study in 2004, where 3,153 participants reporting severe reflux symptoms in the last 12 months served as cases, while 40,210 people without GERD symptoms were the controls. Interestingly, those who predominantly ate bread with at least 7% dry weight of dietary fiber had about half the risk of GERD symptoms compared with those who ate mainly low fiber (about 1–2%) white bread (Odds Ratio [OR] 0.5; 95% Confidence Interval [CI] 0.4 to 0.7) (9).

Recently, a randomized, parallel, double-blind study in Spain evaluated 50 patients who met Rome IV criteria for functional dyspepsia as well as constipation that was suspected to impair evacuation through dyssynergic defecation. The study compared improving dyssynergic defecation through biofeedback combined with daily exercise instructions versus fiber supplementation. Findings from this study found that fiber supplementation did not reduce dyspepsia symptoms. However, the results of this study are

limited to a specific subgroup of individuals (10).

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Protein

There is very little literature evaluating the relationship of dietary protein with dyspepsia, GERD, or PUD. The 2005 El-Serag et al. cross-sectional study investigating the impact of dietary macronutrients and micronutrients on GERD symptoms is the most noteworthy evidence to date. This was a comparative study of individuals with frequent GERD symptoms (n = 103) versus those with rare or no GERD symptoms (n = 268). Also, a subgroup analysis was performed for those who underwent a previous endoscopy with findings of erosive esophagitis (n = 40) compared to those without (n = 124). Participants completed 100-item, Block's food frequency questionnaires estimating average portions and frequency of foods consumed over the last year. No significant differences in protein intake were found between those with and without GERD symptoms when controlling for covariables. However, individuals with a history of erosive esophagitis had significantly higher daily intake of fat and protein compared to their counterparts (p <0.05) (11).

Fats

High-fat foods, especially fried foods, are routinely associated as a potential trigger for dyspepsia; however, the literature is varying to support this. It is hypothesized that fat is more challenging to digest, which causes decreased gastric motility. To digest fats, the body initiates increased production of enzymes and hormones to break down the food, creating bile salts that can irritate the esophagus and cholecystokinin (CCK) to reduce the lower esophageal sphincter (12). El-Serag et al. found that patients with GERD symptoms and erosive esophagitis were more likely to ingest a diet high in fat, especially saturated fat. Notably, these associations were only statistically significant in overweight individuals (11). A very small population-of-15 study found fat potentiating GERD symptoms, but body mass index and calorie density may have confounded these findings (8).

Dairy

The role dairy plays in dyspepsia, GERD, and PUD is not fully understood due to limited data in the area. The few studies assessing dairy foods date back to a 1998 large, cross-sectional population study of 1,135 subjects, which found that higher intake of fermented milk products (e.g., yogurt, cheese) seemed to confer reduced risk of peptic ulcer, whereas consumption of unfermented milk was associated with increased risk. This effect may be attributed to the antimicrobial properties of fermented dairy products; *Lactobacillus* and casein inhibit the replication of *Helicobacter pylori* (13).

The most rigorous study to date, a 2018 prospective, randomized, double-blind, placebo-controlled, parallel-group study, assessed the beneficial effects of *Bifidobacterium bifidum* YIT10347 in fermented milk in healthy Japanese adults with functional dyspepsia who experienced temporary gastric symptoms. Participants consumed 100 mL of milk fermented with *Bifidobacterium bifidum* YIT10347 every day for 4 weeks, while the control group consumed 100 mL of placebo-fermented milk during this period. Based on survey responses, there was no significant difference in reflux-syndrome scores or acid-related dyspepsia score but significant changes between the two groups in greater relief rate of postprandial discomfort epigastric pain score. The study appears to have been unbiased and robust, but of note, this study was funded by Yakult Honsha Co. Ltd (14).

To summarize, current systematic reviews and meta-analysis have found that majority of studies point to positive outcomes of pre- and probiotics on dyspepsia and GERD (15,16).

Specific Diets

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Dietary patterns rich in fruits and vegetables has been shown to reduce the GERD symptoms (17). As an example, the Mediterranean Diet, which is rich in fruits and vegetables, as well as whole grains, legumes, fish, and unsaturated fats, has proved efficacious in some studies, seemingly comparable to, but not more effective than, medication suppressive therapy (8). Considering the Mediterranean diet has additional established benefits aside from possibly improving GERD, it is important to consider this when choosing a patient-centered management plan.

Carbonated Beverages

Although carbonated beverages have anecdotally been suggested to worsen GERD, a 2010 systematic review found there to be no apparent evidence of such (18). Nonetheless, clinical discretion should be used as carbonated beverages are commonly sugar-sweetened beverages, which can promote weight gain, in turn contributing to upper GI symptoms.

Weight Loss

Obesity is an established risk factor for GERD, with a pathogenesis that higher body weight equals increased abdominal pressure, causing a disturbance to the gastroesophageal junction (19). Females with a normal baseline BMI who gained weight equal to 3.5 or more BMI point were at greater risk for reflux symptoms compared to their counterparts with no weight change (OR 2.80; 95% CI, 1.63–4.82) (20). A handful of randomized, controlled trials has demonstrated that losing weight led to reduced GERD symptoms (2). More specifically, a large 2013 prospective cohort study suggested a dose-response relationship between BMI and the severity and frequency of GERD symptoms. Compared to men who achieved 5–10% total body weight loss in this study, women only experienced improvement in their symptoms once they achieved 10% or greater in body reduction (21). As a result, weight loss is recommended to improve GERD for individuals with excess body weight.

Alcohol

Opinions are mixed regarding the role of alcohol in GERD symptoms, according to a 2018 systematic review assessing diet's role in functional dyspepsia (12). For example, as mentioned earlier, the findings from the Nissan et al. 2004 large case-control study demonstrated fiber as protective against GERD but found no relationship with alcohol. Additionally, the study performed by Yuan et al. in 2019 looked at 21 variables of diet and their impact on GERD, and they found alcohol consumption significantly related to increased GERD symptoms (4). In reviewing the observational studies data collectively, a 2019 meta-analysis concluded that a potential association did exist between alcohol and GERD, but no correlation was determined in reviewed case-control studies. More specifically, in consumption frequency sub-analysis, subjects who frequently consumed alcohol at least three to five times per week had a strong association with GERD (22). Finally, with regards to PUD, prior studies have found increased odds of ulceration associated with alcohol use (23,24). For those with active ulcers, heavy alcohol consumption (≥ 15 drinks/week in men and ≥ 8 drinks/week in women) was a strong risk factor for PUD symptoms (24).

Food Allergies

Eosinophilic esophagitis (EoE), although rare, is in the differential diagnoses when evaluating the cause of dyspepsia in a patient. EoE is a T-helper 2-type (Th2) inflammatory disease considered to be a form of

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food allergy. The pathogenesis is multifactorial, including genetic predisposition, microbes, antibiotic exposure, and food allergens. The symptoms of EoE can vary, depending on the age of presentation. In adults, the primary symptoms are refractory heartburn and dysphagia. The diagnosis is confirmed on histological endoscopic findings of >15 eosinophils per high power field. Treatment modalities include proton-pump inhibitors, corticosteroids, immune-suppressing therapies, dietary management, and for those with esophageal strictures, esophageal dilation (25). A trial of dietary therapy is recommended for all children and motivated adults with a diagnosis of EoE (26). The most common diet approach for EoE is the six-food elimination diet (SFED), which removes the most common foods to invoke an immune response in EoE. These include milk, wheat, soy, eggs, peanuts/nuts, fish, and shellfish (27).

The evidence of association between diet and gastric carcinoma is addressed in Chapter 12.

NUTRIENTS, NUTRACEUTICALS, AND FUNCTIONAL FOODS

Capsaicin

Capsaicin, which mediates burning and pain through the gut transient-receptor potential villanoid-1 (TRPV1), is responsible for evoking the sensation of heat associated with spicy food (28). The belief that capsaicin contributes to dyspepsia or symptoms of heartburn associated with GERD is widespread, with the mechanism thought to be direct esophageal mucosal irritation (8). Evidence in the medical literature for an effect of capsaicin-containing foods, however, is limited. Individuals with a reported preference for spicy food have been found to be at a great risk for GERD symptoms (4). Recently, researchers have experimented with the use of capsaicin pills on subjects, finding that they can trigger dyspepsia; hence, it could potentially serve as a form of diagnostic testing for dyspepsia (29).

Coffee

The exact mechanism of how coffee could potentiate dyspepsia symptoms is not fully understood. It is speculated that coffee may operate directly on the esophagus, decreasing Lower esophageal sphincter (LES) tone, and/or because of its caffeine component that it triggers gastric acid production. There is some data that support such (9,30). However, a 2013 cross-sectional study of 8,013 healthy subjects in Japan performed a multivariate analysis of coffee consumption where no correlation was found with GERD and PUD. A meta-analysis was also performed and did not find any significant association (31). Additionally, a 2014 meta-analysis showed no correlation between coffee intake and GERD symptoms, even after a sub-analysis looking at high intake users (>5 cups/day) versus low intake users (<4 cups/day) (32).

Tea Polyphenols

Data are limited; however, two studies found tea consumptions to be reported by participants as triggers for functional dyspepsia (12). Meanwhile, a 2018 meta-analysis of the effect of tea consumption on GERD found no significant relationship (33).

Plants, Herbs, and Spices

There is very scant data in this area, but complementary alternative medicine (CAM) is becoming popularized in the Western world. Curcumin, the active ingredient of the turmeric rhizome, often found as a ground spice in local grocery stores, may improve dyspepsia and gastric inflammation (34). Ginger has anti-inflammatory and analgesic properties and has therefore been used in complementary and alternative

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medicine roles for treating a variety of GI ailments (35). However, no human studies have investigated the efficacy of ginger for ameliorating PUD (36). Chili peppers are a frequently used ingredient in cooking, anecdotally reported to cause dyspepsia; however, there is scant number of clinical studies evaluating this (34). Even a commonly used ingredient such as table salt has been associated with GERD symptoms (9), although another study found higher sodium consumption was associated with reduced prevalence of PUD in Korean women (7). The active components of peppermint oil (l-menthol) and caraway oil (carvone and limonene) alone or in combination have shown beneficial in relieving functional dyspepsia symptoms. Most recently, a 2019 RCT of 95 participants with functional dyspepsia received a novel formulation of L-menthol and caraway oil. The result was rapid relief of their symptoms within 24 hours (37). There may be promise in the originally developed German compound, STW 5, made up of nine herbal extracts, including milk thistle fruit, caraway fruit, peppermint leaf, greater celandine, garden angelica root, bitter candytuft, licorice root, German chamomile flowers, and lemon balm leaf. The suspected mechanism of action of STW 5 to ease dyspepsia is acting as an anti-inflammatory, improving GI motility, and decreasing gastric acid secretion (36). Finally, apple cider vinegar has been a trendy diet approach to improve numerous medical conditions, from improving glucose levels to preventing overgrowth of gut bacteria. Nonetheless, apple cider vinegar's ability to prevent GERD is severely lacking (36).

Although mentioned as common triggers anecdotally, there are no trials to date assessing improvement in dyspepsia with elimination of citrus foods, tomato products, and chocolate (37). Chocolate, derived from the cocoa bean, contains caffeine and is suspected to cause relaxation of the LES, leading to GERD symptoms. However, one study showed eating large amounts of chocolate per day among 500 Italian adults did not result in increased symptomology (8).

In summary, evidence is limited, and recommendations should be individualized.

CLINICAL HIGHLIGHTS

There is a growing body of evidence demonstrating that diet, nutrients, and functional foods may play a role in dyspepsia, GERD, and PUD. Dietary and lifestyle changes are part of first-line treatment for these upper GI conditions, although the degree of evidence for some practices versus others may vary. A trial of dietary therapy is recommended for individuals with a diagnosis of EoE.

Dietary and lifestyle practices consistent with health promotion (see Chapter 45) and appropriate for purposes of preventing or managing dyspepsia should be recommended. For example, a diet high in fiber is likely to be of benefit, as is a diet high in fruits and vegetables. For individuals who smoke, smoking cessation should be highly recommended (B, E). Because weight loss has been prospectively associated with a dose-dependent reduction in GERD symptoms (20), weight management assistance is recommended for individuals with excess body weight.

At this time, only a small number of interventional studies have been performed that demonstrate improvement in dyspepsia through the avoidance of trigger foods (2,4). Nonetheless, interventions supported by clinical judgment, such as restriction in alcohol, dietary fat, spice foods, tomato products, citrus products, chocolate, and/or caffeine intake, are reasonable to consider on a trial basis for individual patients. Avoidance of eating in close proximity to bedtime is also a standard and sensible practice in the management of GERD, as are positional adjustments that may diminish reflux (36). Advances in the pharmacotherapy of dyspeptic syndromes, including treatment of *H. pylori* and the use of proton-pump inhibitors, are such that most patients need not impose dietary restrictions. However, in the setting of emerging evidence from observational studies for increased risks of bone fractures, B_{12} and magnesium deficiencies, and *Clostridium difficile* infection in older and hospitalized patients with long-

term proton-pump inhibitor use (19), a trial of dietary and lifestyle management is warranted in an effort to minimize reliance on pharmacotherapy.

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Chapter 20

Diet, Dyspepsia, and Peptic Ulcer Disease

John Nowicki

INTRODUCTION

Interest among patients in dietary management of various inflammatory diseases of soft tissue and joints generally exceeds the availability of rigorously obtained scientific evidence. Much of the evidence in support of nutritional therapies for rheumatologic conditions is preliminary or anecdotal. There are, however, clear links between diet and the natural history of certain arthritides. Further, there is a biologically plausible link between dietary patterns and general inflammatory activity.

Preliminary evidence of the beneficial effects of *n*-3 fatty acids in rheumatoid arthritis (RA) is fortified by the clearly established role of polyunsaturated fats in the manufacture of inflammatory and anti-inflammatory cytokines. The impact of diet on weight may indirectly have important effects on the degree to which arthritis of any etiology translates into functional limitations and on its rate of progression. Rheumatologic diseases arising from errors in intermediate metabolism, such as gout, are decisively influenced by diet. There is sufficient evidence of possible benefit and limited evidence of likely toxicity to support consideration of nutritional interventions for osteoarthritis (OA), RA, and gout.

Nutritional and pharmacologic interventions should be considered potentially complementary. Several drugs commonly used to treat rheumatologic diseases may put patients at risk of certain nutritional deficiencies; supplementation may therefore be warranted. The dissemination of unsubstantiated claims for nutrients with healing properties in diverse rheumatologic conditions does a disservice to patients by cultivating misapprehensions and perhaps even more so to physicians, among whom this trend may cultivate inattention to the actual potential benefits of nutritional therapies. However, in situations in which conventional treatments are undesirable, ineffective, or inadequately effective, dietary therapy may be appropriate.

OVERVIEW

Diet

Overall dietary pattern may influence the risk of rheumatologic disease as well as the risk of functional limitations in the advent of such disease. Mechanisms for these associations are both direct and indirect. Directly, there is a link between dietary pattern and immune function, mediated by a variety of micronutrients, including antioxidant substances and zinc (Chapter 4), as well as the pattern of fatty acid intake (1). Indirectly, diet influences the impact of arthritic conditions on function by contributing to overall health status and the extent of comorbidities, including vascular disease.

Most of the claims for an effect of general dietary pattern on the development and progression of rheumatologic conditions are consistent with dietary recommendations for general health maintenance. Excess body weight secondary to caloric excess increases joint stress and particularly may exacerbate and accelerate OA. In other forms of arthritis, the spondyloarthropathies, and related conditions, obesity

may contribute to functional limitations.

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General recommendations for abundant fruit and vegetable intake are mostly consistent with the literature on diet and rheumatologic conditions, with some exceptions. Although there is little solid evidence to support the hypothesis, lay literature consistently raises concerns about a link between the nightshade vegetables and “arthritis” in general based on the contention that solanum alkaloids may have proinflammatory effects in some individuals.

One of the limitations of the abundant, unreviewed literature on nutrition and arthritis is the tendency to refer to arthritis as a collective entity and a failure to distinguish among the many types, etiologies, and pathophysiologies the category includes. Claims for the effects of a particular nutrient or class of nutrients on the whole spectrum of arthritic diseases seem inherently implausible, although some argument may be made for the generalized anti-inflammatory properties of certain aspects of diet. In particular, the anti-inflammatory properties of *n*-3 fatty acids may confer benefit in a variety of inflammatory conditions, although the effect on RA is most studied (2,3).

Diet and Specific Rheumatologic Disorders

Osteoarthritis

Degenerative arthritis of the weight-bearing joints is convincingly accelerated by obesity; therefore, weight management is an important element in both the prevention and management of OA of the knees and hips (4–7). Rapid, substantial weight loss through dietary restriction may have significant benefits on symptoms and functionality in overweight patients (6,8). A systematic review of the scientific literature indicated the Mediterranean diet (MD) was associated with a lower prevalence of OA (9). Physical activity is beneficial in OA directly by maintaining mobility and indirectly by contributing to weight maintenance (10,11). Weight loss and exercise have been used independently to decrease the causative effects and confer clinical improvement in OA, but a comprehensive diet and lifestyle approach is likely the most effective. Messier et al. (12) demonstrated in a large randomized trial that the combination of dietary weight loss plus exercise (compared to either alone, or a control group receiving educational materials) resulted in significant long-term symptomatic improvement in obese sedentary people with OA. If OA is advanced, exercise may need to be selected to minimize stress to joints; swimming is often appropriate.

The relationship between obesity and OA in non–weight-bearing joints such as the hands is poorly understood (13,14), though adipokines (15) may play a role, and systemic inflammation (16) may affect muscle strength.

Observational data suggested an association between low vitamin K levels and increased OA of the hand and knee (17), though clinical trial data suggest no relationship (18). A limited number of cohort and randomized trials suggest that antioxidant supplements may confer some benefit in OA, though evidence from clinical trials has been conflicting (19). In particular, benefit has been seen in observational studies with high dietary intake or supplementation of vitamin E, carotenoids, and vitamin C (13), as well as in clinical trials of various antioxidant supplements of botanical origin (20,21). Vitamin D has a range of effects on cell types involved in OA-affected joints, acting through the vitamin D receptor and thus altering gene expression. Data from the Framingham OA Cohort Study suggest that low dietary intake and low serum levels of vitamin D may contribute to the progression of OA; high intake may offer some protection (13,22), although this remains uncertain (23) and under active investigation (24). In a meta-analysis, results indicated that vitamin D supplementation had a statistically significant but small-to-moderate effect on pain control in patients with knee OA. However, no effects were observed for the

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change in tibial cartilage volume or joint space width (25). Methylsulfonylmethane (MSM), an organosulfur compound marketed as a dietary supplement, has shown some promise for the treatment of OA symptoms in two small clinical trials (26,27).

Gout

Gout is a condition characterized by uric acid accumulation, neutrophil infiltration, and increased leukotriene levels, and is decisively influenced by diet. Foods rich in purines facilitate uric acid production and should be avoided; such foods include beer, organ meats, yeast, shellfish, sardines, herring, and bacon (4,28,29). Alcohol, long implicated in gouty flares, leads to increased purine production and decreases renal urate clearance (4,30). Choi et al. (31) demonstrated definitively that there is an increased risk of gout with increasing daily alcohol intake, particularly from beer. In many individuals, the elimination of alcohol is all that is necessary to avoid gout flares. Fructose intake may adversely affect uric acid levels (32), though data supporting this association are conflicting (33). Low-fat dairy products and wine may offer protective benefit (33,34). Obesity is associated with hyperuricemia and flares of gout. The available evidence supports the benefits of weight loss for overweight gout patients. Epidemiological studies have confirmed a clear dose–response relationship between body mass index (BMI) and the risk of gout (35,36); increasing obesity levels may in part explain the rapid rise in prevalence of gout among Americans over the past two decades (37). Preliminary evidence suggests beneficial effects of low-carbohydrate, calorie-restricted diets generous in monounsaturated fats and higher in total daily protein than has previously been recommended for patients with gout (38). Coffee consumption (caffeinated or decaffeinated) appears to decrease the risk of gout, possibly related to antioxidant effects and reduction of insulin (39). The bioflavonoid quercetin has demonstrated several effects in experimental studies, indicating its possible benefit to individuals with gout (40). Diet interventions, including low-calorie diets (but not fasting), low-purine diets, and different variations of the MD, can decrease serum uric acid in patients with asymptomatic hyperuricemia or gout (41).

Rheumatoid Arthritis

The major principal dietary approaches to RA are the addition to the diet of foods with anti-inflammatory properties and the elimination of foods with apparent proinflammatory properties (4). Clinical benefits arising from dietary modification may be attributed to a variety of mechanisms, including the modification of gut flora, reducing intestinal permeability, and the ingestion of dietary substances (which may or may not be metabolized by the gut microbiota) that exert immunomodulating effects (39,42). For example, a randomized control trial (RCT) in patients with RA found that *Lactobacillus casei* significantly decreased disease activity when compared with placebo, and also lowered the levels of tumor necrosis factor (TNF), interleukin (IL)-6 and IL-12 while raising the levels of IL-10 (43).

Dietary salt has been shown to interfere with the regulatory mechanisms of both the innate and the adaptive immune systems enhancing proinflammatory responses by inducing Interferon (IFN)-gamma production and reducing the activation of IL-4 and IL-13 macrophages. A cross-sectional study demonstrated a significant dose-dependent association between total sodium intake in the fourth quartile and a diagnosis of RA (44).

Autoimmune diseases, including RA, have been associated with elevated zonulin, suggesting that increased intestinal permeability may be a contributory etiologic factor. Reestablishing the zonulin-dependent intestinal barrier function may represent an additional strategy by which to approach treatment and prevention of autoimmune disease (45).

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A systematic review has confirmed consistent evidence that the addition of *n*-3 fatty acids to the diet may be beneficial in RA (42). Some patients receiving fish oil supplements may be able to reduce or even stop their usage of nonsteroidal anti-inflammatory drugs (NSAIDs) (46,47). As this practice is of apparent benefit for several other conditions (see Appendix E) and consistent with recommendations for general health promotion, there is little reason not to include it among routine interventions for RA.

Specific recommendations in the literature include intake of up to 12 g/day of linoleic acid and 4 g/day of *α*-linolenic acid (ALA), while restricting arachidonic acid intake to less than 50 mg/day (48). Supplementing with fish oils bypasses the metabolism of ALA by directly supplying eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Therapeutic benefit is often seen with 2 to 3 g/day of EPA and DHA found in fish oil. Higher doses (>3 g/day) of *n*-3 fatty acids are associated with reduced production of reactive oxygen species (47). Arachidonic acid, found only in animal foods, is eliminated from the diet in strict vegetarians; vegetarianism has been associated with symptomatic relief in RA (48–50). Fasting appears to confer benefits in RA. Possible mechanisms of the benefits of fasting include increases in serum dehydroepiandrosterone sulfate (DHEA-S) and decreases in serum IL-6, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR or sed rate), and disease activity (51). However, the benefits are lost when an omnivorous diet is resumed.

A vegetarian diet may sustain the benefits of a fast; clinically significant benefit has been measured in RA patients who undergo fasting followed by vegetarian diets for at least 3 months (52). Other studies report symptomatic relief of RA symptoms with gluten-free vegan diets (53). In a survey of RA patients, 27% reported intolerances to cow's milk, wheat, and gluten, though no relationship was seen between patients reporting food intolerances and food challenges in rectal mucosa. One randomized trial found that a gluten-free vegan diet significantly decreased oxidized low-density lipoprotein levels and slightly elevated anti-phosphorylcholine Immunoglobulin M (IgM) and Immunoglobulin A (IgA) levels (54). A gluten-free vegan diet was shown to significantly reduce the number of Immunoglobulin G (IgG) antigliadin and IgG anti-*b*-lactoglobulin antibodies (49). A double-blind crossover trial found that a low-arachidonic acid ("anti-inflammatory") vegetarian diet supplemented with fish oil was found to improve clinical signs of inflammation in patients with RA (55).

There is some evidence that a combination of antioxidant nutrients, including vitamins E and C and selenium, confers benefit in RA (48,56), while other evidence demonstrates no effect of combination antioxidants (57). Dietary recommendations for the management of RA include a diet rich in antioxidants, avoidance of animal fat, regular ingestion of fish or soybeans (or both), and avoidance of alcohol (48). There is inconclusive evidence to date linking coffee consumption and risk of RA; further research may be warranted (58–60). Despite conflicting evidence for specific antioxidant supplements, foods containing high amounts of antioxidant nutrients should be emphasized.

Evidence regarding the role of food allergy in RA is inconsistent. As many as one third of RA cases may be influenced by food (4). Foods commonly implicated include cereal grains, corn, and dairy products. A 2004 epidemiological study found a significant association between inflammatory polyarthritis and high intake of red meat, animal protein, and total protein (OR = 1.9, 2.3, 2.9, respectively) (61), though a 2007 follow-up prospective cohort study found no clear relationship between meat and protein intake and the incidence of RA using Nurse's Health Study data (n = 82,603 women). Assessment for dietary precipitants of arthritis flares, generally by use of a food and symptom diary, is reasonable if not prudent in most cases, with trial elimination of implicated food items (see Chapter 24).

The variability in food allergy requires that such hypotheses be tested on an individual basis, using elimination diets, as some patients can achieve symptomatic relief with restricted diets (50). Suspected foods are eliminated from the diet, and clinical status is monitored. If there is improvement, the same food

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is reintroduced into the diet. If symptoms recur in convincing association with re-exposure to the implicated food, it should be permanently removed from the patient's diet (62).

Although there is considerable interest in the role food sensitivity might play in RA, the evidence to date is still very limited (50,63). A study of elimination diets in 63 children with chronic arthritis revealed in only one case an association between dietary intolerance and disease state (64). The authors concluded that food intolerance is likely to be pertinent to occasional patients with inflammatory arthritis and is not the principal etiologic factor. However, a controlled study measuring antibodies to dietary antigens found significantly increased production of cross-reactive antibodies in the intestinal fluid of RA patients compared to healthy controls. The authors suggested that the combination of multiple minor hypersensitivity reactions may have had adverse additive effects in RA patients, resulting in the production of autoimmune reactions in their joints (65).

RA is thought to influence dietary intake in terms of the symptoms of the disease and its treatment. Symptoms of RA may cause discomfort during eating or limit access to food; pharmacotherapy may cause anorexia or nausea. There is some evidence that micronutrient deficiencies may be relatively common among patients with RA (66,67). Several trials have shown reduced gastrointestinal (GI) side effects in patients receiving folate supplementation when taking methotrexate, a drug commonly used in RA and a known folate antagonist (68). Although the role of some of the nutrients in question regarding RA is speculative, intake meeting the dietary reference intake (DRI) is advisable. Given the available evidence, multivitamin/multimineral supplementation for all patients with RA seems a prudent recourse.

Ankylosing Spondylitis

The association between the seronegative spondyloarthropathies and the human leukocyte antigen B27 (HLA-B27) histocompatibility sequence is well established. Efforts to explain this association led to the identification of molecules on *Klebsiella* organisms in the gut with similar sequencing and generated speculation that the bacteria are causally involved in the diseases (69). Small studies suggest that starch restriction reduces serum immunoglobulin A and symptoms in patients with ankylosing spondylitis (AS), apparently by inhibiting the growth of enteric *Klebsiella* (70), while other studies found no relationship between diet and AS disease activity (71). Vitamin D plays a significant role in immune function, and studies demonstrate that AS patients have lower vitamin D levels, total bone mineral density (BMD)-femur, and BMD-femur neck values (72).

Other Rheumatologic Conditions

Subsumed under the rubric of rheumatologic conditions is a wide array of pathologies involving joints and soft tissue by mechanisms known in some cases and unknown in others. The autoimmune basis for inflammatory conditions of blood vessels, neurons, skin, and so on is clear in many cases, even if the specific antigens are not. In conditions including vasculitis, dermatitis, polymyositis, polyarteritis, and systemic lupus, dietary interventions directed toward reduced inflammatory response (see earlier section, and Chapters 11 and 21) are appropriate. Dietary adjustments such as reduced intake of saturated fat and trans fat as well as increased intake of fruits, vegetables, and unsaturated oils, with particular emphasis on *n*-3 fatty acids, conform to the features of a health-promoting diet and are advisable even in the absence of confirmed, condition-specific utility. As Mediterranean-style diets tend to be health-promoting and can reduce risk of a variety of chronic disease, as well as possibly provide symptomatic relief (73), they are prudent recommendations in a variety of inflammatory conditions. Obesity is a proinflammatory condition (74,75) and can exacerbate disease activity, targeted weight-loss programs can also be beneficial in obese patients with inflammatory rheumatologic conditions.

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In some cases, the etiology and pathogenesis of rheumatologic conditions are entirely unclear. Salient examples include fibromyalgia and chronic fatigue syndrome (CFS). Autoimmune mechanisms have been suggested for both but are unconfirmed theories that compete with others (76–84). Dietary management has been espoused for both conditions, although in neither case is there definitive evidence of efficacy for any specific treatment (83,85–90). However, there is general support for improvement of overall dietary pattern for health promotion, along with *n*-3 fatty acid supplementation and consideration of food sensitivities and intolerances. Nutrient deficiencies (vitamin C, vitamin B complex, sodium, magnesium, zinc, folic acid, L-carnitine, L-tryptophan, essential fatty acids, and coenzyme Q10) appear to be important in the severity and exacerbation of CFS symptoms (91).

The use of an intravenous nutrient infusion known as the "Myers' cocktail" (92), containing B vitamins, vitamin C, magnesium, and calcium, is a popular treatment modality for both fibromyalgia and CFS (as well as other conditions) in complementary/alternative medicine (CAM) practice. Until recently, reports of therapeutic efficacy were anecdotal, if widespread. The first clinical trial of the Myers' cocktail for fibromyalgia was completed in the author's lab with equivocal results (92).

NUTRIENTS, NUTRACEUTICALS, AND FUNCTIONAL FOODS

Fatty Acids

As discussed in Chapters 6, 7, 11, 12, 44, and 45, the prevailing diet in the United States provides a preponderance of *n*-6 over *n*-3 polyunsaturated fatty acids. Modern diets provide *n*-6 to *n*-3 fatty acids in an approximate 11:1 ratio. Paleolithic intake apparently ranged from 4:1 to 1:1 (93). The metabolism of *n*-3 fatty acids leads to generation of anti-inflammatory cytokines. EPA and DHA, ingested as marine oils or manufactured endogenously from α-linolenic acid, inhibit the production of arachidonic acid-derived proinflammatory eicosanoids (94).

Dietary *n*-3 fatty acids have been shown to ameliorate symptoms in RA (47,66,95). Studies have demonstrated fish oil competitively inhibits COX-2, which is overexpressed in the RA synovium (96). A systematic review of 23 studies found a consistent, modest improvement in joint swelling and pain with *n*-3 fatty acids (47). See Chapter 45 for other lines of argument supporting increased *n*-3 fatty acid intake.

Vitamin D

In addition to effects on bone and calcium metabolism, vitamin D can have immunosuppressive effects. Vitamin D also plays a role in neuromuscular and immune function as well as reduction of inflammation. 1,25-dihydroxyvitamin $[OH]_2$ D_3, the biologically active form, interacts with vitamin D receptors that are expressed on osteoblasts, T cells, dendritic cells (DCs), macrophages, and B cells (97).

Adequate vitamin D may be a protective factor for various autoimmune diseases (98); vitamin D supplementation may be beneficial for B cell-mediated autoimmune diseases such as RA and systemic lupus erythematosus (97). Thus, clinicians should routinely assess vitamin D status and supplement as warranted in persons with rheumatologic conditions.

Probiotics

Some probiotics have anti-inflammatory properties that are strain specific and species specific (97,99). Some strains have antitumor necrosis factor effects (100), while others can interact with toll-like receptors or downregulate the transcription of genes that encode pro-inflammatory effectors (101). These anti-inflammatory effects may be modulated through interactions with intestinal epithelial cells. Gut

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immune function can be modified by the composition of intestinal flora and can affect intestinal barrier function (97). There are shared inflammatory pathways in the GI system and joints; arthralgia and spondyloarthropathy of axial and peripheral joints are often found in patients with inflammatory bowel diseases (102). Thus, targeted probiotic supplementation may be a reasonable intervention in a multimodal approach to inflammatory conditions. There is emerging evidence that alterations in immune stimulation in early childhood (the "hygiene hypothesis") promote inflammation and autoimmunity (103). Consequently, reduced exposure to parasites and microorganisms may contribute to the increased incidence of a variety of immune-mediated conditions (104). This is an area of active research and interest in treatments such as fecal microbiota transplantation (105).

Glucosamine Sulfate

Glucosamine is found in the body as a precursor of glycosaminoglycans, which are used by chondrocytes in the production of proteoglycans incorporated into articular cartilage. The body's manufacturing of glucosamine declines with age at variable rates leaving some people vulnerable to deficiency. The use of supplemental glucosamine is promoted as a means of compensating for a decline in endogenous production, thereby reconstituting worn articular surfaces.

Although glucosamine is available in various forms, its use as a sulfate salt is most convincingly supported by available evidence, perhaps because sulfur is another integral component of cartilage. Glucosamine available as a nutraceutical agent is typically derived from the exoskeletons of shrimp, lobsters, and crabs, although biosynthetic preparations are increasingly available.

Data from a number of methodologically rigorous studies, including double-blind, randomized trials, have suggested the efficacy of glucosamine in OA of the lower limbs (67,106–108). Glucosamine works slowly by reconstituting cartilage and has no known direct analgesic properties, although anti-inflammatory effects have been reported (109). Therefore, pain relief is faster with NSAIDs. One controlled trial found that glucosamine significantly reduced arthritic joint space narrowing over a period of 3 years (110).

A double-blind trial demonstrated superior pain relief with ibuprofen at 2 weeks but a superior effect of glucosamine at 4 weeks (111). There is evidence that NSAIDs, while alleviating symptoms, may actually accelerate the degeneration of articular cartilage (112,113). There is no known toxicity of glucosamine sulfate. Doses up to 1,500 mg daily are generally recommended (108); higher doses may be required in obese patients or for individuals on diuretics.

A 2009 Cochrane review assessing randomized controlled trials of glucosamine for OA concluded that glucosamine was superior to placebo for treating pain and improving functionality in OA, with a safety profile comparable to placebo (106). Additional data demonstrated equivalent effects of glucosamine sulfate, celecoxib (a COX-2 inhibitor), and placebo on pain and function in adults with moderate-to-severe knee OA (114). However, other trials have shown mixed beneficial effects. A 2013 meta-analysis concluded that glucosamine is ineffective for pain control in OA of the knee, but may have functional benefits when used for more than 6 months (115).

Cartilage Extracts and Chondroitin Sulfate

Some alternative medicine publications advocate the use of various cartilage extracts, including shark cartilage, sea cucumber, chondroitin sulfate, and green-lipped mussel for chronic, degenerative arthroses. These products either contain glycosaminoglycans or, in the case of chondroitin, are glycosaminoglycans and putatively function by incorporation into joints (116). However, chondroitin is a large molecule and absorption is poor, with undetectable serum levels of dietary chondroitin sulfate in rigorous trials, and

may reduce absorption of glucosamine in combination (117).

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The available evidence and the established pharmacokinetics support the use of glucosamine over these products, although chondroitin does show highly significant efficacy over placebo in some trials (118,119). The combination of chondroitin sulfate and glucosamine sulfate has become popular, and as noted previously, a recent large multicenter trial found evidence of significant pain reduction in a subgroup of subjects with moderate-to-severe OA of the knee (120), while other studies have found no particular benefits of the combination (119). Thus, as with glucosamine, the therapeutic efficacy of chondroitin deserves further investigation.

S-Adenosyl-L-Methionine

A popular alternative therapy for OA, S-adenosyl-L-methionine (SAMe), is a compound derived from the amino acid L-methionine and adenosine triphosphate (ATP). SAMe inhibits enzymes involved in cartilage degradation and deficiency may compromise cartilage integrity. Although evidence is limited, a meta-analysis by Soeken et al. (121) found SAMe to have efficacy equivalent to that of NSAIDs in reducing functional limitation and pain in patients with OA and to have fewer side effects. Most clinical trials have used 600 to 1,200 mg/day.

Nightshade Vegetables

The nightshade family of plants, known scientifically as the *Solanaceae*, has been implicated in the alternative medicine literature as a cause of arthritis. The literature is poorly substantiated, and specific forms of arthritis are rarely specified.

The family *Solanaceae* is diverse and includes potatoes, tomatoes, red peppers, eggplant, tobacco, paprika, pimento, cayenne pepper, and chili pepper. There is little evidence to support elimination of one or more of these foods from the diet to manage any type of arthritis. Elimination diets, however, are occasionally helpful in RA, and the elimination of nightshades might be considered in that context to manage refractory disease.

Herbal Products

Several botanicals have shown promise in alleviating symptoms of OA (122). Capsaicin, derived from chili peppers, has shown benefit in improving pain and articular tenderness in patients with OA when applied topically (123) and is conditionally recommended as an initial pharmacologic intervention for OA by the American College of Rheumatology (124). Preliminary evidence is promising for ginger as a treatment for pain in patients with OA (125,126). A systematic review found encouraging evidence for avocado–soybean unsaponifiables, although further research is clearly needed (127). The most clinically effective formulation of avocado–soybean unsaponifiable is considered a prescription drug in some countries (128). Devil's claw (*Harpagophytum procumbens*) may have benefit, but it is thought to be an herbal COX-2 inhibitor, so caution is warranted (129).

Other Nutraceuticals

Genistein, an isoflavone found in a variety of plants (including soybeans) and pycnogenol, an antioxidant derived from pine bark (as well as other sources) has demonstrated some preclinical anti-inflammatory properties. Other nutraceuticals demonstrating anti-inflammatory effects include epigallocatechin-3-gallate (found in green tea), as well as resveratrol (found in red grapes) (128).

Nutrigenomic Considerations

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Nutritional factors can affect gene expression through epigenetic modification, and may be an area of focus in autoimmune and inflammatory conditions. Some inflammatory response disease genes have been shown to be affected by epigenetic regulatory mechanisms (130). For example, Rho iso-alpha acids from hops have been shown to have properties that inhibit nuclear factor (NF)-kappaβ-mediated inflammatory markers in some cell models (131). This emerging area of therapeutics has the potential to help tailor nutritional interventions to persons with specific genetic polymorphisms.

Diet–Drug and Nutrient–Drug Interactions of Importance

As RA is a progressive disease, it often requires the successive use of more toxic drugs with serious effects on nutritional status. There is also a risk of developing drug-induced osteoporosis with longer regimens of corticosteroids and cytotoxic drugs (132).

Many cytotoxic drugs (e.g., methotrexate) are folate antagonists, and will thus decrease folate levels and increase homocysteine levels. Supplemental folate may decrease the efficacy of the drug. Methotrexate can also cause mouth ulcers that can affect food consumption. Cyclosporine can induce hyperglycemia, hypercholesterolemia, electrolyte disturbances, and renal insufficiency.

Other drug–nutrient interactions of significance in rheumatic disease:

- NSAIDs should be taken with food to prevent GI upset.
- Glucocorticoids and corticosteroids can cause stomach upset and should be taken after eating a meal. They may also cause protein wasting.
- Penicillamine is a chelating agent for copper, iron, and zinc, and can cause sodium depletion and vitamin B_6 deficiency.
- Avoid grapefruit juice with cyclosporine.
- Sulfasalazine reduces the absorption of folic acid.

CLINICAL HIGHLIGHTS

There is sufficient evidence to justify offering tailored dietary advice to patients suffering from various forms of arthritis. Avoidance of obesity is a mainstay (see Chapter 5). A Mediterranean-style diet conforming to recommendations for health promotion (see Chapter 45) is advisable on general principles and for its favorable influences on inflammation.

A vegetarian diet may be advantageous in RA and, provided that all nutrient needs are met (see Chapter 43), is conducive to health-promotion goals. Alcohol intake should be restricted or avoided. Regular consumption of fish and regular use of flaxseed oil as a means of increasing *n*-3 fatty acid intake are advisable both for arthritis management and on general principles (see Chapter 45). Fish oil supplementation containing 1 g of *n*-3 fatty acids daily is reasonable, and in progressive RA, a trial of higher-dose therapy may be warranted.

The use of glucosamine sulfate shows mixed results regarding efficacy and is safe, but published evidence to date demonstrates greater effects for functionality rather than pain control. A trial of glucosamine sulfate 500 mg three times daily for patients with chronic joint pain seems appropriate, and even more so in patients intolerant of NSAIDs. Fasting and elimination diets may offer at least temporary relief to a minority of patients with RA. The avoidance of nightshade vegetables does not appear to offer any consistent benefit, although the practice is supported by anecdotal reports. Salt appears to promote inflammation via several mechanisms, whereas curcumin, capsaicin, chocolate, coffee, vitamin D, and resveratrol might attenuate an overactive immune response. Use of food and symptom diaries to identify

food sensitivities and intolerances is advisable in virtually all rheumatologic or autoimmune conditions refractory to initial interventions.

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Chapter 21

Diet and Neurologic Disorders

Laurie K. Mischley

INTRODUCTION

Evidence in support of a direct role for diet in most neurologic disorders affecting well-nourished populations has been steadily increasing in recent decades. Malnutrition, which affects more than hundreds of millions of people worldwide, is a well-established contributor to cognitive, psychological, neuroinflammatory, and neurodegenerative impairment. Diet and nutrition are notoriously difficult to study due to limitations of assessment tools, recall bias, diversity in food sourcing and processing, individual aspects of intestinal (mal)absorption, diversity of the microbiome, genetic polymorphisms related to nutrient metabolism, and other variables associated with biochemical individuality. In nutritional medicine, personalized evaluation and management is paramount, as an effective intervention for one person's symptoms is rarely applicable to the entire affected population. For example, nutritional medicine is essentially curative for patients with gluten ataxia or dementia due to niacin deficiency, while gluten-free diets and niacin supplementation are unlikely to help most people with ataxia and dementia, respectively.

Even if the neurological condition was not caused by a nutritional deficiency, the chronic physiological stress associated with neuroinflammation and neurodegeneration itself can increase metabolic burden and nutritional demands. The conditionally essential nutrients associated with different neurological disorders are only beginning to be described.

In neurology, targeted dietary prescribing began with the ketogenic diet in the 1920s to control intractable childhood seizures. Ketogenic diets are low-carbohydrate, high-fat diets that shift metabolism to produce ketones, now understood to be neuroprotective. Not only are ketogenic diets still one of the most effective therapies for intractable epilepsy today, maintaining a state of ketosis is now being explored as a therapeutic across a host of neuroinflammatory and neurodegenerative conditions (1). While promising, ketogenic diets increase anorexia and risk of malnutrition, potential threats for individuals with an underlying disease.

In population-based studies, plant- and fish-based diets that are low in meat, dairy, and processed food, such as the MIND and Mediterranean diet, have been shown to protective against Alzheimer's disease (AD), Parkinson's disease (PD), and cardiovascular disease (CVD). That a similar diet seems to be protective across diseases suggests the mechanism of action may be related to curbing oxidative stress and inflammation, common across these diseases. Another potential mechanism for diet-modulating neurological disease is via modulation of the intestinal microbiome, now understood to regulate immune response and systemic inflammation (2). Alternatively or additionally, it is also possible Mediterranean or ketogenic diets may be a source of conditionally essential nutrient(s), such as polyphenols, glutathione, or ketones, or that some foods contain a neurotoxicant, such as aspartame or ochratoxin A (3,4). The mechanisms by which diet influences neurological health and function are complex and may be patient specific.

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Diet

Cognition

A detailed discussion of the myriad effects of nutriture on cognition, via direct and indirect mechanisms, is beyond the scope of this chapter. Dementia is addressed in Chapter 35, early brain development in Chapter 29, and senescence in Chapter 31. The influence of nutrition on the vitality of the various organ systems addressed throughout this text is obviously germane to brain health as well. Healthy brain function is dependent on the steady delivery to the brain of glucose, amino acids, fatty acids, and micronutrients. The brain of an adult constitutes roughly 2% of body mass but requires nearly 20% of calories consumed. In newborns, nearly 60% of caloric intake is directed toward brain function and growth. Due to the rapid development that occurs during infancy, nutritional deficiencies during the first 1,000 days can result in lasting consequences on brain development, cognitive, and psychological processes. Ensuring nutritional adequacy in childhood is essential for long-term neurological health (5).

Iodine and iron deficiencies contribute to cognitive impairment, especially during the vulnerable period of childhood development. As many as 300 million people globally have cognitive impairment related to iodine insufficiency, which is largely a function of geographic soil concentrations (6). Once virtually eliminated in the United States with salt iodization, the growing popularity of non-iodized sea salt is once again introducing a risk of iodine deficiency, even in countries that provide fortification.

Iron deficiency, one of the most common nutritional disorders in the world, induces cognitive impairment in children through multiple pathways, including impaired oligodendrocyte growth, decreased myelination of white matter during critical periods of infant brain development, and altered neurotransmitter synthesis. In animal models, iron deficiency-induced alterations in cognitive, motor, social, emotional, and physiologic development. Iron supplementation following an extended period of deficiency may not fully compensate. While iron-fortification of grains has reduced the incidence of childhood cognitive impairment, there is emerging evidence that iron fortification may be detrimental to iron-replete individuals. In iron-replete children, iron fortification has been associated with reduced infant growth (7) and increased risk of infections (8).

Cognitive decline with age is a major cause of global disability. In the Nurses' Health Study, higher intake of nuts and moderate consumption of alcohol were associated with better cognitive function over time (9). Intake of fish, particularly the polyunsaturated fatty acid (PUFA) docosahexaenoic acid (DHA), has consistently been associated with reduced risk of dementia and Alzheimer's disease (10). The MIND and Mediterranean diets show a general positive effect on cognition, mood, and other neurodegenerative diseases (11,12).

Headache

A nationwide survey of over 12,000 revealed that 22% of respondents reported suffering from severe headaches or migraines (13). Headaches can be caused by vascular, neurological, psychological, hormonal, and metabolic perturbations, and their proposed mechanism of action includes neuronal hyperexcitability, inflammation, oxidative stress, hypometabolism, vascular dysfunction, and activation of the trigeminovascular pathway (14). Obesity is a well-established risk factor for headaches in children and adults, and weight loss can reduce headache frequency (15). In the National Health and Nutrition Examination Survey (NHANES) cohort, individuals with the highest intake of omega-3 PUFAs had a lower prevalence of severe headache or migraine (13). Between 45 and 100% of individuals with

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headache have been reported to have vitamin D deficiency. Supplementation with 25 to 100 mcg/d (1,000–4,000 IU/d) may be effective in reducing headache frequency (16).

While contributors may vary greatly between individuals, there are several well-established dietary risk factors for headaches that clinicians should be aware of. The mechanisms vary but are thought to include inflammation, activation of the sympathetic nervous system, release of nitric oxide-induced vasodilation, and modulation of neuropeptides and ion channels (14). Mild dehydration is common and can cause headaches. A small pilot trial demonstrated an additional 1-L water/day reduced the number of hours and intensity of headaches within 2 weeks (17). Fasting has also been shown to trigger headaches, especially in chronic headache sufferers, and the risk rises with the duration of the fast. Researchers found length of migraine episodes were three times greater in fasting patients when compared to their nonfasting state (18,19). In habitual caffeine consumers, caffeine withdrawal can be a trigger, and in others, exposure to particular foods or ingredients, such as aspartame or alcohol, can be a trigger (20).

Induction of vascular or cluster headache may occur in individuals sensitive to dietary histamine. Intolerance is thought to be fairly common and that headache is among the relatively frequent reactions (21). Concentrated food sources of histamine include cheese, sausages, sauerkraut, tuna, and tomatoes, in addition to alcoholic beverages. In an open-label study of individuals with chronic headache, at the end of a 1-month histamine-free diet, 33 of 45 participants reported considerable improvement in headaches (22).

A meta-analysis evaluating the relationship between celiac disease and headache resulted in a mean pooled prevalence of headaches in 26% of adults with celiac and 18% of children (23). In a survey in Argentina of 866 individuals with celiac-positive biopsy and headaches, 24% of participants revealed that headache was the main symptom that led to their celiac diagnosis. Following initiation of a gluten-free diet, headache frequency and headache improved (24).

While diet can trigger a headache, evidence suggests that headache frequency and intensity can be modulated with the therapeutic use of special diets and nutrient supplementation. A randomized controlled crossover study of 42 chronic migraine sufferers demonstrated a low-fat, vegan diet was able to reduce headache frequency, average intensity, and maximum intensity within 4 weeks (25). In two separate randomized controlled trials of prescription diets, Mediterranean-based diets (low-fat, high in omega-3 fatty acids) decreased the frequency of migraine and other headaches, while another study suggested a ketogenic diet was capable of reducing migraine attacks (14). Ketogenic diets have shown promise for migraine management, with benefit attributed to the capacity of ketones to enhance brain metabolism and mitochondrial respiration (26). A 2015 study of overweight women showed that ketosis was superior to weight loss alone, with improvements in migraine frequency, headache days, and use of pain relievers during the ketogenic period of the study (27). In individuals with chronic cluster headaches, 15/18 study participants responded favorably to a modified Atkins-ketogenic diet (28).

Magnesium is the fourth most abundant mineral in the human body and serves as a cofactor in hundreds of enzymatic reactions. Magnesium deficiency is common in the United States, and especially so in individuals with headaches (29). A meta-analysis evaluating the use of magnesium for acute treatment of migraine headaches found intravenous magnesium significantly relieved acute migraine within 15 to 45 minutes and the benefits were sustained 24 hours following the infusion, while oral magnesium reduced the frequency and intensity of migraines over time (30).

When other explanations for chronic or recurrent headache are not identified, consideration of food allergy is both reasonable and warranted (see Chapter 24). Because dietary triggers tend to be idiosyncratic, a standard elimination diet for migraine is not generally recommended. Rather, a food and symptom diary may prove useful in elucidating triggers unique to a given patient. Reduced headache

frequency and/or severity often ensue when exposure to such triggers is eliminated or reduced.

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Seizure

The ketogenic diet has been used as primary or adjunctive therapy of childhood seizures since the 1920s and remains one of the most effective therapies today for intractable epilepsy (31). The diet originally was developed following observations that seizure activity was suppressed in epileptics during fasting and starvation. The utility of high-fat diets in raising the seizure threshold has been demonstrated in animal studies. The ketogenic diet is designed to induce ketosis and to shift brain metabolism from glucose to ketone bodies, as occurs during a period of caloric restriction. The diet is initiated with a fast, generally lasting about 38 hours. Foods are introduced when ketones are detectable in serum and target a ratio of fat to protein and carbohydrate combined in the range from 3:1 to 4:1 (32). A mild degree of dehydration is advocated by some to preserve circulating ketone levels (33), but the need for this is not well substantiated. Recent modifications of the original diet have been developed in an attempt to facilitate compliance, such as the medium-chain triglyceride (MCT) diet. A randomized trial compared the classical ketogenic diet to MCT, showing comparable efficacy in treating epilepsy (34). The mechanism by which ketosis influences seizure activity is uncertain, although progress in this area is being made (35).

Observational studies suggest that approximately one-third of treated patients respond favorably to the ketogenic diet, corroborated by a meta-analysis with data from more than 1,000 patients (36). Furthermore, patient response to the ketogenic diet was found to be comparable to modern antiepileptic medications in a Cochrane review (37). A systematic review suggests that roughly 15% of patients may experience complete relief of seizure activity with the regimen, and another 15% or so may experience a reduction of seizure frequency of 50% or more (38). Numerous adverse reactions to the ketogenic diet have been reported, including micronutrient deficiencies, particularly carnitine deficiency, hypoglycemia, hyperlipidemia, osteoporosis, abnormal liver function, optic neuropathy, urolithiasis, and hemolytic anemia (39). Adherence to the diet is difficult due to the strict nature, having limited access to foods that will maintain ketosis, or not finding those foods appetizing. Seizure relief is greatest among those who adhere strictly to the diet, although this association likely goes both ways (38). Furthermore, families reported preparation time and the restrictive nature of the diet as large barriers to compliance. Interestingly, socioeconomic status and family stability were not noted to be factors associated with an inability to maintain the ketogenic diet (40). Given the potential adverse effects and the difficulties in achieving compliance, the ketogenic diet is generally indicated only for those patients resistant to or intolerant of pharmacotherapy. However, some advocate more widespread use of the ketogenic diet because it is less expensive, ostensibly safer, and potentially more effective than most available drugs.

The low-carbohydrate and ketogenic diet advocated by the late Dr. Robert Atkins for weight loss has been tested for seizure control, as an alternative to the more restrictive ketogenic diet typically used in this context. Several studies have evaluated pediatric patients with epilepsy in relation to the Atkins diet and demonstrated that long-term adherence (>6 months) to the Atkins diet resulted in a decrease in seizures similar to that seen in patients who followed the Atkins diet for only a short-term basis (41,42). A modified Atkins diet led to a modest 25% reduction in seizures in adults with drug-resistant focal epilepsy and a 50% reduction in children (43).

Multiple Sclerosis

MS is a complex disease with both inflammatory and neurodegenerative components. Most individuals have a relapsing-remitting, inflammatory, immune-based disease defined by demyelinating lesions. Later

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in the disease, a subset of individual progress to a degenerative form of MS, secondary progressive that includes neurodegeneration in the absence of new inflammatory lesions. Thus, a dietary strategy that might be effective during the early active phase, may be less so during the degenerative stage, or vice-versa. The slow progression, lack of a biomarker, and relapsing-remitting nature of the disease all contribute to making MS very difficult to study.

Epidemiologic research done in Norway in the 1940s demonstrated individuals living on the farms, consuming a diet high in pork, beef, and diary, were at higher risk of MS than those individuals living nearby, in the fishing villages. The Swank Diet, developed based on the epidemiologic findings, recommends a diet high in vegetables, fruit, whole grains, fish, and supplemental fish oil, with strict avoidance of beef, pork, dairy, and refined carbohydrates. Adherents to the diet were followed over three decades and demonstrated those who adhered to the diet had less disability and reduced mortality rates (44). The diet remains one of the most popular among individuals with MS today (45).

Several studies demonstrate intake of fatty fish and omega-3 fatty acids are protective against MS diagnosis (46,47), although it is less clear whether administration of omega-3 fatty acids following diagnosis is able to improve disease outcomes. Conversely, several studies have identified an association between diary intake and MS risk. The milk protein, butyrophilin, shares an antigenic protein sequence with myelin oligodendrocyte glycoprotein (MOG), a common target for MS demyelination (48). Among individuals with MS, those with food allergies had more clinical relapses and evidence of disease activity on imaging (49).

There is an abundance of epidemiological evidence to support an association between vitamin D deficiency and MS incidence on progression. Individuals with higher 25-hydroxyvitamin D levels are less likely to be diagnosed with MS and those with MS are more likely to have an improved clinical course (50). A recent meta-analysis found non-significant trends in favor of vitamin D administration and concluded supplementation may have a role in the therapeutic management of MS (51).

Neurodegenerative Disorders: Alzheimer's Disease and Parkinsonism

Alzheimer's disease (AD) is the most common neurodegenerative disease and with the aging population, an estimated 131 million people are projected to develop dementia by the year 2050. Malnutrition is common in older individuals with mild cognitive impairment (MCI), a precursor to dementia, and is associated with exacerbation of symptoms such as "verbal aggressiveness/emotional disinhibition" and "apathy/memory impairment" (52). Ascorbic acid plays a role in neurotransmitter synthesis and modulation, myelin formation, neuronal differentiation, and antioxidant recycling and has thus been investigated for its role in preventing cognitive loss. A review of 50 studies evaluating vitamin C in cognition found higher mean vitamin C concentrations in the cognitively intact cohorts compared to the cognitively impaired groups (53).

While there is evidence that a Mediterranean diet and some nutrients, such as B vitamins and omega-3 fatty acids, can prevent cognitive decline (54), it is less clear whether nutritional fortification or special diets can improve outcomes in those already affected (55). A systematic review of 35 randomized clinical trials published between 2014 and 2017 found moderate evidence that changing dietary patterns and/or nutriceutical supplementation improved cognitive domains or biomarkers, with the strongest evidence for long-chain poly-unsaturated fatty acids, non-flavonoid polyphenols, and flavonoid supplementation (56). Given the existing data, healthy adults should be encouraged to eat a Mediterranean-like diet and ensure adequate intake of DHA, ascorbic acid, and B vitamins as dementia-prevention strategies.

Individuals with Parkinson's disease (PD) are at increased risk of malnutrition due to anorexia, hyposmia, apathy, intestinal malabsorption, hypochlorhydria, constipation, fatigue, depression, and

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trouble swallowing. Malnourished individuals with PD are more likely to be constipated, have insomnia, dystonia, depression, and cognitive decline (57,58). Levodopa, the gold standard treatment for PD motor symptoms, competes with dietary protein for uptake; to optimize levodopa availability, patients must avoid combining dietary protein with levodopa. Epidemiological evidence consistently demonstrates an association between diary and risk of PD incidence (59,60), while total caffeine intake and high intake of fruit, vegetables, legumes, whole grains, nuts, fish, and poultry have been shown to be protective against PD diagnosis (61,62). Adherence to a Mediterranean diet has been associated with reduced odds of PD diagnosis and later age of PD onset (63).

Only one study has attempted to evaluate the role of diet and supplements in PD progression following diagnosis. A survey of over 1,000 individuals with idiopathic PD demonstrated intake of canned fruits and canned vegetables, soda, fried food, beef, ice cream, yogurt, and cheese were associated with more rapid PD progression, while diets high in fresh vegetables, fresh fruit, nuts and seeds, non-fried fish, wine, coconut oil, olive oil, fresh herbs, and spices were associated with reduced rates of progression. In the same study, individuals that reported supplementing with iron reported accelerated rates of PD progression, whereas coenzyme Q10 and fish oil supplementation were associated with slower progression (64). Glutathione insufficiency has been associated with PD (65), and attempts are being made to supplement glutathione and N-acetylcysteine, a glutathione precursor, to augment brain and blood levels of glutathione in Parkinson's and related disorders (66–68).

Neuropathy

The Diabetes Prevention Program (see Chapter 6) tested the effects of the lifestyle intervention on lower extremity neuropathy in 32 adults with impaired glucose tolerance but not frank diabetes. The same lifestyle intervention that ameliorated glycemic responses to a glucose tolerance test resulted in reduced neuropathic pain and improvement in intraepidermal nerve fiber density, as measured by biopsy (69).

The potential for nutrient deficiencies to induce a variety of neuropathic syndromes is well established. Thiamine deficiency is associated with polyneuropathy and the Wernicke–Korsakoff syndrome, usually in the context of alcoholism though also reported in the context of impaired dietary intake following bariatric surgery (70). An epidemic of optic, peripheral, and mixed neuropathy in Cuba in the early 1990s has been attributed principally to deficiencies in B complex vitamins (71). One study demonstrated an alleviation in symptoms of diabetic neuropathy when treated with L-methylfolate, methylcobalamin, and pyridoxal-5'-phosphate (72). Another study suggested supplementation of 50,000 IU/week of vitamin D_3 for 12 weeks, which was associated with improvement in signs and symptoms of diabetic neuropathy (73.)

NUTRIENTS, NUTRICEUTICALS, AND FUNCTIONAL FOODS

Docosahexaenoic Acid

DHA is a long-chain omega-3 fatty acid found in high concentrations in the brain, especially neuronal cell membranes. Low DHA is associated with cognitive decline during aging, impaired reaction times, anxiety, irritability, dyslexia, and susceptibility to stress. In addition to the structural role of DHA in neuronal membranes, DHA metabolites play a pivotal role in neuroprotection. Synaptamide is an endocannabinoid-like DHA derivative that has been shown to promote neurogenesis and neuroplasticity (74), and the DHA metabolite neuroprotection D1 is thought to enhance neuroplasticity, mitigate inflammation, reduce oxidative stress and prevent apoptosis (75). The well-established importance of this nutrient class to neurologic development and health is addressed in Chapters 27 and 29.

Vitamin D

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Low vitamin D status is associated with increased risk of ischemic stroke (76) childhood and adult demyelinating disease (77), degree of disability in MS (78), more monthly days with headaches among migraineurs (79), neurodevelopmental disorders such as autism spectrum and attention deficit and hyperactivity disorders (80), Parkinson's disease (81), and dementia (82). The dose of vitamin D required for neuroprotection has yet to be determined. Providers are encouraged to screen for vitamin D insufficiency in all patients with neurological disorders and provide supplementation when necessary.

Vitamin B_{12}

Neurons have an especially high cobalamin requirement, and deficiency is common due to atrophic gastritis, autoimmune disease, or a vegetarian diet. Use of acid-lowering medications (83) and metformin (84) have also been shown to interfere with vitamin B_{12} absorption and increasing risk of deficiency. Vitamin B_{12} deficiency can cause demyelination, peripheral neuropathy, optic neuropathy, impaired cognition, depression, as well as a host of movement disorders, such as parkinsonism, chorea, dystonia, or myoclonus (85). Plasma cobalamin is not considered a reliable marker of B_{12} deficiency; evaluation of homocysteine holotranscobalamin and/ or methylmalonic acid should also be considered in a patient suspected of vitamin B_{12} deficiency (86).

Alpha-lipoic Acid

An essential cofactor for cellular energetics, ALA also recycles other antioxidants and has a variety of anti-inflammatory and antioxidant properties. There is a growing body of evidence that ALA may have therapeutic potential in MS and other central nervous system (CNS) diseases (87).

Aspartame

Controversies over the health effects of aspartame have long been debated. Aspartame increases the concentration of phenylalanine and aspartic acid in the brain, which reduces the synthesis and release of dopamine, norepinephrine, and serotonin. Symptoms associated with aspartame intake include headaches, migraines, irritability depression, anxiety, insomnia, and seizures (88). A more detailed discussion of the chemical nature of aspartame can be found in Chapter 42.

Therapeutic Diets

Ketogenic Diet

Effectively used since the 1920s for intractable epilepsy, the therapeutic utility of the ketogenic diet is now being explored in MS, PD, AD, and autism (26). Ketogenic diets are very-low carbohydrate, high-fat diets that forces a shift in metabolism from glycolysis to fatty acid oxidation, which in turn generates ketone bodies. Ketone bodies have been shown to be neuroprotective, anti-inflammatory, and improve the cellular energetics of the cell (89). Ketogenic diets restrict fruit, an essential source of [phyto]nutrients, and can cause anorexia and weight loss, all of which increase risk of malnutrition. This highly restrictive diet, difficult-to-maintain diet should be undertaken under supervision of an appropriately trained clinician. While ketones may themselves offer short-term benefit, the dietary pattern commonly used to maintain a state of ketosis (e.g., high in meat and dairy and low in fruit, vegetables, grains, and legumes) are incongruent with the patterns associated with neuroprotection in the epidemiologic data (e.g.,

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abundant fresh fruit, low in meat and dairy). While it is theoretically possible to maintain ketosis on a plant-based diet, little is known about whether such a restricted diet is sustainable or whether it would offer additional benefits over a ketogenic- or plant-based diet alone.

Mediterranean-DASH diet Intervention for Neurological Delay Diet

The MIND diet was designed not only to incorporate elements of the Mediterranean diet and the Dietary Approaches to Stop Hypertension (DASH) diet but also to incorporate foods reflective of the current evidence for neuroprotection. A prospective study of over 1,000 Australian individuals demonstrated that the MIND diet, but not the Mediterranean diet, reduced the risk for cognitive impairment of the 12-year observation period (90).

Mediterranean Diet

The Mediterranean Diet is one of the most well-studied dietary interventions for neurological disorders. The phenols of extra-virgin olive oil have been proposed as one of the primary bioactive constituents of the Mediterranean Diet, although the abundant intake of fresh fruit, vegetables, and fish are also components (91). The Mediterranean Diet is being studied for a range of neurological disorders, particularly Alzheimer's disease, PD, and amyotrophic lateral sclerosis (ALS) (92).

Gluten-Free

Neurological symptoms, such as seizure, ataxia, confusion, or neuropathy, may be the first or only symptoms of celiac disease. Celiac disease and non-celiac gluten sensitivity are associated with inflammation and nutrient malabsorption, which can result in nutritional deficiencies with neurological consequences. Celiac screening is indicated for individuals with otherwise unexplained neurological symptoms (93).

CLINICAL HIGHLIGHTS

The specific role for nutritional management of neurologic conditions as defined by outcome data is accumulating at a rapid pace. Malnutrition is a common sequela of chronic, disabling neurologic conditions and can be prevented through continual monitoring and early intervention. Diet and symptom diaries are a simple and expedient means of identifying dietary triggers of headaches, in particular migraines. The use of dietary interventions for the management of seizures, alone or in combination with pharmacotherapy, is well established. The therapeutic efficacy of the ketogenic diet is supported by definitive evidence, but the circumstances under which it should be applied remain controversial. Modifications of this dietary approach, such as the Atkins diet, may offer therapeutic efficacy along with relative ease and palatability. Vitamin D supplementation, n-3 fatty acid supplementation, and restricted intake of saturated fats, particularly dairy, beef, and pork, may offer specific benefit in MS and are defensible on the basis of other likely health benefits (see Chapter 45). A growing body of evidence suggests that Mediterranean and MIND diets offer protection against development of AD and PD.

Although direct evidence of specific neurologic benefit is lacking, the preponderance of evidence suggests a nutrient-dense, plant-based diet high in marine-based omega-3 fatty acids could be expected to be supportive of optimal neurologic health on theoretical grounds. This is the dietary pattern that has been attributed to the longevity observed in the Blue Zones and the pattern that offers benefit with regard to immune function (see Chapter 11), susceptibility to inflammation (see Chapter 20), cognitive function (see Chapter 35), brain development (see Chapter 29), and susceptibility to cerebrovascular disease (see

Chapter 10). Thus, although largely indirect, the evidence linking dietary practices to the prevention and mitigation of neurologic disorders is substantial in the aggregate.

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Chapter 22

Diet and Dermatoses

Tarah Freyman

INTRODUCTION

Common ailments of the skin are often related to hypersensitivity and autoimmunity. These states are in turn influenced by diet. Cutaneous manifestations of food allergy and intolerance are prevalent; many of the dermatologic conditions influenced by food are atopic responses to food itself (see Chapter 24). Atopic dermatitis (AD) is a condition that may respond to dietary manipulations. Gluten enteropathy often presents with dermatitis that may be evident even in the absence of overt gastrointestinal symptoms. Some studies suggest benefits of microbiome modulation and omega-3 fatty acid supplementation in the treatment of dermatitis. There is an array of dermatopathology associated with alcohol consumption, and there is some evidence that ethanol tends to exacerbate autoimmune dermatoses. In nickel-sensitive individuals, the nickel used in stainless steel cookware may induce dermatitis. Increasing evidence is suggestive of a link between high-glycemic-load foods with acne development and psoriasis. Further, psoriasis symptoms may be improved with low-energy diets rich in fruits, vegetables, and *n*-3 fatty acids. Highly processed diets, refined sugar, saturated fat, and trans fat may exert adverse influences, whereas vegetables, fruit, and organic foods free of contaminants may reduce the risk of nutrition-related dermatopathology.

OVERVIEW

Effects of the overall quality of the diet on the health and integrity of the skin are well established. Skin is a complex tissue, or group of tissues, with a high rate of cellular turnover, and is thus dependent on a consistent intake of diverse nutrients. Epidermal regeneration requires approximately 2 weeks, and malnutrition can affect this process, resulting in skin dryness, atrophy, and wrinkling. Acute dermatitis has been observed with mixed nutrient deficiencies in the aftermath of surgery (1). The influence of specific micronutrients on skin health is addressed in Chapter 4, and the importance of diet and nutrients to wound healing (2,3) is covered in Chapter 23. The effects of nutrition on vascular health, immune function, and even weight have important indirect effects on the health of skin, also addressed in other chapters.

Nutrition can affect the development of allergies during intrauterine development, after birth during breastfeeding or bottle-feeding, and later after weaning when other foods are introduced (4). Cutaneous reactions, encompassing pruritus, urticaria, angioedema, AD, and even contact dermatitis of the oral cavity, are a common expression of food allergy and intolerance (5,6) (see Chapter 24). Food additives have been implicated in chronic urticaria, although it appears that often combinations of additives are responsible, increasing the challenges in identifying the offending compounds and removing them from the diet (7).

Food allergy has been attributed to abnormal permeability of the bowel wall to dietary antigens. When a “leaky gut” develops, the immunogenic molecules, bacterial toxins, and pathogens penetrate deeper and may accumulate in the skin, disturb the epidermal barrier, and lead to chronic skin inflammation and

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immune response (8). The inability of the small intestine to operate as a barrier may lead to subsequent vascular alterations and malabsorption with secondary vitamin and amino acid deficiency (9). Chronic urticaria has been associated with increased gastrointestinal permeability in at least a subgroup of affected patients (10). Research also indicates the possible role of a gut–skin connection in rosacea, and in one particular study patients with rosacea were 13 times more likely to have Small intestinal bacterial overgrowth (SIBO), which may trigger increased circulating cytokines (11). Probiotic bacteria (see Chapter 18) are posited to improve gut barrier function and to consequently offer a defense against and potential treatment for dermatoses like AD and rosacea, in addition to other manifestations of food allergy and intolerance (12). A previous clinical trial suggests that a 3-month course of synbiotics (probiotic bacteria in combination with "prebiotic" fructo-oligosaccharides) and prebiotics alone can both significantly ameliorate the course of AD in children age 2 and older (13). A more recent study demonstrated that supplementation with *Lactobacillus rhamnosus* reduced the cumulative risk of eczema by age 2 (14). Multiple reviews examining randomized controlled trials on the effects of probiotic use for reducing AD have shown some evidence for the benefits of probiotics (15,16). Data from animal models strongly suggest a protective role for short-chain fatty acids produced upon fermentation of fiber and oligosaccharides (propionate, butyrate, acetate) as a mechanism for microbiota influence on allergies (4).

Atopic eczema is known to flare following the ingestion of allergenic foods. A reduced ability to metabolize histamine in food may contribute to dermatitis in a subgroup of patients (17). Identifying and avoiding culprit foods may ameliorate the course of the condition. Associations between AD and high intake of refined sugar, high intake of saturated fat, low intake of *n*-3 fatty acids, low intake of fruits, and low intake of vitamin D have been reported, although the clinical importance of these observational data remains uncertain (18).

The clinical manifestations of gluten enteropathy (see Chapters 18 and 24) often involve the skin (19). Gluten and its major protein fractions, gliadin and glutenin, are present in wheat, rye, barley, oats, related species and hybrids, and processed foods (20). Well-characterized clinical associations include dermatitis herpetiformis (DH). Patients with DH often have malabsorption. A gluten-free diet improves absorption of essential nutrients and prevents alimentary deficiencies of iron, vitamin B_{12}, and folate (21). Alopecia, angular stomatitis, aphthous ulcerations, and psoriasis have been associated as well (22). Chronic, intermittent urticaria may also be seen in children and adults (23). Occasionally, cutaneous manifestations of celiac disease are seen in the absence of any other overt signs or symptoms (24). A high index of suspicion is required in such cases, and diagnosis is facilitated by general awareness of the potential link between food intolerances and otherwise chronic, enigmatic dermatopathology. Removal of gluten from the diet reliably ameliorates the cutaneous as well as the gastrointestinal symptoms resulting from celiac disease.

The association between heavy, chronic alcohol intake and pathology of the skin is long established. Less well known is the potential contribution of lesser alcohol consumption to dermatopathology (25). Alcohol intake may induce, or exacerbate, psoriasis, cutaneous infections, and eczema. *Excessive consumption of alcohol*—a term that implies variable intake depending on individual vulnerability to adverse effects—is also associated with acne, rosacea, porphyria cutanea tarda, pruritus and urticaria, seborrhea, and increased susceptibility to superficial skin infections (26,27). Many of these conditions develop long before the well-characterized cutaneous stigmata of chronic alcohol abuse and liver disease, such as spider angiomata. Familiarity with the diverse dermal manifestations of alcohol may help reveal an otherwise occult alcohol problem (27). Control of alcohol intake may meaningfully improve the course of otherwise refractory dermatoses, particularly psoriasis (28). Studies have shown that serum biotin levels are significantly lower with chronic alcohol abuse, and animal studies suggest decreased

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intestinal biotin absorption and decreased renal biotin reabsorption with chronic alcohol feeding (29,30). Biotin deficiency (BnD) is commonly associated with skin inflammation, including seborrhoeic dermatitis. BnD causes abnormalities in fatty acid composition, such as accumulation of odd-chain fatty acids and abnormal metabolism of long-chain polyunsaturated fatty acids (31). Loss of epidermal Langerhans cells and subsequent acrodermatitis enteropathica-like erythema are common phenomena in diseases related to nutritional deficiencies (31), as is seen in chronic alcoholism.

The important influence of essential fatty acid intake on eicosanoid production and inflammation is addressed extensively throughout the text (see Chapter 11). Essential fatty acids influence inflammatory markers relevant in dermatitis (32,33), and there is evidence that *n*-3 fatty acid intake may influence the course of several chronic skin conditions. The pattern of fatty acid intake may have some effects on overall atopic tendencies, with *n*-3 fatty acids exerting a protective influence (34). The evidence in this area is preliminary, and debate over the relative importance of total amounts of ingested fat in various classes versus the ratio of one intake level to another (in particular that of *n*-6 to *n*-3 polyunsaturated fatty acid) is lively.

A trial of alpha-linolenic acid, an *n*-3 fatty acid, for AD in a mouse model was negative (35). In a small sample of adults hospitalized with AD, Mayser et al. (36) saw improvement with infusion of either *n*-3 or *n*-6 fatty acid emulsions. Others have seen beneficial effects of both *n*-3 and *n*-6 fatty acids (37). Consistent with this finding is a suggestion that atopic eczema may derive, at least in some cases, from a minor defect in essential fatty acid metabolism, specifically the failure to convert linoleic acid to gamma-linolenic acid, an *n*-6 fatty acid, and other long-chain polyenes, for which supplementation may be compensatory (38). Newer studies have demonstrated that gamma-linolenic acid supplementation has limited to no effects on reducing AD (39–41). Further, a recent review failed to support that *n*-3 and *n*-6 supplementation was beneficial for prevention of allergic disease (42).

Maternal diet components, such as polyunsaturated fatty acids, probiotics, and prebiotics, may have a protective effect on allergy development (4). There have been studies demonstrating the risk of breast milk high in saturated fats and low in *n*-3 fatty acids in the development of AD in infants (43). A study showed *n*-3 supplementation during pregnancy resulted in decreased childhood asthma and food allergy (44). Dunstan et al. (45) tested the influence of fish oil supplementation during pregnancy, beginning at gestational week 20, on atopy in newborns. There was no difference between groups in the rate of AD, but disease severity was less in the supplemented neonates. Cytokine levels and skin prick test responses differed significantly between groups, suggesting a reduction in atopy with fish oil administration. Others have suggested that *n*-3 fatty acids may show more promise in the prevention than in the treatment of atopic disease and that supplementation in utero or infancy may be of particular benefit (46). A recent randomized control trial observed a decrease in atopic eczema and egg sensitization with *n*-3 fatty acid supplementation in pregnancy; however, the overall incidence of immunoglobulin E-associated allergies was not diminished (47).

Atopic and Contact Dermatitis

Delayed introduction of solid food in infancy is thought to attenuate the risk of atopy, although recent birth cohort data do not lend much support to this notion (48,49). Some benefit of delaying solid food past 4 months of age is possible, though studies do not support an association between delayed introduction of solid foods beyond 6 months of age with AD prevalence (50). A recent study showed early weaning, defined as the introduction of solid foods at 4 or 5 months of age, was inversely related to the risk of AD, with children weaned at 4 months having lower AD risk (Odds ratio [OR] = 0.41, 95% Confidence interval [CI], 0.20–0.87) compared to those exclusively breastfed (51). Whether more extended periods

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of breastfeeding defend against food allergy is uncertain; however, exclusive breastfeeding for 6 months or longer is advisable on other grounds (see Chapters 27 and 29). Breastfeeding may decrease AD in infants, and hydrooverall atopic tendencies, with lyzed formulas may be preferred over cow's milk formulas if breastfeeding is not an option (52). Antigen avoidance during pregnancy and lactation has been considered as a possible strategy for minimizing atopy in high-risk patients, yet a recent systematic review failed to demonstrate adequate evidence for antigen avoidance. Of note, it is important to consider the possible nutritional deficiencies that may arise from suggesting such a diet (53). Evidence suggests that strict diet management is not effective in the treatment AD in the vast majority of patients (54). Dietary change should likely be guided by the results of testing (11).

Several foods that are universally consumed throughout the world contain potent allergens, including nickel, balsam of Peru, trace metals, urushiol, and sesquiterpene lactones, as well as a host of others that may cause a distinctive clinical picture (55). Nickel, which may be present in black tea, nuts, seeds, chocolate, cocoa powder, grains like oats, buckwheat, and wheatgerm; certain vegetables like asparagus, cauliflower, and spinach; certain fruits like bananas and pears; and certain canned goods and processed foods, can potentially induce contact dermatitis with secondary generalization (56). Systemic contact dermatitis is a distinct T-cell-mediated immunological reaction, in which dietary exposure to specific allergens results in dermatitis (57). Nickel from food, from water, or released from stainless steel cookware has been implicated (56,58). The removal of nickel from stainless steel formulations is suggested (58). Nickel-sensitive individuals should substitute alternatives for stainless steel cooking utensils.

Acne

There has been an association between diet and acne since the 1930s. Bowe et al. (59) provided epidemiologic data suggesting an association between dairy and acne, and high glycemic loads may exacerbate acne. Additional studies have added further support for the influence of high-glycemic-load diet, milk (possibly more so with skim milk (11)), and hormonal mediators on increasing acne risk (60–63). Western diet influences acne by increasing insulin and modulating Forkhead box protein (FOX01)/Target of Rjpamycin (mTOR), resulting in over-expression of cytokeratins, hyperproliferation of keratinocytes, and hypercornification of the follicular wall (64). A low-glycemic-load diet, one rich in plant fibers and low in processed foods, has been linked to an improvement in acne, possibly through attenuation of insulin levels or gut changes (65). Gut microbiota may indeed be involved in the pathogenic process of acne. For example, stress has been hypothesized to aggravate acne by altering the microbiome and increasing intestinal permeability, which potentially contributes to skin inflammation (66). We may also assume that Western diet affects the gut flora in a way that leads to the increased induction of the Insulin-like growth factor (IGF-1) pathway (8).

Psoriasis

Psoriasis, an inflammatory skin disease marked by keratinocyte hyperproliferation and abnormal differentiation, is primarily a genetic disease but has been associated with certain dietary habits. Specifically, low-energy, plant-based diets rich in *n*-3 fatty acids, and gluten-free diets have shown to improve psoriasis symptoms (67). Nutrition is not well studied in regards to psoriasis treatment; however, obesity and diets low in fruits and vegetables have been associated with worse symptoms. A prospective randomized trial found that obese psoriatic patients treated with a low-energy diet had improved dermatologic involvement and significantly better Dermatology Life Quality Index (68). There have been several findings of decreased antioxidant levels in psoriatic patients, which could potentially

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be remedied by adequate fruit and vegetable intake. Additionally, psoriasis is common in patients with insulin resistance, which is in turn exacerbated with foods containing a high glycemic index (69). Further, oral vitamin D supplementation can decrease keratinocyte proliferation, as well as minimize psoriatic arthropathy (70). In terms of nutritional supplements, vitamin D and fish oil appear to have the most promise, while there is limited evidence for benefit of vitamin B_{12} and selenium (11).

Skin Cancer

The effects of nutritional factors on cancer has been an active area of research for several decades. Early epidemiological studies have demonstrated an association with diet and cancer, specifically, a reduced risk of cancer at all sites with increased fruit and vegetable intake (71). There are emerging data suggesting that certain dietary factors may alter the risk for developing skin cancer in particular. Adherence to the Mediterranean diet is associated with a lower skin cancer risk in women, particularly melanoma and Basal cell carcinoma (BCC), when compared to a typical Westernized diet (72). It was originally thought that beta-carotene supplementation may be protective for patients with prior nonmelanoma skin cancer against tumor recurrence; however, subsequent studies were unsupportive (73). Selenium supplementation was also not beneficial in preventing basal cell carcinoma in skin cancer patients and, interestingly, increased the risk of nonmelanoma skin cancer (74). Meanwhile, recent research shows that nicotinamide (a derivative of vitamin B_3) may be chemopreventive against skin cancer due to its ability to augment cellular Deoxyribonucleic acid (DNA) repair mechanisms and counteract Ultraviolet (UV)-induced immunosuppression (75). Numerous studies have demonstrated the ability of nicotinamide to decrease the incidence of new nonmelanoma skin cancers (NMSCs) and Actinic keratosis (AKs) in susceptible individuals (75). The effect of a low-fat diet intervention on skin cancer patients demonstrated a significantly lower recurrence of nonmelanoma skin cancer after 8 months of intervention (76). Further, plasma levels of beta-carotene, as well as other micronutrients, including lycopene, retinal, alpha-carotene, alpha-tocopherol, carotene, and vitamin E, did not alter risks for malignant melanoma. Although, reduced risk for melanoma was observed with decreased alcohol consumption (77). A Danish population-based case–control study, however, found no association of diet and alcohol on risk for malignant melanoma (78). Caffeine has been associated with a lower risk of melanoma, while alcohol and surprisingly citrus fruits with increased risk (79). Because vitamin C has preferential toxicity for melanoma cells, the increased melanoma risk associated with citrus fruits high in dietary vitamin C is likely the effect of other components (e.g., photoactive compounds such as psoralens and furocoumarins, a group of naturally occurring chemicals that, through sensitizing the skin to UV radiation, may have photo-carcinogenic properties) (79). Associations between polyunsaturated fatty acid, niacin/nicotinamide, folate, and vitamin D with melanoma remain controversial (79). Diet likely influences melanoma development through several potential mechanisms, such as enhancing UV-induced apoptosis and increasing photosensitivity (79).

CLINICAL HIGHLIGHTS

The adequacy and quality of the diet have important implications for the overall health and integrity of skin. Food intolerance and food allergy commonly manifest with cutaneous reactions, and chronic dermatitis often relates to food intolerance. AD in children and chronic dermatitis or pruritus in adults warrants assessment of the diet with a food and symptom diary to probe for dietary triggers. Elimination of such foods or food additives can be of therapeutic value. Gluten enteropathy is a noteworthy example of food allergy in which skin manifestation may predominate, at least early, and for which removal of the

offending food item, in this case gluten, is considered standard treatment.

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Irritants in both food and cookware may induce dermatitis; nickel in stainless steel is a notable example. Contact dermatitis of the mouth may secondarily generalize, but a careful history that reveals the original site of symptoms will help disclose the source.

Alcohol intake, in some cases at levels that would not otherwise be deemed excessive, can induce and exacerbate a wide array of dermatoses, including eczema, cellulitis, and psoriasis. In patients with chronic dermatitis or pruritus, a therapeutic trial of alcohol avoidance is warranted.

The anti-inflammatory effects of *n*-3 fatty acids are well established; a role in the treatment of inflammatory skin conditions is less clear. Fish oil supplementation in pregnancy may reduce atopic tendencies in newborns, raising the prospect that *n*-3 fatty acids are of greater utility in preventing than treating AD. The evidence of treatment effects is equivocal, but there is a strong case for *n*-3 fatty acid supplementation on other grounds. Thus, a trial of fish oil for any chronic or refractory dermatitis is reasonable. A standard adult dose of fish oil is roughly 1 g, twice daily.

Abnormal intestinal permeability has been invoked to explain food allergy and associated dermatoses. The literature is suggestive of potential benefits of probiotics (live bacteria, found in foods with active cultures and supplements), prebiotics (plant fibers that feed the microbiome), and their combination in synbiotics. A course of probiotics is of potential benefit and unlikely to cause harm in any case of chronic dermatitis or pruritus. However, the optimal dose, bacterial strains, and treatment duration remain unclear (11).

There is some suggestion that dermatitis risk increases with intake of refined sugar and saturated fat typical of a Westernized diet, and declines with intake of several micronutrients, fruits, and unsaturated oils. The link between high-energy foods and worsening acne and psoriasis has become increasingly evident. Additionally, current studies are observing new associations between nutritional factors (like nicotinamide found in legumes, nuts, grains, and mushrooms) and skin cancer. Overall, these associations indicate that a dietary pattern emphasizing consumption of whole, plant-based foods advisable for purposes of general health promotion (see Chapter 45) may reliably offer some protection against and treatment of various important dermatoses as well.

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Diet and Wound Healing

Victoria Fischer

INTRODUCTION

Overall nutritional status influences the response of the body to metabolic stress. Wound healing requires sufficient nutritional substrate to support the formation of granulation tissue. Adequate intake of energy, protein, and various micronutrients before, during, and after either surgical or traumatic injury can influence the speed and vitality of tissue repair. Nutritional assessment and management strategies for the promotion of optimal wound healing have been investigated, although evidence for certain interventions remains preliminary.

OVERVIEW

A patient's nutritional status is of vital importance to tissue repair in the advent of injury. Susceptibility to skin breakdown and the development of pressure injuries are related in part to nutritional status (1), whereas wound development increases metabolic demand (see Table 23.1 and the following paragraphs). The adequacy of various micronutrients, total protein, and total energy influences wound healing. Metabolic demand increases during wound healing, increasing the likelihood of negative nitrogen balance and catabolism. Energy, protein, and micronutrient deficiencies are among the most common impediments to optimal wound healing (2).

Additionally, wound infection has the potential to disrupt the healing process, while placing further metabolic demands on the patient. The adequacy of nutrition during wound healing has systemic effects on immune function (see Chapter 11) and healing, thereby influencing susceptibility to infections and delayed healing (3).

Wound healing takes place in three phases. It starts with an inflammatory phase that typically lasts up to 6 days. The proliferative phase starts within 3 to 5 days after injury and lasts for up to 3 weeks. In this phase, fibroblasts proliferate, new blood vessels emerge, and epithelialization and wound contraction occur. The third phase starts about 2 weeks post injury and lasts up to 2 years. In this phase, collagen maturation and stabilization take place, for increased tensile strength and scar formation. Obviously, the length of each phase varies with individual conditions (4).

Nutritional Implications of Wounds

Energy Requirements

Metabolic demands can be expected to vary in each phase, and even within each phase of healing, as clearly seen in extreme wounds like large surface area burns. Overall, caloric needs increase, depending on age, comorbidities, body weight, severity of wounds, etc. Requirements of 30 to 35 kcal/kg/day are estimated, with higher requirements for underweight patients (4). Both overfeeding and underfeeding lead to adverse outcomes, particularly in critical care patients (5).

Protein

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There is also no question that protein requirements are increased in wound healing. Protein is essential to the process for immune response, formation of new cells, and extracellular matrix. Loss of lean body mass (LBM) occurs easily in wound healing and can be extreme, with severe wounds or aggravating circumstances or comorbidities (4). The associated risk is impairment of immune reactions, starting at a loss of about 10% of LBM, and increasing competition between the demands of wound healing and demands from the muscle tissue. This leads to decreases in the rate of wound closure at about 20% of LBM lost. Loss of about 30% of LBM halts wound healing and predisposes the patient to new wound formation, and higher losses are less compatible with life (4). Specific recommendations for protein provision vary between wound types (see Table 23.1).

TABLE 23.1

Summary of Nutrition Recommendations for Wounds

	Energy	Protein	Lipids and carbs	Other nutrients
Surgical wounds	25 kcal/kg (6)	1.5 g/kg (6)	*n*-3 fatty acids to be considered (4,6)	Glutamine at 0.5 g/kg/day to be considered, others under investigation (2,6,15) Synbiotics under investigation
Pressure injuries	30–35 kcal/kg (8)	1.0–1.5 g/kg (8)	No specific recommendation	Arginine 4.5 g/d, or 500 mg vitamin C with 17 mg zinc and 3.0 g arginine daily (7,8,21)
Chronic wounds	No specific recommendation	No specific recommendation	No specific recommendation	Deficiencies to be corrected: Vitamin A, E, zinc (4,9,11,25)
Burn wounds	Up to 170% of BMR (26)	1.5–2.0 g/kg for adults, 2.5–4.0 g/kg for children (2,26)	Lipids maximum 15% of total energy (2), carbohydrates limited by maximum glucose oxidation rate, ~7 g/kg/day (2)	Vitamin C at 500–1,000 mg/day in divided doses, up to 2 g/day in severe wounds (2)

BMR: Basal Metabolic Rate.

Lipids

Provision of lipids must be seen in the context of the severity of injury; see burn wounds later. One specific aspect to consider is the ratio between omega-3 and omega-6 fatty acids. Both are needed for production of various signaling molecules. Inflammatory mediators built from omega-6 fatty acids have a stronger inflammatory effect than the same type of mediator built from omega-3 fatty acids. The balance between the two types accordingly matters to achieve a level of inflammation that optimally promotes healing. A 1:1 ratio between omega-6 and omega-3 fatty acids has been proposed (4). Supplementation of n-3 fatty acid postsurgically, and potentially perioperatively, is somewhat supported, although evidence is not strong enough at this point for a definitive recommendation across guideline-issuing entities (6).

Fluids

Fluid requirements are affected by wounds, both in terms of losses from the wounds and as a consequence

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of the metabolic reaction to the wounds as physiologic stress, which can lead to initial fluid accumulation. Aggressive fluid resuscitation can aggravate the situation, and fluid status has to be taken into account during nutrition assessment. The risk of dehydration is particularly high in the older population as they may experience a decreased sense of thirst, in addition to psychological, physiological, medical, and other difficulties associated with their age that can prevent them from taking in enough fluids (1).

Amino Acids

Much attention has been given to specific nutrient and non-nutrient components for wound healing. Based on their physiologic functions, arginine and glutamine have received substantial attention in research, and glutamine supplementation at 0.5 g/kg/day is recommended for consideration during major surgery (6), in line with other suggestions of 25 to 35 g/day (2). Glutamine improves gut function, presumably because it serves as fuel to some immune cells and enterocytes and improves insulin sensitivity. It furthermore plays a central role in maintenance of cellular redox balance as part of glutathione (2).

Arginine is a precursor for nitric oxide needed for the inflammatory process, and as precursor for proline, needed for production of collagen (2). Its use is not without risk though, so it should be considered in the context of the specific type of wound and patient circumstances. It is, for example, part of recommended supplements for malnourished patients undergoing major cancer surgery (6). One of the major difficulties evaluating the potential benefit of arginine is that it is often given with other supplements, making it difficult to evaluate separately (7). It is specifically recommended for use in patients with pressure injuries, in combination with zinc and antioxidants (8).

Vitamins

It has long been known that vitamin A, or retinoids, exerts an anti-inflammatory effect in open wounds and enhances wound healing even in non-deficient states. Deficiency impairs wound healing (9). Wounds like burns, fractures, or surgical interventions all cause decreased plasma levels of vitamin A and retinol-binding protein, and increased urinary excretion of vitamin A. This decrease can turn a subclinical vitamin A deficiency, which does exist in the United States, into a clinical deficiency. Increased cortisol activity, from endogenous or exogenous sources, further decreases plasma levels and additionally decreases levels in liver and adrenal glands, worsening vitamin A status (10). Supplementation of 25,000 IU before and after surgery has been suggested, particularly for patients with sepsis, fractures, tendon damage, vitamin A deficiency, immunodeficiency, or treated with corticosteroids (10), and similar short-term regimen for patients with chronic wounds and some other situations are used in practice (e.g., 15,000–20,000 IU daily orally, for 14–21 days)(11). These protocols are based on expert opinion though as most experimental data on vitamin A supplementation still stem from experiments in rodents. Some evidence from studies with human subjects supports use of topical retinoids around cosmetic surgery, to reduce scarring and improve age-associated wrinkles. Topical use for chronic wounds has also shown benefit in chronic leg ulcers and diabetic foot ulcers (11). Those trials are as of now insufficient in size and number for reliable conclusions.

Vitamin C deficiency in wound healing is best known for carrying the risk of wound dehiscence. It is also needed for the immune response and to maintain redox balance as it acts as a reducing agent (4). Vitamin C is often included in mixed supplements.

There is some evidence that pantothenic acid (vitamin B_5) supplementation can increase the tensile strength of aponeuroses and dermal scars. Thiamine is essential to bridge formation of collagen, for metabolism and when body reserves are small (12). Neither, however, has been sufficiently researched to be included in recommendations in the United States.

Minerals

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Zinc is required for multiple enzymes involved in wound healing, for cell replication, nucleic acid metabolism, and redox balance (e.g., superoxide dismutase). Accordingly, decreased levels impair the immune system and affect all phases of wound healing. The hypermetabolism associated with stress, sepsis, and burns is considered a common cause for zinc deficiency, and levels below 100 µg/dL are associated with decreased fibroblast proliferation and collagen synthesis (9). Thus far, it is thought that supplementation is only helpful in patients who are zinc deficient though, and excessive zinc interferes with absorption of iron and copper (4,9). Recommended amounts range from 40 mg/day up to 220 mg twice daily, for 10 to 14 days (4). A recent systematic review and meta-analysis of controlled clinical trials on zinc supplementation for healing of pressure injuries support these recommendations by demonstrating that the supplementation significantly improves healing (13).

Iron deficiency impairs immune function and decreases tensile strength and synthesis of collagen. However, supplementation may prolong inflammation and does not appear to benefit wound healing (4). Deficiencies need to be carefully diagnosed and are then readily treated (9).

Copper is required for crosslinking of collagen, as part of the enzyme lysyl oxidase (4); thus, its involvement in wound healing is clear. It is supplemented with beneficial effects in patients with burn wounds, together with zinc and selenium (14).

Selenium is needed for redox balance, particularly via glutathione peroxidase, and reduced serum levels have been observed (e.g., in patients with burn wounds) (14). However, the benefit of supplementation is uncertain (4), beyond its use in the mixed supplements of trace elements.

Non-nutrients

Use of probiotics for wound healing has been studied extensively in animal models. Oral administration of probiotics has only been investigated in humans in surgical patients. Results generally show positive findings, though not in all studies. Surgical site infections tend to occur less frequently, and some studies show a statistically significant lower incidence of systemic infections and infections at sites distinct from the surgical wound (e.g., urinary tract infections and pneumonia) which improves healing indirectly (6,15). Much more work in this area is needed to define whether there is consistent benefit, if benefit depends on surgical site or intervention, and which combination of strains of probiotics is most helpful.

A few bioactive components are under discussion for possible benefit for wound healing. One such component is curcumin. Curcumin reduces the expression of pro-inflammatory cytokines and inhibits nuclear factor kappa B. It acts as a reducing agent, thus as antioxidant, and contributes to the production and activity of antioxidant enzymes, including glutathione. It promotes cell migration and differentiation needed for wound healing (16). As curcumin is hydrophobic and subject of extensive first-pass metabolism, bioavailability from oral administration is low (16). Numerous studies have been conducted successfully in rodent models, but clinical studies in humans are missing at this point. Research is underway to improve bioavailability.

Another bioactive component in early stages of research is Pricroliv, from roots and rhizomes of *Picrorhiza kurroa*. Picroliv improved re-epithelialization, neovascularization, and migration of various cells into the wound bed in a study on rats, at a dose of 12 mg/kg body weight (17). Arnebin-1 from the root of *Arnebia nobilis* has also been used successfully for wound healing in rats topically (17).

Mixed supplements used as “immunonutrition” receive mixed reviews, and it is difficult to evaluate evidence in meta-analyses as the interventions differ in many aspects. A recent Cochrane review, for example, found no significant effect except for reduced likelihood of fistula formation in adult head and neck cancer patients provided with immune-nutrition formulas containing arginine, typically in

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combination with omega-3 fatty acids, glutamine, and ribonucleic acids. It must be noted though that 7 out of 16 of the studies used for this meta-analysis excluded malnourished patients (18). This note alone underlines the heterogeneity of available studies that makes it difficult to draw conclusions from available data.

Studies in other subgroups of patients are more supportive of use of immunonutrition. A meta-analysis of about 2,000 patients undergoing upper gastrointestinal surgery, for example, found strongly supportive evidence for immunonutrition, showing reduced risk of wound infection without increasing other morbidities and mortality, in addition to reduced length of hospital stay. In this review, immunonutrition was compared to standard enteral nutrition (19). Similarly, a meta-analysis on about 1,000 patients undergoing surgery for colorectal cancer supports use of enteral immunonutrition, compared to standard enteral nutrition, with reduced length of hospital stay, and reduced complications from infections (20). A meta-analysis on 273 patients with pressure injuries supports efficacy of supplements typically containing zinc, arginine, and antioxidants to support healing when support is given for at least 8 weeks (21). Based on these data, use of immunonutrition supplements must be evaluated specific to the patient's medical condition (e.g., characterized by location of the wound or underlying condition).

A different aspect of therapy is the use of nutrition to assist in removal of fibrin barriers. Proteases including chymotrypsin and trypsin, bromelain, papain, some fungal proteases, and serratia peptidase have been used successfully for this purpose to restore circulation to areas blocked off by fibrin clots that result from fibrin exudates following trauma to soft tissue or skeletal injury. Interestingly, these enzymes can be absorbed without losing functional activity. They are then bound by circulating enzyme inhibitors that usually block fibrinolysis and maintain the inflammatory edema. Provision of the additional enzymes facilitates the action of plasmin by binding its inhibitors (22). Trypsin, for example, is known to enhance activity of natural killer cells, and reduce the effect of pro-inflammatory cytokines like tumor necrosis factor alpha, interleukin 1 and interferon gamma. A randomized controlled trial testing the efficacy, safety, and tolerability of three different combinations of enzymes for wound healing on surgical wounds after orthopedic surgery found that a combination of trypsin and chymotrypsin, applied orally, yielded good results in various aspects of wound healing. Unfortunately, the study was small and did not include a control group with no enzyme treatment (22).

It should be noted that in addition to adequate nutritional support, pain control, conditioning exercises, and anabolic agents may contribute to preservation of LBM and to wound healing (2,6).

Nutrition Support for Different Types of Wounds

Surgical Wounds

Surgery is a form of trauma, and accordingly leads to a stress response (6). Evaluation of all patients' nutritional status should be performed before elective surgery. In patients with no clinical evidence of compromised nutritional status and who are clearly robust preoperatively, no laboratory testing is indicated. Patients with recent weight loss or who are chronically underweight require a more extensive evaluation (see Chapter 26 and Appendices A and D). A comprehensive assessment of nutritional status includes measures of dietary intake pattern, anthropometry, and biochemical assays. Dietary consultation in such cases is indicated. Preoperative nutritional support may be important to postoperative healing (6). Total parenteral nutrition (TPN; see Chapter 26) is an intervention of last resort; it has been shown to reduce noninfectious complications of surgery in select patients while increasing infectious complications. Accordingly, enteral or oral nutrient intake is the preferred route, and combination of enteral with parenteral nutrition can be used when the enteral nutrition is insufficient (6).

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In general, preoperative nutrition support, or prehabilitation, is recommended for patients with severe nutritional risk, and surgery may have to be delayed where possible, for up to 14 days. Severe risk is defined as weight loss of more than 10% to 15% within 6 months, body mass index (BMI) <18.5 kg/m_2, Subjective Global Assessment grade C or Nutrition Risk Score >5, or preoperative serum albumin <30 g/L with no evidence of hepatic or renal dysfunction (6).

Additionally, preoperative fasting recommendations have been reduced in their length, and provision of carbohydrates two to three hours before surgery has been found to reduce insulin resistance and to prevent hypoglycemia. Nitrogen loss is lower with this regimen (6). Administration of pre- and probiotics presurgically is used to improve mucosal immunity (6). There is some evidence that preconditioning with glutamine, antioxidants, and green tea extract is beneficial in pancreatic surgery (6).

Postoperatively, delayed gastric emptying and ileus may prevent early feeding. Post-pyloric feeding is often possible in these situations, and access can be placed intraoperatively to enable early feeding, which yields better outcomes (6). A combination of PN with the preferred route of enteral/oral nutrition is recommended to be started on postoperative day 4 for the latest. If the supplementation with PN is expected to be between 4 and 7 days, hypocaloric nutrition with 2 g carbohydrate and 1 g amino acids/kg body weight is deemed acceptable (6). Intensive insulin therapy is recommended when close monitoring of blood glucose levels is possible (6). Additional research is needed to support the benefits of supplementation with omega-3 fatty acids, synbiotics, and immunonutrients like arginine. Supplementation with omega-3 fatty acids for patients who cannot be adequately fed enterally should be considered. Similarly, supplementation with glutamine at 0.5 g/kg/day may be considered, even pre- and intra-operationally. While available evidence is encouraging, studies are too heterogeneous to draw final conclusions (6).

Application of these measures is intended and based on outcomes like reduced infection rate, reduced length of stay in intensive care and in the hospital, indirectly linked to improved healing (6).

Pressure Injuries

Pressure injuries are often counted into the category of chronic wounds. They are treated separately here because of their clear nutritional implications. Pressure injuries have received considerable attention, and several sets of guidelines exist regarding their management. That may be due to their high incidence, at a rate of about 7.48% in long-term care facilities, and 4.5% in hospitals, with an associated cost of $9.1 billion a year (7). As malnutrition is associated with higher risk of pressure injuries (12), nutrition screening and assessment to detect malnutrition are recommended. Food intake, medical diagnosis of malnutrition, anthropometric and biochemical data are to be used. Among anthropometric data, skinfold thickness and arm circumference are included in addition to weight, BMI, and other markers. Attention is drawn to sarcopenia in obese patients (1). It must be noted that pressure injuries are age independent: prevalence of pressure ulcers in neonates and children can be as high as 35%, with the highest rate found in intensive care units, and related to medical devices. They should accordingly be screened for nutrition status, including growth assessment, with weekly re-assessments (1). Oral supplements and nutrition support, as well as feeding strategies are part of the care plan.

For treatment of pressure injuries, the recommended calorie amounts are 30 to 35 kcal/kg body weight (8), although evidence supports a range of 30 to 44 kcal/kg, or a resting energy expenditure × activity factor of 1.1 × stress factor of 1.3 to 1.5 (1). Protein requirements are estimated in the range of 1.25 to 1.5 g protein/kg body weight/day, and oral supplements and enteral nutrition should be considered if food intake cannot be sufficiently improved (1,12). Additionally, supplementation of arginine of 4.5 g/day is suggested, and combinations of 500 mg vitamin C, 17 mg of zinc, and 3 g L-arginine have been used

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successfully. Even though evidence for the latter therapy is not entirely convincing, it appears safe (4,9), is supported by a recent meta-analysis (21) and is included in international guidelines, even though without specific amounts (1,8). The Japanese Dermatological Association additionally recommends monitoring of Thiamin (12).

Chronic Wounds

Chronic wounds differ from other wounds via their prolonged inflammatory response, low levels of growth factors, and increased bioburden on the wound, and malnutrition often contributes to chronicity (4). Chronic wounds include venous leg ulcers, ischemic leg ulcers, mixed arteriovenous ulcers, and diabetic foot ulcers. Pressure injuries are also included (23) but treated separately here (see previous section). Malnutrition is an independent risk factor for chronic wounds (9,23). A systematic review and meta-analysis of nutritional supplementation in chronic wounds finds nutritional supplementation beneficial. However, based on the extreme heterogeneity of interventions and study protocols, no specific regimen could be recommended (23).

A recent systematic review focused on patients with venous leg ulcers found that the majority of those patients are overweight and obese and that being overweight or obese is associated with delayed healing of the ulcers. Additionally, vitamin D, folates, and omega-3 fatty acids may be involved in healing of venous leg ulcers (24). The authors accrue some evidence in favor of folate and flavonoid nutriceutical supplementation. Lower serum vitamin A and D levels were associated with delayed healing, with limited data for this finding. Both being overweight or obese and being underweight (BMI <20) were associated with worse outcomes. Surprisingly, serum vitamin C levels were positively correlated with wound severity. Intake was found below recommendations in about half of patients studied in two small studies (25). While deficiencies in vitamins A, E, carotene, protein, and zinc have been identified and that ulcers heal better when deficiencies are corrected, further supplementation has no effect (25). Supplementation with glutamine for chronic wounds is not as clear-cut as for other wounds, as they are not associated with a chronic inflammatory state. However, if intestinal mucosal atrophy and overall LBM decrease are present, it may still be helpful (4).

Collagen synthesis can also be enhanced with supplementation of a combination of arginine, glutamine, and beta-hydroxy-beta-methylbutyrate (HMB), a leucine metabolite, and improved healing of diabetic foot ulcers in patients with serum albumin levels below 40 g/L in one study (9).

Burn Wounds

Patients with burn wounds experience a hypermetabolic state with severe catabolism, the associated loss of LBM, and a decline of immune function (2). The severity of burns is measured, among other measures, as fraction of total body surface area (TBSA) wounded. Metabolic changes maximize at about 40% TBSA (26). The associated hypermetabolism leads to loss of LBM that can be fatal (2). Nutrition support is needed, yet data on optimal nutrition support of burn victims is still somewhat conflicting. There is some evidence that muscle protein catabolism is lower with early aggressive nutrition, while this intervention is simultaneously associated with increased energy expenditure (2). Other beneficial effects of early nutrition support include decreased stress hormone levels, improved gut integrity, improved wound healing, decreased risk of Curling ulcer formation, and shorter stay in intensive care (2). The International Society for Burn Injury recommends initiation of oral diet or enteral feeding as soon as possible, based on a risk-benefit analysis of early feeding, to maintain intestinal integrity, stimulate the gut-associated lymphatic tissue, and reduce bacterial translocation (26). Provision of nutrition via the enteral round is preferred, with post-pyloric feeding possible in case of gastric ileus (2).

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Total energy requirements of burn victims fluctuate and are poorly predicted by currently available formulas, and overfeeding leads to difficulty weaning from ventilatory support. Despite their shortcomings, the use of predictive formulas is considered an element of best practice (26), and nutrition assessment at least twice weekly is recommended as well (26). Indirect calorimetry remains the gold standard for measurement of energy expenditure though (2). Basal metabolic rate increases to up to 170% in patients with severe burns and can increase even further if excision of burn eschar is not performed early (26). Of note, there are no specific recommendations, due to absence of data, for energy provision in burn patients with obesity (2). Body weight in burn victims must be used with caution as fluid status may change with fluid resuscitation, infections, and other superimposed conditions (2).

Protein requirements in burn victims are estimated at 1.5 to 2.0 g/kg/day for adults and up to 4.0 g/kg/day for children (2,26). High carbohydrate formulas are favored, although the amount of carbohydrates that can be administered is limited by the rate at which it can be utilized (7 g/kg/day in patients with severe burns), without causing hyperglycemia, glucosuria, dehydration, and respiratory problems (2). Therapy with insulin supports healing, among other parameters, such as LBM, bone mineral density, and length of stay. Lipid provision is recommended at a maximum of 15% of total energy, as utilization of fatty acids is limited, and accumulation in the liver has been observed. Provision of excess lipids impairs immune function. There is some evidence that lipid formulas with increased omega-3 fatty acids yield better outcomes in terms of immune response (2), but recommendations have not been issued.

For burn victims, glutamine supplementation has been helpful at a suggested dose of 25 to 35 g/day. This recommendation is supported by research on the multiple mechanisms by which glutamine improves outcomes for burn victims, including decreased infections, decreased length of stay, and reduced mechanical ventilation days (27). Vitamin C supplementation is recommended at 500 to 1,000 mg/day in divided doses, and up to 2,000 mg for extensive burns (2). Supplementation with zinc, copper, and selenium appears safe, with no reported adverse effects, and may be beneficial based on the available data. One meta-analysis showed reduced infectious episodes and suggested reduced length of stay in intensive care (14). Another meta-analysis that included use of vitamins A, C, and E in addition to copper, zinc, and selenium, shows reduced wound healing time, decreased mortality rate, reduced length of stay. and reduced incidence of infection (28). Overall, studies on supplementation in burn victims are heterogeneous in various aspects, making comparison of outcomes difficult, and subject number is small (14).

Special Populations in Terms of Wound Healing

Of increasing relevance is the adverse influence of obesity on wound healing (1). Surgical wound closure and wound perfusion may be compromised by excess subcutaneous fat. Metabolic derangements associated with obesity (see Chapter 5) may interfere with tissue recovery as well. Obese individuals frequently face wound complications, including skin wound infection, dehiscence, hematoma and seroma formation, pressure ulcers, and venous ulcers (1). An increased frequency of wound complications has been reported for obese individuals undergoing both bariatric and non-bariatric operations. Obese patients experience increased operative time, blood loss, length of stay, and wound infection rate. There was no difference in wound dehiscence or venous thromboembolisms reported in one meta-analysis. This analysis included 4,311 subjects who underwent surgery for inflammatory bowel disease (29). Some of these increased risks may be due to a reluctance of surgeons to operate on patients with obesity (29). The visceral fat in particular appears to be predictive of risk, even independent of a high BMI, in some studies (30,31), though not in all (32). Many of these complications may be a result of a relative hypoperfusion and ischemia that occurs in subcutaneous adipose tissue. This situation may be caused by a decreased

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delivery of antibiotics as well. In surgical wounds, the increased tension on the wound edges that is frequently seen in obese patients also contributes to wound dehiscence. Wound tension increases tissue pressure, reducing microperfusion and the availability of oxygen to the wound (33).

Because older patients have reduced appetite possibly compounded by impaired sensorium or functional status, they are highly subject to protein–calorie malnutrition and involuntary weight loss during wound healing (1). In addition, there is no doubt that patients with preexisting malnutrition are more susceptible to complications, including infections and delayed wound healing. With respect to elective surgery, it is recommended to delay surgical intervention to allow improvement of nutrition status (6), and multiple meta-analyses document the increased rate of complications even when using serum albumin as indicator of nutrition status (34,35).

CLINICAL HIGHLIGHTS

The relevance of nutritional status and continued provision of nutrients for wound healing is generally recognized, based on strong evidence. Evidence for specific nutritional manipulations to enhance wound healing capacity is generally less definitive. Patients scheduled for elective surgery should routinely be assessed for the adequacy of their diets, recent weight loss history, and preservation of LBM. Preoperative nutrition supplementation in marginally malnourished patients may be of benefit and is of clear benefit when malnutrition is advanced.

Energy and protein needs are increased in patients recovering from surgical trauma as well as during healing of traumatic wounds. Multivitamin/multimineral supplements are advisable in older adults on general principles and may be of particular benefit in wound healing, as trace minerals (magnesium, copper, and zinc) are involved in wound healing. Supplementation with glutamine and arginine (and combinations) may be of benefit, with rapidly increasing evidence in their favor for specific situations. A beneficial role of n-3 fatty acids has been suggested, and the use of probiotics and synbiotics is under intense investigation, with some promising results.

Dietary consultation to optimize nutrition is prudent in patients with nonhealing wounds, as case reports of rapid recovery following nutritional adjustments have been published. In general, the nutritional guidelines to promote wound healing are consistent with those that can be advocated on general principles. While the use of various supplements has shown promise, no single regimen has yet emerged as the clearly preferred, evidence-based approach (6). Thus, the mainstay of nutritional care in wound healing is individualized assessment and care, with general principles of healthful nutrition underlying.

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Chapter 24

Food Allergy and Intolerance

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INTRODUCTION

Adverse reactions to food include intolerance, a non–immune-mediated abnormal physiologic response, and true food allergy, an immunologic reaction to ingested antigens. Intolerance may be mediated by metabolic processes (e.g., lactose intolerance), contaminants (e.g., bacteria or toxins), or pharmacologic effects of ingested food chemicals (e.g., alcohol, caffeine). True food allergy is typically an antibody-mediated, immediate hypersensitivity response. A cell-mediated, delayed hypersensitivity reaction is well established only for gluten but is posited to occur with other food antigens as well. Other adverse reactions are idiosyncratic. Although there is considerable uncertainty about the epidemiology of food allergy, due to methodological differences and uncertainty in diagnostic testing, the data suggest an increasing prevalence over the past decade with a 2010 meta-analysis displaying a range between 2% and 10% (1), with a reported fatality rate of 1.35 to 2.71 per million person-years (2). The overall improved public health measures and vaccination systems have led groups to believe that the “hygiene hypothesis” is to blame for our increase in atopy. The hygiene hypothesis indicates that the lack of early childhood exposure to infectious disease, crowded environments, and unhygienic conditions increases susceptibility to allergic diseases, such as eczema, allergic rhinitis, and asthma (3). The hygiene hypothesis is supported by observations (3) and by an increasing number of detailed studies regarding the interplay of the microbiota and immune reaction including allergies (4–6).

Generally, the predominant antibody reaction to ingested antigen is mediated by immunoglobulin A (IgA). Systemic hypersensitivity reactions to food are predominantly mediated by immunoglobulin E (IgE), and thus IgE-mediated food allergy is generally deemed most important. True food allergy is broken down into three categories: IgE-mediated (i.e., acute urticaria/angioedema, anaphylaxis, oral allergy syndrome), non-IgE-mediated (i.e., food protein-induced enterocolitis, Heiner’s syndrome), and mixed IgE and non-IgE (i.e., atopic dermatitis, eosinophilic esophagitis). The majority of our discussion will focus on IgE-mediated reactions; these are unique in that they are associated with mediator release from tissue mast cells and circulating basophils. Therefore, these reactions are very rapid in onset (minutes to 2 hours), mainly affecting the skin, gastrointestinal (GI) tract, and respiratory and/or cardiovascular systems. Ingested antigens must traverse the intestinal mucosa and enter the circulation to elicit a hypersensitivity response; thus, food antigens are stable, water-soluble proteins of predictable size. Categorically, any food may cause an allergic response, and over 170 of them have been reported to be linked to IgE-mediated reactions. The foods most commonly responsible for hypersensitivity reactions include eggs, peanuts, other nuts, milk, soy, wheat, fish, and shellfish. Bovine milk allergy is common in infancy.

OVERVIEW

Diet

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The prevalence of true food allergy is estimated at approximately 2% to 10%, although in most self-reported surveys, a much larger fraction of the population believe themselves to have food allergy. A recent study of over 40,000 U.S. adults showed a prevalence of food allergies of 10.8%, while nearly 19% of U.S. adults believe they have a food allergy (7). The gold standard for food allergy testing is a double-blind, placebo-controlled oral food challenge; however, due to the increased risk of anaphylaxis, most of the data relies on retrospective case series studies. Intolerance to food additives is quite uncommon, estimated to be 1 per 10,000 population. The prevalence of food allergy in children under age 1 is estimated at 19.4% to 20.3% in Europe based on positive IgE tests (8); the early identification, management, and prevention of food allergy in infants remain challenging despite improvement in recent years (9). There is some controversial evidence that infections with *Helicobacter pylori* could be inversely related with food allergies, allergic asthma, rhinitis, and eczema (10–13), supporting the hygiene hypothesis. Mechanistically, *H. pylori* infection is a double-edged sword. While it increases permeability of the gastric epithelium, allowing passage of intact food proteins (13), it also includes immune-modulating proteins undergoing research as therapeutics for asthma (10,14).

With the exception of hypersensitivity to peanuts, tree nuts, fish, and shellfish, most food allergies occur in infancy and are outgrown by early childhood. Overall, approximately 40% of food allergies in children subside by age 5. Once a food allergen is identified and excluded from the diet, rechallenge after 1 to 2 years is appropriate, as most allergies abate with time. Allergies to tree nuts, peanuts, and seafood are particularly persistent, and rechallenge at 4- to 8-year intervals is more appropriate when these foods are implicated. Recent attention has been drawn to the particular hazards of food allergies in adolescence. Social circumstances frequently appear to increase adolescents' risk of exposure to known allergens, and they may forgo use of injectable epinephrine, suggesting a need for targeted educational programs. Adolescents frequently have a false sense of security concerning their food allergies, are often inadequately trained, and may find it difficult to manage their emotions surrounding emergencies (15). Additionally, food allergies can be developed during adulthood, with one study reporting that about 1 in 4 adults developed food allergy as adult (7).

Theoretically, exposure to food antigens in early infancy may be particularly likely to lead to hypersensitivity in susceptible individuals because of low levels of secretory IgA. Limited binding of antigen in the GI tract leads to greater absorption and more IgE generation. These theories contributed to the previous recommendations by the American Academy of Pediatrics (AAP) in 2000. These recommendations once advised for the most hyperallergenic foods to be introduced slowly into the atopic infant's diet by adding cow's milk at 1 year old, eggs at 2 years old and peanuts, tree nuts, and fish at 3 years old (16). The goal was to discourage the likelihood of reaction to these foods; however, with the increasing prevalence of food allergies, there have been drastic changes in the recommendations by the AAP. In 2008, and again in 2019, the AAP stated that there was no convincing evidence to delay the introduction of these hyperallergenic foods (17,18). In fact, more recent studies indicate that the delayed introduction of many of these foods actually may increase the risk of allergy and allergic disease. In addition, guidelines published in the American Academy of Allergy, Asthma & Immunology in 2012 have now recommended against restricting highly allergenic foods in nonatopic infants during lactation, as well as against restricting essential foods like milk and eggs during pregnancy. Some evidence points to an association of dysbiosis in early infancy and risk of food allergies (5,19,20). This may be altered by maternal use of probiotic supplements during pregnancy and lactation. However, while this supplementation is safe, probiotics or prebiotics do not appear to reduce the risk of development of food

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allergies, with the exception of cow's milk allergies (21). Similarly, supplementation with omega-3 polyunsaturated fatty acids is being investigated as a protective factor but needs further study to reach levels of certainty (21).

There is no evidence that the substitution of soy-based formulas for milk-based formulas attenuates the risk of atopy (22), nor that use of partially hydrolyzed formula reduces the risk for allergic disease in non-exclusively breast-fed infants without parental history of allergy (23). A number of hypoallergenic formulas are available and are preferred, at least for high-risk infants weaned before 6 months. Apart from use for treatment of infants with allergies to cow's milk protein or soy, some evidence points to the benefit of extensively hydrolyzed casein formula and partially hydrolyzed whey formula for prevention of allergies (24). Although strict avoidance of these hyperallergenic foods is the primary therapy, it is essential that families have close clinical follow-up with a dietician to ensure proper nutritional adequacy of the diet. The current literature has hypothesized a so-called window of opportunity, described as a loosely defined period of time in which children develop tolerance to foods requiring direct exposure to these foods (25,26). Not exposing children to these hyperallergenic foods may actually make them more susceptible to reactions in the future. The dual-allergen exposure hypothesis also heavily challenges the current debate that the allergic sensitization to food is best accomplished through elimination diets. This hypothesis has been studied extensively in murine models (27) and evaluated thoroughly in retrospective studies. The theory is based on the idea that allergic sensitization is mainly achieved through cutaneous sensitization and that the early consumption of food protein leads to oral tolerance. Therefore, the order and balance of exposure to specific antigens will determine the child's development of allergy or tolerance. Children with severe eczema by definition have highly disruptive cutaneous barriers, and this hypothesis has linked the presence of early severe eczema with early development of food allergies. Approximately 40% of patients with atopic dermatitis have food allergies (28). Oral exposure to the allergen, however, seems to reduce the risk of food allergies, specifically in those infants at higher risk. A 2015 study showed a reduction in peanut allergy prevalence of about 80% in high-risk children with regular consumption of peanut starting in the first year of life (29). These studies offer some fascinating insight into early oral exposure of known allergens to infants and have the potential for drastically shifting the approach for introduction of complementary foods in the near future.

The most common manifestation of true food allergy is cutaneous, ranging from urticaria and angioedema to atopic dermatitis; the link between food allergy and atopic dermatitis is particularly important. The spectrum of cutaneous manifestations of food allergy has been reviewed (30). GI reactions such as nausea, vomiting, and abdominal pain (IgE-mediated) tend to occur acutely within 1 hour of ingestion, while symptoms like blood in stool (non-IgE-mediated or mixed) tend to be more associated with infants and young children and often are delayed/chronic in onset taking >2 hours to present. A condition known as Heiner's syndrome is a form of pulmonary hemosiderosis associated with hypersensitivity to bovine milk protein or, less commonly, egg or pork. Symptoms resolve with avoidance of the implicated food.

Oral allergy syndrome (pollen-food allergy syndrome) is also an IgE-mediated response that is more of a contact hypersensitivity of the oropharynx and typically associated with fresh fruits and raw vegetables. These reactions tend to occur minutes after ingesting the allergen and result in mild swelling of lips and throat, pruritus, and localized irritation. Only 1% to 2% of these cases ever result in full blown anaphylaxis (31). Specifically, the syndrome is induced in individuals with respiratory allergy to birch pollen, potatoes, carrots, celery, hazelnuts, and apples; in individuals with respiratory allergy to ragweed pollen, melons and bananas are implicated. The putative mechanism is antigenic cross-reactivity, although the responsible antigens have, for the most part, not been identified.

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Among the varieties of food intolerance distinct from allergy is pseudoallergy, in which symptoms are related to the release of histamine. The histamine release appears to be related to chemical rather than immunologic mechanisms, and it requires a large exposure. Dietary chemicals with pharmacologic properties often produce intolerance. Caffeine may be poorly tolerated, as may be vasoactive amines such as histamine in fermented deli meats (sausage) and sauerkraut and tyramine in cheese, chocolate, and red wine. Monosodium glutamate, typically associated with Chinese food, may lead to flushing and palpitations. Sulfites added to wine may be poorly tolerated, as may be strong spices and capsaicin.

An association between “colic” in infants and the presence of bovine milk immunoglobulin G in breast milk has been established, suggesting that hypersensitivity may account for some cases of colic (10% to 15%). Chronic constipation in young children may be a manifestation of allergy to bovine milk proteins (32). Although isolated respiratory manifestations of food allergy are relatively less common, rhinitis and exacerbations of asthma have been convincingly associated with foods in blinded challenges.

Food-mediated anaphylaxis does occur, as does a variant, in which food hypersensitivity and exercise are required in combination to induce the anaphylactic response. Both are IgE-type reactions that result in systemic reactions often involving combinations of systems including the skin, respiratory, and GI tracts or less commonly may involve cardiovascular functions. As described previously, the potent vasoconstrictor epinephrine is crucial in individuals experiencing anaphylaxis, and use is usually limited to two pens in the home setting for unrelenting symptoms spaced 5 to 15 minutes apart. Although the epinephrine pen has played a crucial role in preventing many fatalities, there are cases in which early and repeated administrations of the pen have still resulted in fatality (26). Peanuts and tree nuts are the most common triggers for these reactions, and delayed use of epinephrine is far and away the most common associated factor leading to death. Other common factors include being a teenager/young adult with asthma, absence of skin symptoms, or reliance on oral antihistamines (26,33).

Mixed-IgE- and non–IgE-mediated reactions commonly involve the GI tract. Eosinophilic gastroenteritis may be induced by milk protein hypersensitivity in infants, among other food allergies, and may require 12 weeks to resolve after removal of the offending antigen from the diet; short-term corticosteroid therapy may be indicated for both eosinophilic gastroenteritis and food-induced enterocolitis (34).

Food allergy has been implicated in some cases of migraine headache (35). Although there is interest, and even a suggested mechanism, in the possible role of food allergy in inflammatory arthritis, inflammatory bowel disease, dysmenorrhea, chronic fatigue, and a variety of other constitutional symptoms (36), there is currently no convincing evidence. The means by which allergens are presented to cells of the GI tract and how these mechanisms might be used in vaccine development are topics of ongoing investigation (14), as is a potential role for food allergy in irritable bowel syndrome (36).

The diagnosis of food allergy is facilitated by a history that establishes a temporal link between ingestion and the manifestations of hypersensitivity. Food allergy is much more likely when a family history of atopy is present. A diet diary is useful in identifying potential allergens.

Skin testing is fairly reliable and speedy in excluding IgE-mediated food allergy, as the test is quite sensitive, although skin testing to rule out food allergy has recently been challenged. Skin testing is generally not considered reliable for ruling in food allergy because of limited specificity. Specifically, the extracts used for the tests are problematic, and not standardized, and their abundance, even in foods, and stability differs widely (31); such tests perform poorly for soy allergy in particular (37). A more specific test is serum IgE immunoassay testing. This testing is also very reliable and is more sensitive than the often previously performed serum radioallergosorbent tests (RAST). In combination, these tests with a thorough clinical history and physical examination provide invaluable information to make more complete

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medical decision-making. A more reliable test for pollen and food allergies is a basophil activation test. It is reported to be very specific, to discriminate between sensitized and symptomatic patients, and to even estimate the threshold of allergic reactions. However, it is complex to be performed and therefore very limited in its applications (31). No laboratory tests are available for the detection of non-IgE-mediated food allergies. Thus far, however, no testing method fully substitutes for food elimination and blinded challenges (38,39).

Elimination diets are useful both diagnostically and therapeutically, requiring that the correct food antigen be entirely eliminated from the diet for a period of 1 to 2 weeks. Apps to facilitate the detection of food allergens and safe foods for patients are available. As mentioned previously, the most definitive diagnostic and specific method is double-blind, placebo-controlled oral challenge with the suspected antigen; such testing is potentially hazardous and should be done only when truly necessary and then only under carefully controlled circumstances. The diagnostic approach to food allergy has been reviewed (39).

There are multiple advances being introduced in the arena of curative medicine for food allergies, including oral immunotherapy, extensively heated egg and milk diets, sublingual immunotherapy, epicutaneous immunotherapy, modified recombinant food protein vaccines, and adjuvants such as Chinese herbal formulations, anti-IgE monoclonal antibody therapy, and the use of helminths (40). In addition, there is great promise shown in the arena of gut microflora and food allergy prevention and treatment. It is evident that gut microflora plays a crucial role in development and maintenance of building tolerance to antigens, most likely by a combination of factors including T-cell regulation. Support for this connection stems from epidemiological studies, mechanistic studies, and studies in rodent models (6,20,41,42). The use of probiotics, however, does not yet have support from clinical studies for prevention of food allergies (21), while it is considered safe even in pregnancy and may be effective for protection from other diseases (20). At present, the treatment of food allergy depends on elimination of the implicated antigen(s) from the diet (9). Whenever possible, the antigenic proteins should be identified, rather than the whole food most likely to contain them, as the proteins may be present in other foods. For example, milk proteins responsible for hypersensitivity, casein and whey, may be included on ingredient lists independent of milk. Lecithin often is derived from either soy or egg, but the source is frequently not included on ingredient labels. Additionally, there is emerging evidence that nanoparticles widely used as food preservatives and as drug carriers may cause food allergies (43).

Because food allergens tend to be widely distributed in the food supply, elimination requires expert dietary advice both to achieve full elimination and to avoid nutrient deficiencies. Importantly, families must continue to be very vigilant concerning their higher-risk atopic children and practice the necessary preventive strategies in order to promote wellness while still maintaining a sense of normalcy. Other treatment approaches, such as herbal remedies, are receiving increasing attention in the research literature but are not yet advisable as standard clinical practice (44). The development of immunotherapies is ongoing (6,40). Thus far, while tolerance is yet unachievable, the individual’s reaction threshold can be raised, so that contamination of food products with the allergen, like peanut, is less likely to trigger a reaction (40). The hope for these alternate therapies is that they one day will provide true clinical tolerance, in order for the patient to experience permanent freedom from allergic response even if the allergen is eliminated and later reintroduced.

The most common food allergies in adults are to fish, shellfish, nuts, and peanuts. In children, the most common reactions are to milk, eggs, peanuts, soy, and wheat. Peanuts are in the legume family and, therefore, have antigens that do not generally cross-react with those of other nuts.

Lactose

Intolerance to lactose, a milk sugar, results from deficiency of the enzyme lactase. Deficiency actually is considered the normal condition for adult mammals, with preservation of enzyme activity into adulthood the result of a genetic mutation. Lactase deficiency is considered the most common enzyme deficiency; more than half of all adults are affected. Deficiency is especially common in individuals of African, Asian, Mediterranean, and Native-American origin. These individuals typically have enough lactase enzyme until around 5 years of age and then have a precipitous drop in lactase, causing a variability in tolerance of lactose loads in the large intestines. Lactose tolerance is highly prevalent in northern Europeans.

Lactose intolerance is distinct from allergy to milk proteins. For individuals allergic to bovine milk protein, alternative milks may be substituted. However, all milks (cow, goat, sheep) contain lactose. Milk products such as cheese and butter contain milk protein, so they cannot be eaten by individuals with true allergy, but they contain trivial amounts of lactose. Most individuals with lactose intolerance of genetic origin can tolerate about 12.5 g of lactose contained in 250 mL of milk with minimal to no symptoms (45).

Concern persists that avoidance of dairy products may lead to health impairments. However, relations between consumption of dairy products and diseases are often modest and not considered causative (45). The most substantial concern regards calcium intake. Dairy foods are an excellent source for the nutrients required for bone maintenance, and sufficient intake of calcium without dairy products is difficult, although the use of supplements and fortified foods with similar calcium bioavailability has reduced the relevance of dairy products in terms of calcium provision (45). Nonetheless, recent data suggest that decreased intake or avoidance of dairy, related to lactose intolerance, leads to reduced bone density and fragility fractures, particularly in cultures that typically include dairy in their diets. The effect size in different studies is generally small, however (46). For lactose-intolerant patients consuming more than 15 g per day of lactose, a variety of lactose-free or hydrolyzed-lactose products are available (see **Appendices H and J**).

Gluten

Gluten is a protein found in many cereal grains, and it is especially abundant in wheat. Other implicated grains include rye and barley. Other products under these categories include products cross-contaminated with wheat, rye, or barley and products containing triticale (cross between wheat and rye), along with wheat products (e.g. spelt, kamut, semolina, bulgur, farina). Intolerance to gluten has a variety of conditions including non-celiac gluten sensitivity, wheat allergy, and celiac disease. The definitions and diagnostic criteria for non-celiac gluten or wheat sensitivities continue to be discussed, as diagnosis is difficult (47–49). Non-celiac gluten sensitivity is by far the most common, with an assumed prevalence of up to 13% of the U.S. population (47). These individuals may present with similar GI manifestations common to celiac disease, but also Crohn’s disease and irritable bowel syndrome (50), such as bloating and abdominal pain, in addition to a variety of other symptoms including headaches, confusion, and ataxia. However, there is no associated damage to the small intestine and no specific celiac antibodies, and it is mainly considered a diagnosis of exclusion. Symptoms usually resolve after onset of a gluten-free diet. In a large number of patients, a low fermentable oligo-, di-, and monosaccharides and polyols (FODMAP) diet also leads to resolution of symptoms (47). Wheat allergy on the other hand is an IgE-mediated reaction and occurs in <1% of children and rarely in adult populations. The most well-studied

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gluten-related disorder is celiac disease, which is autoimmune in nature, with its prevalence being about 1% of the population. Its hallmark is gluten-induced villous atrophy that occurs in the small intestine (51). Dermatitis herpetiformis and gluten ataxia are other autoimmune conditions associated with gluten intolerance. A test for IgA to tissue transglutaminases is diagnostic (51). The prevalence of gluten intolerance is estimated to be 1 in 300 for individuals of European origin. Gluten intolerance is lifelong, and exclusion of gluten from the diet is the only known treatment to date, even though it is not necessarily curative for all aspects of the disease or all patients (52). Efforts to reduce the burden of patients on gluten-free diets by development of gluten-free wheat are advanced (53). While gluten enteropathy is immune mediated and thus a true food allergy, it is cell mediated and manifests as a delayed hypersensitivity reaction rather than an acute, antibody-mediated reaction; thus, it is atypical. Many sources do not explicitly classify Celiac disease or gluten intolerance as food allergy (52,54,55,57,59), possibly because of this atypical nature.

The increased prevalence of gluten intolerance is often challenged and considered difficult to define (48). However, there is a rising amount of literature leading toward a likely increase in prevalence throughout the world. It is correlated with the widened spectrum of disorders associated with gluten sensitivity, along with the empiric evidence of increased purchasing and ingestion of gluten-free products (54,55). The reason for this increased prevalence is unclear but has been speculated to be associated with multiple factors, including human genetics, environmental toxins, intestinal infections, autoimmune diseases, increased ingestion of Westernized gluten diets, infant feeding patterns, and also changes in quantity and quality of ingested gluten (55,56). These factors are common in popular science and remain speculations due to limited data availability. It is clear that Western diets are becoming more common all over the world, and as more gluten-rich products are introduced into cultures, we are likely to see more cases of gluten intolerance (56). In addition, it is conceivable that as wheat products, starches, and other foods have been modified, there may also be an association between such modifications and increased prevalence of gluten intolerance. Genetic modification to reduce the pathogenicity without altering the gastronomic and agronomic properties, reversing this potential change, is far along in development (53,57). Evidence for involvement of the microbiota and intestinal permeability, in contrast, is becoming hard to ignore (41,42,47,58). Disruption of the intestinal barrier leads to systemic and intestinal damage and is often associated with gluten intolerance. Several therapeutic approaches are in development to alleviate the burden of a gluten-free diet (57).

Lymphoma risk rises with celiac disease but is mitigated by adherence to a gluten-free diet (59). As gluten is virtually ubiquitous in the diet, expert dietary advice is essential (e.g. registries of gluten-free foods are available online; see Appendix J.). Most gluten-free diets traditionally exclude oats, due to cross-contamination, but this may prove to be unnecessary for some patients (see Chapter 18). Facilities that process oats often process wheat as well, and thus contamination of oats with wheat proteins may complicate inclusion of oats in a gluten-free diet. For further discussion of gluten enteropathy, see Chapter 18.

CLINICAL HIGHLIGHTS

Food allergy is sufficiently common that most clinicians are likely to encounter it. The condition often imposes a considerable burden on patient and family alike, particularly when children are affected (60). The manifestations span a wide spectrum, although the most common manifestations are fairly prototypical. The prevalence of true food allergy is higher in children than in adults, but many children can be expected to outgrow their allergies. Diagnosis can be confirmed with non–IgE-mediated reactions

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by elimination diets, and IgE-mediated reactions require food challenges with IgE-specific immunoassays or skin testing. The most common food allergies in adults are to fish, shellfish, nuts, and peanuts; in children, the most common reactions are to milk, eggs, peanuts, soy, and wheat. If food allergy is confirmed, a dietitian should be consulted to help the patient (or the patient's parents) develop a nutritionally complete diet completely free of the offending antigen. Allergy to gluten can produce celiac disease or be associated with non-celiac gluten intolerance, and both require nearly complete and permanent elimination of gluten from the diet (see Chapter 18).

Food intolerance, as opposed to allergy, is not immune mediated. Lactose intolerance is perhaps the most common and best-known example. Although patients with lactose intolerance may report an inability to tolerate any milk, randomized double-blind trials are consistent in demonstrating that most individuals can tolerate up to 15 g/day of lactose and that adequate calcium intake from dairy sources remains feasible. Breast-feeding up to the age of 4 to 6 months may reduce the risk of cow's milk allergy but not general food allergy before the age of 2 years. Providers are encouraged to tell families to not delay introduction of highly allergenic foods between 4 and 6 months unless the child has a sibling or first-degree relative with peanut allergy, worsening moderate-severe eczema, or previous reaction to other foods. In these cases, foods may continue to be introduced, but recommendations are to refer to an allergy specialist for more structured introduction and allergy testing (25). The role of food allergy in a host of conditions and constitutional symptoms is being vividly researched at present. Progress is considerable in identifying common food antigens. The modification of food antigenicity through bioengineering to remove offending proteins is an area of intense activity and considerable promise (53). The use of probiotics to adjust intestinal microflora also shows promise for the prevention and management of food allergy (42).

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Chapter 25

Eating Disorders

Sarah Hornack

INTRODUCTION

Eating disorders refer to atypical, problematic eating behavior, with or without discernible physical consequences. The prototypical conditions are anorexia nervosa (AN), bulimia nervosa (BN), and binge-eating disorder (BED).

Obesity is the result of a multitude of factors creating an imbalance of energy needs and energy intake; therefore, it might be considered a disorder of eating. However, it is generally categorized and managed differently, partly because of its prevalence. Obesity now afflicts approximately 42% of the adult population in the United States, with severe obesity presenting in 9.2% of adults (1) (see Chapter 5). Rates in children have risen rapidly in the last several decades and currently nearly one in five youth are affected by obesity (2,3). By virtue of prevalence alone, obesity cannot be considered “aberrant” though extreme degrees of obesity share characteristics with the other eating disorders. In these cases, elements of management borrowed from the other disorders may be helpful. Conversely, as social pressures increase the prevalence of eating disorders, they potentially become less distinct from prevailing norms and more akin to a public health problem (4) rather than a strictly individualized pathology. Recent trends in the epidemiology of BED are noteworthy in this regard (5).

There is some concern that obesity prevention and treatment efforts may lead to the prototypical eating disorders of anorexia and nervosa; however, this concern is unfounded. Moreover, it is true that childhood-onset obesity is correlated with disordered eating later in life, and that binge eating or unhealthy weight-loss practices increase risk for obesity. Reviews of lifestyle interventions for weight loss find that improved health behaviors can lead to reduced eating disorder psychopathology and improved psychosocial outcomes, like quality of life (6,7). So rather than one disorder causing the other, it seems more likely that obesity and eating disorders are two sides of the same coin.

Occasional or mildly disordered eating, related to cravings, aversions, and dissatisfaction with body image, is very prevalent, if not universal. A clinically relevant eating disorder is earmarked by a great deal of distress and/or resulting impairment in an individual’s daily life, and management relies heavily on psychotherapy. Nonetheless, the disorders are expressed in interactions with food, requiring that dietary management be addressed as well.

OVERVIEW

The prevalence and public health importance of eating disorders has risen steeply since the 1970s, concurrent with a rapid rise in the prevalence of obesity. At the same time, societal concepts of beauty have increasingly prioritized thinness. Thus, although previously considered a consequence of family dysfunction and psychopathology, the link between eating disorders and prevailing imbalance between dietary goals and dietary practices seem self-evident. The biopsychosocial model is germane; social factors interact with biological, genetic, and psychological vulnerability to culminate in the disordered

pattern of eating behavior (8–10).

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Dieting during adolescence appears to increase susceptibility to disordered eating (11,12). A population-based survey in Spain suggests that eating disorders occur against a backdrop of highly prevalent, less extreme, unhealthy eating practices (13), and a recent 10-year longitudinal follow-up found that adolescents who engaged in dieting and disordered eating behaviors were more likely to still engage in such behaviors 10 years later (14).

Exposure to Western culture and ideals of beauty is considered a risk factor for eating disorders (15). However, continued research has shown that eating disorders are not restricted to particular cultures or ethnicities (16–19). Their impact is also seen globally in that high-income and low- to middle-income countries show similar rates of BED (5). Eating disorders are perceived as conditions that overwhelmingly affect young women; however, there is evidence that the disorders occur in men but with a differing presentation. For instance, men with an eating disorder are more likely to have a history of overweight and obesity, are more likely use exercise as a compensatory behavior, and the origin of their weight concerns is more often related to athletic achievement (20–29).

The risk factors for eating disorders are many and include psychological, biological, and cultural factors. Eating disorders are associated with psychiatric comorbidities (30–33) with mood and anxiety disorders co-occurring most frequently (34,35). AN and BN are distinguished from these psychiatric comorbidities by the preoccupation with body weight. Individuals encouraged to be preoccupied with weight control, such as models, actresses, dancers (36), athletes (37–39), and people with type 1 diabetes (40–42) appear to be at increased risk. A personal history of obesity or perceived obesity is commonly reported as well, particularly in bulimia. There is also evidence of increased risk for binge eating and unhealthful weight-control behaviors among teen and young adult vegetarians. Questionnaires administered to large samples of adolescents and college students revealed that females and those who listed health or medical reasons for vegetarianism endorsed higher rates of disordered eating. Further, findings suggest that current vegetarians may experience higher risk for loss of control eating while former vegetarians may engage in more extreme weight-loss behaviors (43,44). Genetic contributions to disordered eating have been demonstrated by familial clustering and twin studies (45,46). Additionally, candidate gene studies have identified genetic risk variants involved in the hypothalamic control of appetite and energy homeostasis that increase one's risk for anorexia (10,47,48). Diagnostic criteria for eating disorders have been codified in the *Diagnostic and Statistical Manual of Mental Disorders (DSM)* and the *International Classification of Diseases (ICD)*.

Anorexia Nervosa

Fundamentally, AN is a morbid fear of becoming fat, an inability to gauge correctly the degree of thinness, and consequent self-starvation (49,50). According to the *DSM-V*, the criteria for AN include restriction of food intake leading to a "significantly low body weight," intense fear of weight gain, and distorted perception of body image. Diet is usually strictly controlled in anorexia, and the patient is apt to deny and genuinely not recognize that a problem exists. AN is further divided into two subtypes: in the restricting type, the individuals do not binge or purge as compared to the binge-eating/purging type in which the individuals engage in recurrent binging and purging (*DSM-V*). In making the diagnosis using *DSM-V* criteria, AN severity is classified based on World Health Organization body mass index (BMI) categories for thinness: "Mild" is a BMI greater than or equal to 17 kg/m^2, "Moderate" is a BMI 16 to 16.99 kg/m^2, "Severe" is a BMI 15 to 15.99 kg/m^2, and "Extreme" is a BMI less than 15 kg/m^2. Corresponding percentiles are used in qualifying AN severity for children and adolescents. In the binge-eating/purging

type, the distinction from bulimia rests on the degree of underweight (51).

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AN most commonly occurs between the ages of 15 and 19; however, cases do develop in preteen children and in middle-aged adults (52). There are indicators that the age of onset is decreasing with each generation (53).

Medical complications of anorexia are those of starvation. Basal metabolism is slowed, with potential hypotension and bradycardia. Amenorrhea due to reduced production of follicle-stimulating hormone and luteinizing hormone and reduced estrogen levels is common and may be one of the earliest indicators. Skin discoloration due to hypercarotenemia may occur, related to either dietary habits or metabolic dysfunction. Osteopenia is a frequent complication and results in an increased long-term risk of fractures. Adolescents with AN are at risk for impaired linear growth that may result in permanent short stature (54). Characteristic features of hypothyroidism often develop. Potentially irreversible bone loss may occur at a rate of up to 15%/year during periods of cachexia and amenorrhea. With protracted and severe starvation, visceral protein loss has the potential to become life threatening. Myocardial protein loss renders the individual with anorexia susceptible to sudden cardiac death. The mortality rate in anorexia is higher than other psychiatric disorders at approximately 5%, with one in five deaths attributed to suicide (55,56). The mean duration of illness is generally thought to be between roughly 2 and 5 years, as reported in epidemiological studies (23,57). However, research in clinical samples frequently finds AN to be a chronic illness. Individuals with a disease duration of 5 years or more have a significantly poor prognosis for recovery and greater associated medical and psychological maladies (58).

Bulimia Nervosa

Data from the 2012 to 2013 National Epidemiologic Survey on Alcohol and Related Conditions suggest that lifetime prevalence of BN is 0.28% (compared to 0.8% for AN). Rates of diagnosis are believed to be increasing due to the lower threshold of binge episode frequency put forth in *DSM-V* (59,60).

In bulimia, as in anorexia, there is a preoccupation with body weight and fear of weight gain. *DSM-V* criteria include recurrent binges characterized by excessive calorie consumption within a discrete time frame and loss of control; recurrent inappropriate compensatory behavior to prevent weight gain (e.g., self-induced vomiting, laxative use, calorie restriction, excessive exercise); and undue preoccupation with body habitus. In order to meet the definition of BN, the binge eating and compensatory behaviors must occur at least once a week for 3 months and the episodes do not occur exclusively in the context of AN, binge-eating/purging subtype. The distinguishing features of BN tend to be the (a) degree of dietary control, which is strict in anorexia but poor in bulimia, and (b) the related degree of thinness (49). Limited data suggest that impaired metabolism of cholecystokinin may contribute to lack of normal satiety signals (61,62). Between 30% and 50% of those with BN also abuse or are dependent on alcohol or drugs, and there is evidence that bulimia itself may represent an addictive disorder (63). Individuals with BN tend to binge eat and then “purge,” engaging in a compensatory behavior or any combination of actions. Unlike individuals with AN, who appear unwell to any objective observer but tend to be unaware of a problem, those with BN generally appear well (unless the condition is advanced or decompensated) and tend to know their dietary behavior is pathological.

In national survey data, BN generally manifests between the ages of 18 and 22 and the mean duration is just over 8 years, comparable to that of BED. Individuals with BN have had the condition for up to 5 years before seeking treatment, and they often get help only because of some acute disruption. National survey data indicate that less than half of individuals seek treatment specifically for their bulimia but rather are more likely to seek treatment for psychiatric comorbidities (23). Medical complications result from trauma to the gastrointestinal tract and electrolyte imbalance (64).

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Since bulimics often appear well and tend to delay seeking treatment, diagnosis can be challenging. However, there are several warning signs and early medical complications that can guide the clinician in identifying this disorder. Russell sign, bruised or callused knuckles as a result of self-inflicted vomiting, may be an early clue to the diagnosis. Repeated bouts of emesis erode dental enamel and can lead to tooth loss and dental caries. Loss of gastric acid can lead to hypochloremic alkalosis and hypokalemia, potentially inducing shock. These electrolyte disturbances in an otherwise healthy patient should prompt suspicion of bulimia. Other medical complications of bulimia include pancreatitis, which may occur following a binge. Enlargement of the parotid glands may be induced by a binge. Binging can lead to gastric rupture. Purging can result in esophagitis and esophageal tear or rupture. Ipecac, a well-known expectorant, taken in high doses is cardiotoxic, potentially leading to myocarditis and dysrhythmia. Laxatives can lead to renal tubular damage and can chronically impair gastrointestinal motility (64).

Binge-Eating Disorder

BED is similar to bulimia in the commonly reported loss of impulse control that leads to binging, occurring at least once per week for 3 months. The distinction is that in BED, as opposed to BN, inappropriate compensatory behaviors, such as self-induced vomiting, do not occur (65). People with BED also tend to be middle aged, and as many as 25% are male (66). Binges tend to take place in private, with normal or even subnormal food intake in public related to the sense of guilt or embarrassment associated with binging. Recurrent binges contribute to the development of weight gain and obesity over time. In patients with obesity who have BED, it is recommended that the binge eating be treated before the patient attempts weight loss (67).

Recent survey data indicate that the prevalence of BED in the United States exceeds that of anorexia and bulimia, with 0.8% lifetime prevalence (59). Some tendency to binge eat is common in most people, and indeed, in many species (see Chapter 44). The case has been made that BED may be more closely related to normal eating behaviors than the other disorders and the rising prevalence may be attributable to environmental and societal influences (67).

Other Specified Feeding or Eating Disorder

Other Specified Feeding or Eating Disorder is a category including disorders that “cause clinically significant distress or impairment in social, occupational, or other important areas of functioning predominate but do not meet the full criteria for any of the disorders in the feeding and eating disorders diagnostic.” Included in this category are atypical AN in which a patient meets all the criteria for AN but is of a normal weight; BN and BED of low frequency or limited duration; purging disorder (a disorder of purging with no associated binging); and night eating syndrome (NES). NES is characterized by evening hyperphagia with nocturnal snacking, which causes significant impairment and distress (*DSM-V*). Unlike the 2,000 to 3,000 kcal binges typical of BED, nocturnal snacking in NES tends to be limited to roughly 400 kcal/episode, with multiple episodes throughout the night (68). It is estimated that up to 1.5% of the general population has the condition. Several studies of NES in individuals with obesity suggest extremely high rates in this population, ranging from about 10% to 15% of obesity clinic patients to 8% to 55% of patients seeking bariatric surgery (69–71).

Atypical Eating Disorders

States of aberrant eating behavior that do not meet criteria for anorexia, bulimia, or binge eating exist but receive limited attention in the medical literature. Such conditions include pica, which is the persistent eating of nonnutritive, nonfood substances for at least 1 month. Avoidant/restrictive food intake disorder

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(ARFID) is an eating or feeding disturbance that results in failure to meet nutritional or energy needs; this is not attributable to another medical condition, does not occur in the presence of AN or BN (there is no concern about weight or thinness), and is not the result of lack of food access (*DSM-V*). Recognition of such disorders may be particularly important in sensitizing the primary care community to the prevalence and clinical impact of disordered eating.

Management: General Principles

The management of eating disorders is multidisciplinary and relies heavily on expert psychiatric or psychological care. Evidence is growing that selective serotonin reuptake inhibitors (SSRIs) may be useful in the treatment of patients with BN and BED (72–76). Only two drugs have been approved by the US Food and Drug Administration for treatment of eating disorders; lisdexamfetamine dimesylate, a stimulant for attention-deficit/hyperactive disorder, for moderate to severe BED and fluoxetine for BN (72,74). There is some evidence that SSRIs may help prevent relapse in patients with anorexia who achieve a normal weight. The evidence on the use of the antipsychotic olanzapine in patients with anorexia is mixed (77–79), though the American Psychiatric Association suggests it may be useful in patients with "severe, unremitting resistance to gaining weight; severe obsessional thinking; and denial that assumes delusional proportions" (80). In addition to the primary care provider, the management team should generally involve a mental health specialist, dietitian, and social worker.

Cognitive-behavioral therapy is considered the treatment of choice for bulimia and BED (66,81,82). Individual psychotherapy may be helpful, but family-based treatment (FBT) is considered the first-line approach for adolescents with AN (82–84). In adults with anorexia, cognitive-behavioral therapy may prevent relapse in those who have achieved a normal weight (85).

The primary care provider has an important contribution to make in both preventing and managing eating disorders. A high index of suspicion is warranted to facilitate early detection. One screening tool that can be used by the primary care physician is the SCOFF questionnaire, a five question instrument that assesses the core psychopathology of anorexia and bulimia (86). If a patient answers affirmatively for two or more of the questions, further investigation is warranted (87). Established screening tools for BED include the Questionnaire on Eating and Weight Patterns (QEWP-5) and the Binge Eating Scale (BES); these self-report measures each assess symptoms on a continuous scale (88). As these could be cumbersome to complete in a primary care setting (they have 26 and 16 response items, respectively), researchers have identified an effective one question binge-eating screen from the MOVE!23 questionnaire, "On average, how often have you eaten extremely large amounts of food at one time and felt that your eating was out of control at that time?" Respondents are asked to indicate how often this happened in 1 week to determine if referral is necessary (89).

Recognition of psychopathology that contributes to disordered eating may allow for preemptive treatment. Efforts to contain societal influences that may propagate distorted body image among young people and to establish educational programs that encourage healthful eating and realistic perspectives on weight should derive support, if not leadership, from the primary care community (90–97).

Excellent and extensive literature is available on the various theories and approaches to the counseling of eating-disordered patients (see "Suggested Readings"). Dietary management per se is an important aspect of the care plan, though it is only one component.

Management: Diet

Severe anorexia may require hospitalization and enteral nutrition support, with meticulous management of electrolytes. A BMI in the very severe range (below 13), severe electrolyte imbalance, suicidality, and

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lack of improvement while in outpatient treatment are all indications for hospitalization. Refeeding should be gradual to avoid refeeding syndrome, characterized by congestive heart failure, hypophosphatemia, and/or prolonged QT interval. Inpatient care should be supervised by a dietitian or another nutrition consultant.

Ambulatory care calls for close follow-up especially since drop-out from treatment is common (98,99). The principles of dietary counseling discussed in Chapter 47 are applicable. Nutritional management should begin with a dietary history (100). The history should include not only a description of current and past dietary behaviors but also the beliefs and motivations underlying them.

Weekly visits are appropriate until a consistent therapeutic response has been achieved. Weight monitoring should be routine. The patient should maintain a food diary, which should be reviewed at office visits. Because preoccupation with weight is predominant, patient education regarding healthy weight and dietary practices conducive to weight maintenance is essential.

Because the pathology is related to a very restrictive diet in anorexia, emphasis should be placed on a prudent but balanced and unrestricted diet. There is no single recommended nutritional regimen, as adequate caloric consumption is paramount (101). A similar goal is pertinent in the management of bulimia and binge-eating disorder, with a need to emphasize that the disordered eating typically is a result of overly restrictive attitudes about food rather than overeating (100,102). Establishment of a consistent, moderate dietary pattern is helpful in resolving the tendencies to binge and purge.

Guidelines recommend gradual weight gain in anorexia at a rate of 0.5 to 1.4 kg/week. Involvement of a dietitian in the development of meal plans to facilitate weight gain or maintenance is indicated. In anorexia, the suppression of basal metabolism is such that seemingly modest intake of food energy may be sufficient to support weight maintenance or gradual weight gain. A large cohort study of inpatient treatment suggested that oral refeeding may begin at 1,200 to 1,500 Kcal/day and advance to 3,500 to 4,000 daily (103).

A dietitian should determine the basal metabolic rate as a means of estimating caloric needs. The diet should be advanced gradually to allay the patient's anxieties about excessive weight gain. There is evidence that weight gain reverses the negative impacts of starvation, such as cognitive rigidity and over-attentiveness to detail, thus having positive effects on patient anxiety and ability to make sound decisions (104). In bulimia, stabilization of the dietary pattern and weight should be addressed initially. An effort should be made to identify foods associated with binges so that they can be avoided or their intake can be strictly controlled for a time, though there is evidence that eventual exposure to "feared foods" and prevention of the response (binging/purging) in therapy can alleviate symptoms (105). There is also recent evidence that limiting food variety results in sensory-specific satiety and thus a more limited diet may help curb binge eating (102). If indicated, a diet for measured weight loss may be developed once the eating pattern has reliably stabilized. Dietary counseling (see Chapter 47) should be coupled to cognitive-behavioral therapy to ameliorate perceptions of body image and establish a sustainable dietary pattern that supports weight-control efforts.

An additional challenge to the physician is the concurrence of an eating disorder and a metabolic disease, such as diabetes mellitus. Girls with type 1 diabetes appear to be at least twice as likely to develop bulimia and BED as peers without diabetes (106). Disordered eating in diabetics has been associated with greater frequency of medical complications including more frequent episode of ketoacidosis and acceleration of the development of retinopathy (41,107). Given the prevalence of both diabetes and eating disorders, the authors encourage consideration of concurrence whenever diabetes proves difficult to manage, especially in a young woman.

CLINICAL HIGHLIGHTS

A pervasive struggle with weight control, epidemic obesity, and propagation of the thin ideal characterize modern society. A rising prevalence of eating disorders may be attributable to both individual susceptibility and environmental conditions. Increased awareness among clinicians with enhanced detection may also be contributory. The environmental contribution is such that every patient may reasonably be considered at some degree of risk for some degree of disordered eating. The incorporation of nutrition education and limited dietary counseling into primary care practice may support efforts at primary prevention of eating disorders, particularly by revealing the dietary habits imparted by parents to their children. Additionally, there are evidence-based programs intended to mitigate eating disorder risk by teaching cognitive-dissonance strategies and countering the thin ideal (108).

Eating disorders generally require a care team that includes a mental health specialist and dietitian. A therapeutic alliance between the patient and a primary care provider with a good working knowledge of nutrition is conducive to early detection and optimal management. Patients need education regarding healthy weight and dietary practices, as well as the adverse effects of disordered eating. A balanced but not overly restricted diet is conducive to overcoming eating disorders and to preventing excessive weight gain, which may precipitate recurrences of disordered eating. Contrary to an often-voiced concern, counseling to forestall obesity need not in any way contribute to eating disorders if delivered appropriately, with a focus on long-term health rather than short-term weight loss or thinness, per se.

Clinicians should encourage a dietary pattern consistent with principles of health promotion and weight control (see Chapters 5 and 45). Frequent follow-up, with monitoring of weight and dietary pattern, is essential until a therapeutic response is achieved and sustained.

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Chapter 26

Malnutrition and Cachexia

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INTRODUCTION

Impaired functional status and anorexia (loss of appetite) of various etiologies may result in nutrient and energy intake inadequate for metabolic demand. Similarly, physiologic stresses including acute illness or injury may raise metabolic demand to a level not easily accommodated by a conventional diet. Often, impaired nutrient intake and increased metabolic demand are concurrent, as is the case in cancer, acquired immunodeficiency syndrome (AIDS), burns, or other acute and chronic disease states. Although there is little evidence to suggest that nutrient deficiency under such conditions strongly influences the course of illness or recovery over the first several days, nutritional status is fundamental to convalescence and health maintenance over time. Nutritional status influences immune function (see Chapter 11) and wound healing (see Chapter 23), both vital to recovery from acute and chronic illness or injury.

To achieve adequate nutriture in the context of disease or disability, nutritional support may be indicated. Whenever possible, that support should be enteral, either by mouth or feeding tube. Parenteral nutrition can meet all metabolic need but at the cost of gastrointestinal (GI) atrophy and a risk of line sepsis. Adjuvant therapies, such as megestrol acetate or growth hormone, have been used with variable success to enhance appetite and promote preferential restitution of lean body mass. Increasingly, nutritional formulas tailored to a patient's particular condition and nutrient needs are available. There is a growing body of research to support the use of specific nutrient combinations to preserve and promote lean body mass. The selection and modification of nutrition support formulas generally should be overseen by a dietitian or other nutritionist; such consultation is typically readily available in the inpatient setting.

OVERVIEW

Decisions about malnutrition risk and nutritional support are based on the nutritional status of the patient as well as the clinical context. A wide variety of screening tools are used in order to assess nutritional risk and determine the need for nutrition intervention. According to the European Society for Parenteral and Enteral Nutrition, the goals of nutritional assessment tools are to predict the probability of a positive or negative outcome due to nutrition and whether nutritional treatment would influence this outcome (1,2). The Subjective Global Assessment (SGA) is one of several validated clinical scoring tools that have been deemed useful for nutritional assessment across various patient populations, including those in critical care settings (3). The SGA incorporates medical history and physical examination results to identify a patient as well-nourished, moderately malnourished, or severely malnourished (4,5). The Patient-Generated SGA (PG_SGA) is based on the SGA and utilizes patient-supplied data as well as those of the clinician (6). Another clinical screening tool, the Malnutrition Universal Screening Tool ("MUST"; see Figure 26.1), uses body mass index (BMI), unintentional weight loss, and effects of acute disease in order to determine adults who are either at risk of or are currently malnourished (7). "MUST"

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has been validated for use in all settings including primary care (predicting rate of hospital admissions and primary care physician visits) and inpatient care settings (predicting length of stay, mortality, and disposition after discharge) (2). The United States Academy of Nutrition and Dietetics (AND) currently takes the position that the Malnutrition Screening Tool (MST), a validated screening tool, which utilizes two questions regarding appetite and recent weight loss, should be the single tool used to screen adults for malnutrition regardless of age, medical history, or setting (8,9). Other clinical screening tools that have been validated and reviewed include the Nutrition Risk Index, the Mini Nutritional Assessment, and the SGA (8). Because no single method or tool has proven sufficient to assess nutritional status with high sensitivity and specificity, the Global Leadership Initiative on Malnutrition (GLIM) is working toward implementing a set of standard criteria, which can be used globally and with other approaches to assess the most accurate picture of a patient's nutritional risk and promote improved outcomes (10).

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Step 1 + Step 2 + Step 3

Step 1 — BMI score

BMI kg/ m²	Score
>20 (>30 Obese)	= 0
18.5–20	= 1
<18.5	= 2

Step 2 — Weight loss score

Unplanned weight loss in past 3–6 months

%	Score
<5	= 0
5–10	= 1
>10	= 2

Step 3 — Acute disease effect score

If patient is acutely ill **and** there has been or is likely to be no nutritional intake for >5 days

Score 2

If unable to obtain height and weight, see "MUST" for alternative measurements and use of subjective criteria

Acute disease effect is unlikely to apply outside hospital. See "MUST" Explanatory Booklet for further information

Step 4

Overall risk of malnutrition

Add Scores together to calculate overall risk of malnutrition
Score 0 Low Risk Score 1 Medium Risk Score 2 or more High Risk

Step 5

Management guidelines

0 Low Risk

Routine clinical care

- Repeat screening
  Hospital–weekly
  Care Homes–monthly
  Community–annually
  for special groups
  e.g., those > 5 yrs

1 Medium Risk

Observe

- Document dietary intake for 3 days
- If adequate–little concern and repeat screening
  - Hospital–weekly
  - Care Home–at least monthly
  - Community–at least every 2—3 months
- If inadequate–clinical concern – follow local policy, set goals, improve and increase overall nutritional intake, monitor and review care plan regularly

2 or more High Risk

Treat*

- Refer to dietitian, Nutritional Support Team or implement local policy
- Set goals, improve and increase overall nutritional intake
- Monitor and review care plan
  Hospital–weekly
  Care Home–monthly
  Community–monthly

* Unless detrimental or no benefit is expected from nutritional support e.g., imminent death.

All risk categories:

- Treat underlying condition and provide help and advice on food choices, eating and drinking when necessary.
- Record malnutrition risk category.
- Record need for special diets and follow local policy.

Obesity:

- Record presence of obesity. For those with underlying conditions, these are generally controlled before the treatment of obesity.

Re-assess subjects identified at risk as they move through care settings

See *The "MUST" Explanatory Booklet* for further details and *The "MUST" Report* for supporting evidence.

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FIGURE 26.1 The "MUST" Flowchart. (The "Malnutrition Universal Screening Tool" (MUST) is reproduced here with the kind permission of BAPEN (British Association for Parenteral and Enteral Nutrition). For further information on 'MUST' see www.bapen.org.uk Copyright © BAPEN 2012.)

BMI, body mass index.

Nutritional status is evaluated using body weight, particularly in comparison with baseline weight, as well as dietary and medical history. The measure "percent usual body weight," actual body weight divided by usual body weight multiplied by 100, is often used in anthropometric assessment. Height can be measured along with weight to obtain BMI in adults (weight in kilograms divided by height in meters squared). Length and head circumference are useful in young children.

Calipers (typically Lange skinfold calipers) can be used to measure skinfold thickness and provide a measure of subcutaneous fat as compared with a reference standard (11); triceps skinfold is used most often because the site is easy to reach and there is usually no edema although it is prone to error as appropriate training is needed (12). In men, a triceps skinfold thickness less than 12.5 mm indicates malnutrition, whereas a thickness above 20 mm indicates over nutrition. The comparable values in women are 16.5 and 25 mm, respectively. Measurement of the mid-arm muscle circumference with a tape measure is also recognized as a proxy for body protein stores, with values under the 15th percentile indicative of under nutrition (13). Measures of body composition, including computed tomography (CT), and magnetic resonance imaging (MRI) are useful in research settings but rarely applied clinically, whereas dual energy x-ray absorptiometry (DXA), considered the "gold-standard" reference, is more widely accessible and recommended for use across most clinical populations (14,15).

Biochemical indices of nutritional status include both somatic and visceral proteins (see Table 26.1). The visceral proteins include albumin, transferrin, prealbumin, and retinol-binding protein. Albumin is used most commonly; its level varies consistently with the adequacy of protein stores. Albumin has a half-life of approximately 20 days and, therefore, cannot be used to measure acute states of malnutrition (16). Conversely, albumin levels tend to drop precipitously in septic states independent of nutritional status. An albumin level from 3.5 to 5.5 g/dL is considered normal, 2.8 to 3.5 g/dL is considered mild depletion, 2.1 to 2.7 g/dL is moderate depletion, and levels below 2.1 g/dL indicate severe depletion of visceral protein.

TABLE 26.1

Cutoff Values for Visceral and Somatic Protein Assays in Clinical Use

Level	Moderate Depletion Albumin (g/dL)	Transferrin (mg/dL)	Prealbumin (mg/dL)	Retinol-Binding Protein (mg/dL)	Urinary Creatinine (% of Reference Value)
Normal	3.5–5.5	250–300	15.7–29.6	2.6–7.6	>90
Mild Depletion	2.8–3.5	150–250	10–15	N/A	80–90
Moderate Depletion	2.1–2.7	100–150	5–10	N/A	60–80

Severe Depletion	<2.1	<100	<5	N/A	<60

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Transferrin, with a half-life of 8 to 10 days, can be used instead of albumin when acute nutritional perturbations are under evaluation. The half-life of prealbumin is approximately 2 days; like the level of albumin, the prealbumin level is acutely depressed by severe physiologic stress. The half-life of retinol-binding protein is approximately 10 hours, but its sensitivity to even minor stress limits the clinical utility of its measurement.

Somatic proteins are those that indicate the state of skeletal muscle mass. The most commonly used index is 24-hour urinary creatinine excretion. The index is expressed as milligrams of urinary creatinine in 24 hours for the patient per milligram of urinary creatinine in 24 hours by a normal subject of the same height and sex, multiplied by 100.

Functional testing—of muscle strength, for example—has advantages over biochemical and anthropometric assessments but is not used consistently. Other indicators of malnutrition include leukopenia and lymphopenia and skin-test anergy. Patients receiving home parenteral nutrition or those with fat malabsorption are at risk of essential fatty acid deficiency (EFAD) (2,8). This condition is diagnosed using the Holman Index, described as the plasma triene to tetraene ratio; a Holman Index of 0.2 is currently considered the upper limit of normal (17). Current preparations of parenteral nutrition used in the United States contain lipids from soybean, olive, safflower, coconut, and fish oils (18,19). Concern that soybean and/or safflower formulations may contribute to liver disease in patients has spawned questions of whether fish oil preparations may be a better alternative. One study evaluated children with Intestinal Failure-Associated Liver Disease who received fish oil–based emulsion, showing that at proper dosages, fish oil emulsions contained adequate amounts of essential fatty acids to prevent EFAD (20).

Malnutrition results from deficient nutrient intake, impaired metabolism, excessive losses, or some combination of these factors. Clinical evaluation for malnutrition should include not only examination for signs of wasting (e.g., at the temples or in the hands) but also examination of hair for thinning or poor attachment, the skin for xerosis, and the mouth for inflammation, all indicative of macronutrient or micronutrient deficiencies (see Table 26.2).

TABLE 26.2

Physical Findings Associated with Common Nutrient Deficiencies

Physical Finding	Responsible Nutrient Deficiency
Muscle wasting (temples, hands)	Protein; energy
Skin: xerosis scaling, bruising	Protein; energy; vitamins A, C, K
Hair: thinning, poor attachment, pigment changes	Protein; energy; vitamins A, E, B

Hospitalized patients are subject to marasmus (a term derived from a Greek word meaning “to waste”), a state of both protein and total energy malnutrition. Marasmus is distinguished from kwashiorkor, a Bantu word meaning “displaced child,” which describes the state of protein deficiency despite adequate energy intake. Kwashiorkor occurs in babies weaned from the breast in low-income countries with subsistence diets. Kwashiorkor can be associated with a serum albumin as low as 1 g/dL as compared with the fourfold higher normal value, resulting in very low oncotic pressure and characteristic edema.

Cachexia is a “multifactorial wasting syndrome defined by continuous loss of skeletal muscle mass

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(with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment" (21). Loss of lean body mass increases the risk of morbidity and mortality in both acute and chronic illnesses (22,23). Cachexia affects between 50% and 80% of cancer patients and may account for up to 20% of cancer mortality (24). The importance of mitochondrial dysfunction in this area is a topic of current scrutiny (24–26). Mitochondrial dysfunction in cachectic skeletal muscle is characterized by increased oxidative stress, decreased protein synthesis, and decreased adenosine triphosphate (ATP) production, which exacerbate muscle cell apoptosis and wasting (27). Elevated inflammatory markers (e.g., IL-6, TNF-α) in cachectic patients may further disrupt mitochondrial function, by reducing rates of protein synthesis and inducing protein hypercatabolism causing accumulation of degraded proteins (28,29). Studies examining the resulting derangement in amino acids in muscle mitochondria have found increased lysine, arginine and proline, and decreased glutamate and aspartate combined with degraded proteins indicative of oxidative phosphorylation system deficits (27). Key to preventing or reversing cachexia includes stimulating autophagy, stimulating mitophagy, and reducing oxidative stress in cells (25). These responses allow cells to optimize the number and functionality of mitochondria, remove oxidatively damaged proteins, and reduce inflammation (30).

Approximately 25% of the body's protein reserves can be consumed to generate energy during starvation, sparing vital functions for a period as long as 50 days. In a well-nourished adult, nearly 3 kg of protein can be turned over to generate 12,000 kcal of energy.

Energy requirements in hospitalized patients can be estimated through application of the Harris–Benedict equation (see Appendix A) or, when available, by use of indirect calorimetry (IC). Limited evidence suggests the superiority of the IC measurement versus estimation of energy requirements using predictive equations in the mechanically ventilated, critically ill (31). One observational study compared various predictive equations, including Harris–Benedict, and measured energy expenditure using IC in critically ill patients with acute brain injury. Although the authors found that predictive equations calculated similar energy requirements as IC, IC provided a more accurate measurement due to interpatient variability (32). Protein requirements rise with metabolic stress. Baseline protein needs of approximately 0.8 g/kg/day nearly triple after a significant burn and rise to lesser degrees with all disease states. Hyperglycemia is a hazard associated with nutritional support; the American Diabetes Association's 2020 Standards of Medical Care in Diabetes in review of pertinent literature concluded that tight glycemic control <180 in critically ill patients provided a mortality benefit (33).

NUTRITION SUPPORT

Dietary Supplements

Anorexia, or simply reduced appetite, may occur in patients with current nutritional deficiencies or patients at risk of developing them. Simple strategies to combat a persistently deficient appetite include frequent spacing of small meals and the prioritization of energy-dense (usually high-fat) foods. When energy-dense foods are proffered, there should still be attention to nutritional quality. Examples of foods rich in both nutrients and calories include nuts/seeds, nut/seed butters, and avocado. Whey, pea, or rice protein powders may also be useful for food supplementation and for concocting nutrient- and energy-dense dishes (34,35).

When efforts to modify the diet fail to provide adequate nutrition, powdered (for reconstitution) or liquid supplements may be indicated. A wide variety of commercial products are available; selection is often best based on the recommendations of an experienced dietitian and patient preference. Some of the

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available supplements (e.g., Ensure, Boost) are nutritionally complete and can be used, if needed, as the sole source of nutrients and energy.

For critically ill and cachexic patients, supplementation with specific amino acids may help regulate essential mitochondrial function and prevent further loss of muscle mass (26,36). Antioxidant supplementation in cachexic patients is controversial as it may benefit deficient patients, but exacerbate cachexia in antioxidant replete patients (37,38). Multifaceted approaches including nutritional supplementation, pharmacology (anti-inflammatory and anticatabolic medications), and exercise training or exercise-mimicking treatment show promising clinical impact (39).

Enteral Nutrition Support

Enteral nutrition (EN) support involves the administration of nutrient formulas into the GI tract through a tube. The weight of evidence clearly favors enteral over parenteral nutrition support whenever either is an option, leading to the axiom that the gut should be used whenever it works (40). When nutrients are not administered via the GI tract, mucosal atrophy occurs, as does dysfunction of the pancreatic/biliary system. Parenteral nutrition also appears to pose increased risk of infection compared to enteral feeding (41). Options in enteral nutrition have been enhanced over recent years with the development of low-risk procedures for tube insertion and the development of a variety of commercial preparations tailored to different clinical situations. For the most part, enteral feeding formulas are classified according to energy density, protein content and source, intended administration route, and molecular complexity.

Feeding Tubes

There are two types of feeding tubes: those that enter the GI tract through the nose or mouth and those that enter through the abdominal wall. Nasogastric (NG) tubes are used for short-duration feeding and when the risk of aspiration is low. Nasoduodenal and nasojejunal (NJ) tubes are preferable for longer-term feeding and when the risk of aspiration is higher. The prevailing view is that the risk of aspiration falls the more distally the tube is placed. A systematic review and meta-analysis of 20 randomized controlled trials found that nasoduodenal and NJ feeding in intensive treatment patients reduced gastric residual volume and risk of aspiration (42).

Tubes placed through the abdominal wall are more appropriate in general for long-term supplementation. Such tubes are less likely to kink or occlude, and they reduce the risk of aspiration (43). Gastrostomy and jejunostomy tubes can be inserted endoscopically, radiologically, or surgically (44). The percutaneous endoscopic gastrostomy (PEG) tube is generally most popular. Insertion requires an endoscopy laboratory and local anesthesia with sedation, and it is routinely done on an outpatient basis. Jejunostomy tubes, placed endoscopically or surgically, may be indicated when the risk of aspiration is considered particularly high. The technical difficulty is greater for jejunostomy tubes, and the complication rate is also higher (43). Advances in technique permit endoscopic tube placement in most circumstances, except when anatomy is distorted by surgery or pathology (44). The low profile of a button gastrostomy is easily covered by clothing making it a convenient option for children or particularly active patients (45).

Enteral Formulas

Standard enteric formulas are polymeric, containing oligosaccharides, intact protein, and triglycerides. Commercial preparations are lactose free or are suitable for lactose intolerance and can provide the estimated daily energy needs. The energy density varies from 1 to 2 kcal/mL, with high-energy-density preparations indicated when fluid restriction is required. Formula proteins are usually derived from

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sodium and calcium caseinates, soy protein isolate, hydrolyzed whey protein, or pea protein (46). The fat is of vegetable origin. Such formulas can be delivered directly into the stomach, duodenum, or jejunum. Fiber-containing formulas or fiber-added supplements often include soy polysaccharide, pea fiber, guar gum, or oat fiber; benefits include prevention of osmotic diarrhea (47) by bulking stool and promoting growth of beneficial gut bacteria, and evening out of serum glucose responses (48,49). Prebiotic forms of fiber such as fructooligosaccharides and inulin, associated with fermentable oligosaccharides, disaccharides, and monosaccharides, and polyols (FODMAPs) are sometimes added to enteral formulas but are poorly absorbed in the small intestine and may cause gas, abdominal distention, and diarrhea (48). A mixture of long-chain triglycerides, which provide omega-3 fatty acids, plus medium-chain triglycerides has shown improved absorption, rates of infection, and hepatic, renal, and immune function (50). Monomeric formulas, sometimes referred to as elemental, are more expensive than standard formulas and contain hydrolyzed protein as free amino acids and monosaccharides and disaccharides for easy digestibility (51). Theoretically, monomeric formulas should offer significant benefit to patients with states of impaired absorption such as acute pancreatitis and Crohn's disease, however, the evidence presents no significant advantage over other formulas such as semi-elemental and standard polymeric (52,53). Essential vitamins, minerals, and trace elements are routinely added to both polymeric and elemental formulas in order to meet all nutrient requirements.

Targeted formulas are intended for use in particular disease states. Formulas specifically tailored for inborn errors of metabolism are of clear value in defined circumstances. Commonly administered enteral feedings in patients with cystic fibrosis include elemental formulas without enzyme replacement, or polymeric formulas with enzyme supplementation; however, due to a minimal number of clinical trials, definitive formula recommendations are not in place (54).

Tailored formulations for many conditions lack evidence of benefit compared with conventional preparations. Use of formulas tailored for hepatic dysfunction, containing a high ratio of branched-chain to aromatic amino acids, is supported by available evidence (55,56). Formulas based on essential amino acids and keto acid analogues in association with very low protein formulae have been developed for renal failure (57). In addition, children hospitalized in the pediatric intensive care unit may be more likely to develop acute kidney injury if underfed, thus stressing the importance of enteral feeding in the acute setting (58). Formulas tailored for pulmonary disease exploit the lower respiratory quotient (RQ) of fat and protein relative to carbohydrate. The RQ refers specifically to the molar ratio of carbon dioxide produced per oxygen consumed. The RQ is 1 for carbohydrate, 0.7 for fat, and approximately 0.8 for protein. Thus, fat and protein can be used to generate energy with less CO_2 production, which is of particular value in states of CO_2 retention (see Chapter 15).

There is some evidence that enteral formulas using keto acids rather than amino acids can slow progression of chronic renal failure (58,59). Glycemic control can be improved with formulas tailored for diabetes (60). Supplementation of EN with n-3 fatty acids (61) and other nutrients designed to enhance immune function have been shown to reduce infection rates, time spent on mechanical ventilation, and intensive care unit (ICU) lengths of stay in certain disease states (61,62). A recent randomized controlled trial evaluated antioxidant-enriched versus immune-enhancing EN in patients who had undergone esophagectomy for cancer. The results showed that there was no significant difference in nutritional markers after patients were given either formulation (63). There is increasing interest in the addition of glutamine to enteral formulas, as it is the preferred energy substrate of the GI tract (64,65). Studies of its use in enteral formulas are encouraging; there is also evidence to suggest increased benefit from high-dose parenteral glutamine as a supplement to nutrition support (66). In mice with induced colitis, enteral

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formula enriched with glutamine, oligosaccharide, and fiber was found to decrease the level of inflammation in the intestine (67). This is a possible avenue for further research regarding EN formulations and patients with ulcerative colitis.

Modular formulas are available to supplement commercial preparations so that nutrient composition can be tailored to the individual patient's need. There are more than 100 commercially available enteral feeding formulas. Selection is best based, other than for the nutrition specialist, on the advice of a consulting dietitian; inpatient use is constrained by the hospital formulary.

Enteral feeding can be delivered as bolus feeds or continuous infusions; bolus feeding is feasible only when the tube is in the stomach. Bolus feeds are more convenient, with infusions typically requiring a pump. Infusions into the small bowel generally can be tolerated at a rate up to 150 mL/hour.

Aspiration is the principal risk of enteral feeding. Risk may be reduced by feeding with the torso at a 30° to 45° angle of inclination rather than supine (68). Patients who are mechanically ventilated due to Acute Respiratory Distress Syndrome (ARDS) may be placed in the prone position to improve oxygenation. In a study comparing EN in 47 ARDS patients in supine and prone positions, percentage of prescribed calories received was similar but in supine position patients received a higher percentage of prescribed protein (69). Concerns about increased aspiration risk in the prone position were not supported (70–72). When the gag reflex is absent or impaired or gastric emptying is delayed, feeding into the jejunum is preferred. Diarrhea occurs not uncommonly, especially in patients taking antibiotics concomitantly. The risk generally is reduced by the use of iso-osmolar formulas.

Emerging evidence suggests that COVID-19 patients present unprecedented EN challenges due to direct effects of the SARS-COV-2 virus on the GI tract and elevated sedation in intubated patients. Effects include low motility, low absorption rates, increased risk of aspiration associated with turning patients to prone position and increased infection risk to medical personnel associated with placement of postpyloric feeding tubes (72).

Parenteral Nutrition Support

The delivery of nutrition directly into the bloodstream poses risks that enteral feeding does not, and it should be avoided when possible. Indications for parenteral feeding include states of severe malabsorption; such states occur in extensive bowel resection, radiation enteritis, and severe inflammatory bowel disease; disordered intestinal motility, obstruction, or persistent vomiting; premature birth; and states of extreme catabolism, such as extensive burns, for which enteral feeding may not be adequate.

Whereas enteral formulas are approved as foods, parenteral solutions must be approved by the Food and Drug Administration as drugs. Intravenous nutrient infusions are intended to meet energy and nutrient requirements completely (total parenteral nutrition; TPN) or incompletely (peripheral parenteral nutrition; PPN). PPN solutions can generally be delivered through a peripheral or central vein, but TPN requires central venous access. Near-complete nutrition support via peripheral access may be achievable in patients who can tolerate a high volume of isotonic solution. To meet energy needs while limiting the proportion of calories from fat, hypertonic carbohydrate solutions must be used, thus requiring TPN and central access.

Access for TPN is generally via the subclavian or jugular veins. Peripheral placement of long catheters threaded into the superior vena cava and creation of an arteriovenous fistula as in dialysis are alternatives. Surgical insertions are used to tunnel the catheter under the skin to reduce the risk of infection. Other vascular approaches are used less frequently. The risk of line sepsis is reduced by strict adherence to aseptic technique and infection control guidelines. Dedicated TPN lines can be maintained

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for months, if not years. Indwelling central venous catheters pose a risk not only of sepsis but also of thrombosis; antibiotic- and heparin-bonded catheters may help.

Various plastics are used for TPN delivery. There is some absorption of insulin by commonly used plastics, so the glucose levels of patients with diabetes should be monitored carefully, with adjustments in infused insulin made accordingly.

Parenteral nutrition is generally indicated when intestinal absorption is impaired. Benefit is convincingly established when there is intestinal failure sometimes caused by short bowel syndrome (73). Meta-analysis indicates that there is no apparent net mortality benefit associated with use of TPN in surgical or critical care patients (74). A multicenter randomized controlled trial evaluated early versus late initiation (48 hours vs. greater than 8 days) of TPN in critically ill adults. The study found that late initiation was associated with fewer complications and quicker recovery time (75). Late initiation of TPN in children resulted in fewer infections, a shorter need for intensive care, and a shorter duration of ICU stay, although mortality was similar in both early and late initiation groups (76). Lipid emulsions are generally provided as adjuvants to TPN formula. Micronutrient doses in TPN formulas are standardized, but they may need to be tailored in certain conditions. Evidence to date supports the use of glutamine-supplemented parenteral formulas in the critically ill (66,74). Glutamine is the preferred fuel of enterocytes.

There are clear disadvantages to over nutrition beyond those related to weight gain (77). In normal states, adults can oxidize glucose at a rate of up to approximately 14 mg/kg/min. This rate is reduced to as low as 5 mg/kg/min in burn patients. Glucose infused beyond this capacity is converted to fat, with elevation of the RQ to above 1 and loss of available energy due to metabolic demand and waste. Fatty liver may result over time from excessive hepatic synthesis of triglycerides.

Lipid emulsions administered with TPN become coated with apolipoproteins in circulation, much the same way as do endogenously produced lipoprotein particles. Because infused lipid particles differ from chylomicrons, they are metabolized differently, eliciting the formation of a novel lipoprotein (lipoprotein X). Emulsified lipid droplets are acted on by endothelial lipoprotein lipase and undergo metabolism much the way ingested fat does (see Chapter 2).

Because lipid solutions are highly susceptible to microbial growth, infusion times of less than 12 hours are recommended. Lipid mixed with the other components of TPN, known as total nutrient admixtures, can allow lipid infusions over 24-hour periods but have disadvantages as well, among them catheter occlusions. Total nutrient admixtures may be particularly useful in premature neonates, who may not tolerate standard lipid infusions.

Lipid infusions increase the risk of bacteremia and rarely can result in fat overload syndrome, which is characterized by fever, hepatosplenomegaly, and coagulopathy due to fat sludging. Impaired pulmonary function and interference with immune function by occupation of the reticuloendothelial system also occur. Structured lipid emulsions contain either synthetically structured triglycerides or physical mixtures of medium-chain triglycerides (MCTs) and long-chain triglycerides (LCTs) and have promising clinical outcomes (78,79).

The use of long-term parenteral nutrition in children is associated with metabolic bone disease. The etiology of the condition is likely multifactorial, with calcium and phosphate deficiencies playing an important but only partial role (80). Strategies to prevent onset of metabolic bone disease include supplementation with additional calcium and phosphorus, which helps avoid the development of chronic metabolic acidosis and subsequent hypercalciuria, and vitamin D supplementation (81).

Use of TPN is associated with gallstone formation due to stasis in the gallbladder (82). Protracted use of TPN warrants periodic evaluation of the gallbladder by ultrasound, with consideration of elective

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cholecystectomy if stones develop. Use of ursodeoxycholic acid and S-adenosyl-l-methionine (SAMe) has shown promise in preventing TPN-induced cholelithiasis (83). Both cholestasis and cholelithiasis associated with TPN may be reduced through emulsions containing n-3 fatty acids (19).

As is the case for enteral solutions, a variety of commercial parenteral formulas are available. The selection and constitution of parenteral solutions should be overseen by a dietitian or nutrition consult service.

Pancreatitis

Acute pancreatitis is an illness with high metabolic demand and an increased catabolic state. Patients can experience rapid nutritional deterioration especially in severe acute pancreatitis. As a result of these dramatic changes in body metabolic processes, much debate over method, formulation, and timing for feeding in acute pancreatitis has developed. Early oral feeds are recommended if tolerated as opposed to nil per os (NPO) status; if oral feeding is not tolerated, early enteral feeding via NG or NJ tube is recommended, especially when severe disease is predicted, to maintain a healthy gut barrier, reduce risk of pancreatic necrosis, and to prevent further disease-related complications (84,85).Two recent meta-analyses showed that EN was superior to TPN in that it decreased mortality, infection, organ failure, and surgical intervention for patients with severe acute pancreatitis and was associated with decreased hospital length of stay (86, 87).

Special Considerations

A recent Cochrane Systematic Review has shown megestrol acetate (Megace®), a synthetic progestin, can improve appetite and promote weight gain in both cancer and AIDS-related anorexia-cachexia (88). Megestrol has also been evaluated for use in older adult dialysis patients with malnutrition measured using the SGA showing an improved appetite, increase in dry weight, and improved quality of life, with few reports of adverse side effects (89). Although effective in stimulating appetite and supporting an increase in body mass, megestrol is associated with an increased risk of deep venous thrombosis.

Growth hormone has been shown to increase lean body mass in human immunodeficiency virus (HIV) wasting syndrome but at the cost of hypertriglyceridemia and insulin resistance. Patients with HIV-associated lipodystrophy treated with growth hormone–releasing factor showed an increase in lean body mass and decrease in visceral adipose tissue (90).

MCTs in either enteral or parenteral preparations may be useful in states of malabsorption. MCTs are more readily oxidized, whereas LCTs are needed to provide the essential fatty acid linoleic acid. Balanced mixtures of MCT and LCT may be particularly advantageous.

Use of both enteral and parenteral feeding may fail to suppress appetite completely because of the dependence of satiety in part on the sensations elicited during ingestion, or due to the timing of enteral feedings (91,92). Supplementation of enteral feeds with pea-fiber and fructooligosaccharides may lead to higher reported fullness among subjects compared to those consuming enteral formulas with otherwise identical macronutrient composition (93).

Preoperative EN support is recommended for malnourished patients if tolerated and with a functioning GI tract to minimize risk of poor postsurgical outcomes, whereas preoperative TPN should be reserved for severely malnourished patients or those at high risk of malnutrition and unable to tolerate EN or without sufficient bowel function (94). Postoperative TPN should be considered only if the period of needed support is likely to exceed 1 week (94,95). Although TPN has been the convention in pediatric patients requiring extracorporeal membrane oxygenation, evidence suggests that EN is both feasible and effective if tolerated (96).

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Nutritional intervention is indicated in patients with HIV who have lost more than 5% body weight in 3 months; oral nutritional supplements or EN is preferable to parenteral delivery, if it is possible (97).

Cachexia is a specific form of malnutrition characterized by muscle wasting and loss of lean body mass. Commonly seen in cancer and AIDS patients, cachexia is associated with anorexia, but a mere increase of nutrition intake is insufficient to reverse the changes associated with this condition (98). Increased protein breakdown is thought to be responsible for the muscle wasting of cachexia. The leucine metabolite *β*-hydroxy-*β*-methylbutyrate (HMB) has emerged as a potential antagonist of cachexia-related protein breakdown. HMB is known to play an important role in protein synthesis (99) and has been used by athletes to help build muscle (see Chapter 32). In *previous* animal and human trials, HMB appeared to help prevent muscle wasting by preserving muscle mass and strength (100,101). Abbott Nutrition produces an enteral supplement called Juven that combines HMB with arginine and glutamine, both of which appear to enhance protein synthesis (102). Preliminary evidence suggests benefit in reversing age-related muscle losses, increasing insulin sensitivity (103,104) and in accelerating diabetic wound repair (105). A randomized, double-blind, placebo-controlled trial was completed evaluating whether Juven improved cancer cachexia. The study experienced a large dropout rate due to patient preference, but ultimately showed, after 8 weeks of treatment with Juven, no change in lean body mass (106).

Malnutrition is a consideration after bariatric surgery. Roux-en-Y and laparoscopic sleeve gastrectomy surgery comprise 38.3% and 45.9%, respectively, of bariatric surgery performed throughout the world today (107). Roux-en-Y bariatric surgery intentionally causes decreased absorption by bypassing the distal stomach, duodenum, and proximal jejunum. Most commonly, bariatric surgery patients may become deficient in iron, folic acid, calcium, and vitamins B_1, B_{12}, and D, and long-term supplementation is recommended (108). Patients may be at increased long-term risk (12 months after surgery) of carotenoids and vitamins C and A deficiencies after Roux-en-Y gastric bypass surgery even after vitamin and mineral supplementation (108–110).

Nutrigenomic Considerations

Cachexia in cancer patients poses challenges for patients' quality of life and ability to recover from treatments. Certain cancers are more prone to causing cachexia, yet within the same subset of cancer types, there remains a variation in the development of chronic wasting between patients. As a result of this paradox, researchers have questioned whether there are genetic variations (in the form of single nucleotide polymorphisms—SNPs) present that result in higher risk for cachexia. At the present time, research shows that multiple polymorphisms may influence the development of wasting and cancer cachexia (111,112).

Aging and Nutrition

Sarcopenia is defined as a decrease in appendicular muscle mass that falls below 2 standard deviations from the mean as compared to young, healthy adults of the same sex and ethnicity. Sarcopenia is an age-related process that increases as a patient grows older. It has been postulated that sarcopenia and dietary factors like consumption of antioxidant-rich foods may be related. A recent study found that higher dietary intake of antioxidant vitamins, particularly vitamin C was associated with higher skeletal muscle mass and sarcopenic indices in women age from 18 to 79 (113). The pathophysiology of aging and muscle mass is detailed further in Chapter 31.

The obesity epidemic has been a serious public health and medical concern since the 1990s. The focus on normal BMI as desirable is based on studies showing that overweight and obese BMI increases morbidity and mortality for patients. Recent studies have called into question this association for the older

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adult population. As a person ages, it may be more "healthy" to have a BMI in the overweight category. A growing body of evidence highlights this by showing that older adult patients with overweight BMI resulted in lower mortality risk, whereas changes in BMI for an older adult patient whether increase or decrease increased mortality (114–116). Higher BMI may be indicative of a greater ability to utilize nutrients consumed or a decreased toll on the body from chronic medical illnesses.

CLINICAL HIGHLIGHTS

Clinical assessment for malnutrition can and should be routinely incorporated into the history and physical examination of both inpatients and outpatients. For chronically malnourished patients able to eat, dietary adjustments or supplements may permit restoration of nutritional adequacy. When eating is precluded by illness, EN support is preferred to parenteral nutrition whenever the GI tract is functioning. Enteral formulas increasingly can be tailored to the condition and metabolic state of individual patients; dietary consultation is indicated to facilitate optimal choices. Feeding in acute pancreatitis has been debated; however, studies now show the superiority of EN to parenteral nutrition in terms of mortality and hospital stay.

Parenteral nutrition support is riskier and costlier than enteral support but is indicated when the GI tract is nonfunctioning. Improvements in the composition of formulas and the techniques for vascular access offer the promise of TPN with lower rates of complication. Nutrition service consultation is always indicated when TPN is to be used.

Evidence is accruing that specific nutrients can be used to promote and protect lean body mass during times of acute stress, with potential enhancement of wound healing and overall recovery time. Proprietary preparations designed specifically for this application are available. There may be times when a higher BMI may actually be beneficial. In the older adult population, overweight BMI may be protective rather than harmful in terms of mortality (see Chapter 5).

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Chapter 27

Diet, Pregnancy, and Lactation

Lauren M. Dinour

INTRODUCTION

Optimal maternal nutrition during pregnancy and lactation is vitally important to the health of the mother and infant. Nutritional needs rise during pregnancy (see Table 27.1) in response to the metabolic demand of the developing embryo as well as to changes in maternal physiology.

There is definitive evidence that periconceptional folate supplementation decreases the incidence of neural tube defects (NTD). The maternal diet is often deficient in calcium, iron, and other micronutrients, and supplementation with a prenatal vitamin throughout pregnancy is indicated. Vitamin A at doses of about 10,000 IU/day is potentially teratogenic and should be avoided during pregnancy. Carotenoids with vitamin A activity are safe. Evidence to date neither supports nor refutes recommendations for omega-3 fatty acid supplementation during pregnancy or lactation (1). Caloric needs rise in pregnancy, and thus energy intake should be increased, but excessive weight gain is potentially disadvantageous to the mother and fetus.

Under most circumstances, breastfeeding is the preferred nutritional source for neonates. Certain components of human milk change in response to maternal diet. A generous intake of dietary choline and continued use of prenatal vitamins are indicated throughout the period of lactation. The pattern of macronutrient intake indicated for general health promotion is appropriate during pregnancy and lactation as well. Biologic maturity occurs on average 5 years after menarche. Before this time, a woman may still be growing herself, creating metabolic demands in conflict with the needs of pregnancy.

OVERVIEW

Diet

Maternal weight should be nearly ideal at the start of pregnancy to prevent complications that may arise from either maternal obesity or underweight. Underweight in the mother is associated with low birth weight (less than 2,500 g) and infants born small for gestational age (SGA; below the 10th percentile), whereas maternal overweight and obesity are associated with macrosomia (birth weight of greater than 4,000 g), infants born large for gestational age (LGA; above the 90th percentile), and increased maternal risks of gestational hypertension, gestational diabetes mellitus (GDM), and preeclampsia (2–4).

Babies of mothers with pre-pregnancy obesity appear to have an increased risk of spina bifida and other congenital anomalies, as well as increased incidence of fetal death, preterm birth, shoulder dystocia, and childhood obesity (4,5). Maternal obesity is a major risk factor for childhood obesity, which persists into adulthood independent of other factors (6–11).

Physiologic changes during pregnancy alter nutritional requirements. Plasma volume expands about 50% during pregnancy. Total mass of red blood cells increases about 30% over pre-pregnancy levels (12). Basal metabolic rate is increased by about 24% toward the end of gestation (13). These changes

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require increased intake of energy, nutrients, and fluid. The greater increase in plasma volume than in red cell mass will cause the hematocrit to fall during pregnancy; however, the mean corpuscular hemoglobin concentration should remain fairly constant, barring a concurrent anemia. Maternal hemoglobin during pregnancy should consistently be higher than 11 g/dL to ensure adequate oxygen delivery to the fetus. Nutritional causes of anemia should be considered if the hemoglobin level falls below this value and another explanation is not evident. A microcytic anemia suggests iron deficiency, whereas a macrocytic anemia suggests folate or vitamin B_{12} deficiency; the former is the more common.

TABLE 27.1

Recommended Nutrient Intake Changes Associated with Pregnancy and Lactation[a]

Nutrient	Recommended Intake by Subject Category				Average U.S. Dietary Intake in Females (≥20 yr)	Content of Representative Prenatal Vitamin[e]
	Female (19–30 yr)	Female (31–50 yr)	Pregnancy	Lactation (Initial 6 mo)		
Calcium (mg)	1,000	1,000	1,000	1,000	845	250
Choline (mg)	425[b]	425[b]	450[b]	550[b]	287	—
Folate (mcg)	400[c]	400[c]	600[d]	500	447	1,330
Iodine (mcg)	150	150	220	290[d]	NA	150
Iron (mg)	18	18	27[d]	9	12.1	27
Magnesium (mg)	310	320	350–360	310–320	272	45
Omega-3 fatty acids (g)	1.1[b]	1.1[b]	1.4[b]	1.3[b]	1.66	—
Niacin (mg NE)	14	14	18	17	21.3	18
Phosphorus (mg)	700	700	700	700	1189	—
Protein (g)	46	46	71[d]	71[d]	69.4	—
Riboflavin (mg)	1.1	1.1	1.4	1.6	1.84	1.4
Selenium (mcg)	55	55	60	70	96.6	—
Thiamin (mg)	1.1	1.1	1.4	1.4	1.35	1.4
Vitamin A (mcg RE)	700	700	770	1,300[d]	598	770
	2.4	2.4	2.6	2.8	4.05	5.2

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Vitamin B_{12} (mcg)	2.4	2.4	2.8	2.8	2.4	2.8
Vitamin B_6 (mg)	1.3	1.3	1.9	2.0*d*	1.79	1.9
Vitamin C (mg)	75	75	85	120*d*	74.2	85
Vitamin D (mcg)	15	15	15	15	4.3	25
Vitamin E (mg TE)	15	15	15	19	8.5	15
Vitamin K (mcg)	90*b*	90*b*	90*b*	90*b*	123.5	90
Zinc (mg)	8	8	11	12*d*	9.4	11

[a]NA, not available; NE, niacin equivalent, which equals 1 mg of dietary niacin or 60 mg of dietary tryptophan; RE, retinol equivalent; TE, alpha-tocopherol equivalent.

[b]Nutrient intake levels are Adequate Intakes (AIs), believed to meet the needs of all healthy individuals. All other data specify the Recommended Dietary Allowances (RDAs), the level sufficient to meet the nutrient requirements of nearly all (97% to 98%) of healthy individuals.

[c]Intake of folate 400 mcg/day is now recommended for all women of child-bearing age to ensure adequate stores at the time of conception.

[d]Nutrient intake levels represent a 50% or more increase over recommendations for nonpregnant adult women.

[e]Nature Made prenatal multivitamins, Pharmavite LLC, 2020.

Adapted from the Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine, National Academy of Sciences. National Academy of Sciences DRI Reports. Available at www.nap.edu; accessed May 26, 2020; and the National Health and Nutrition Examination Survey, Agricultural Research Service, United States Department of Agriculture. What We Eat in America, NHANES 2015–2016. Available at www.ars.usda.gov; accessed May 26, 2020.

Requirements for folate, iron, and zinc rise disproportionately during pregnancy. In general, intestinal nutrient absorption is enhanced during pregnancy as an adaptation to increased metabolic demands. Serum lipids tend to rise during pregnancy, due largely to the effects of progesterone.

Whereas electrolytes, fatty acids, fat-soluble vitamins, and glucose cross the placenta by simple or facilitated diffusion, amino acids, water-soluble vitamins, calcium, and iron are actively transported across the placenta to the fetal circulation.

On average, the second and third trimesters of pregnancy require a calorie increase over baseline of approximately 330 to 540 kcal/day, and lactation during the first 6 months requires 330 to 450 kcal/day over non-pregnant, non-lactating energy requirements (13,14). Nutrients for which the recommended dietary allowance (RDA) is specifically raised in pregnancy include total protein; total energy; omega-3

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fatty acids; choline; folate; iodine; iron; magnesium; niacin; riboflavin; selenium; thiamin; vitamins A, B_6, B_{12}, and C; and zinc. Lactation requires additional increases beyond pregnancy levels in choline; iodine; riboflavin; selenium; vitamins A, B_6, B_{12}, C, and E; and zinc; requirements for iron and folate decline.

Inadequate weight gain during pregnancy is associated with preterm birth and SGA, whereas excessive weight gain is associated with caesarean section delivery, macrosomia, and LGA (15,16). The timing of weight gain may also play a role in adverse maternal or infant outcomes. A recent study found that women experiencing more rapid weight gain earlier in pregnancy had a lower risk of SGA but a higher risk of LGA (17). Data from another study suggest that women with greater weight gain during the second trimester have a lower risk of SGA, and weight gain in the third trimester is associated with a twofold risk of pregnancy-induced hypertension and a reduced risk of GDM (18).

Nutritional support of malnourished women during pregnancy is beyond the scope of this discussion but in general is approached as malnutrition under other circumstances (see Chapter 26). The topic has been reviewed elsewhere (19). The Special Supplemental Nutrition Program for Women, Infants, and Children (WIC) is designed to meet the nutritional needs of women and infants. In 2018, the program assisted nearly 680,000 women in meeting nutritional needs during pregnancy, and over 1 million breastfeeding and postpartum women (20). Because WIC supplements tend to be shared with family members, the nutrient intake of pregnant women in this population is often suboptimal and requires close scrutiny to ensure optimal pregnancy outcomes.

Maternal weight gain during pregnancy should occur predominantly during the second and third trimesters; total energy expenditure changes little in the first trimester but increases thereafter. Evidence suggests that in women with normal body mass indexes (BMI), only a slight increase in energy intake of up to 100 kcal/day is required during the first trimester, while approximately 330 to 340 kcal/day should be added to the diet in the second trimester and 452 to 540 kcal/day in the third trimester (13,14). Among well-nourished women with an average gestational weight gain of 13.75 kg, pregnancy is thought to require an increase in energy consumption of 88,000 to 89,000 kcal over the level required for weight maintenance in the nonpregnant state (13).

Gestational weight gain recommendations aim to optimize outcomes for the woman and the child. In 2009, the Institute of Medicine (IOM) published revised gestational weight gain guidelines that are based on pre-pregnancy BMI ranges for underweight, normal weight, overweight, and obese women recommended by the World Health Organization (WHO) and are independent of age, parity, smoking history, race, and ethnic background. For underweight women with a baseline BMI below 18.5 kg/m^2, average weight gain of 0.51 kg/week during the second and third trimesters is indicated, for a total of 12.5 to 18 kg by the end of pregnancy. Women with a normal pre-pregnancy BMI (18.5–24.9 kg/m^2) are recommended to gain 0.42 kg/week during the second and third trimesters, for a total of 11.5 to 16 kg total during pregnancy. For overweight women (BMI of 25.0–29.9 kg/m^2), weight gain of 0.28 kg/week during the same period is recommended, totaling 7 to 11.5 kg during pregnancy. The IOM recommendations define obesity as a BMI of 30.0 kg/m^2 or greater and do not differentiate between class I obesity (BMI of 30.0–34.9 kg/m^2), class II obesity (BMI of 35.0–39.9 kg/m^2), and class III obesity (BMI of 40.0 kg/m^2 or greater). Given the limited data by class, the IOM recommendation for weight gain is 5 to 9 kg total during pregnancy (0.22 kg/week during the second and third trimesters) for all obese women. All of these guidelines assume a weight gain of 0.5 to 2 kg during the first trimester (12). Weight gain of more than 1 kg/week at any time is generally excessive. Weight loss is always concerning and weight gain of less than 1 kg/month, except for during the first trimester, generally indicates inadequate nutrition. Obligatory

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added weight during pregnancy, attributable to fetal growth, placental growth, amniotic fluid production, uterine and breast enlargement, and expansion of the blood volume, accounts for approximately 7.7 kg on average. Weight gain in excess of this amount represents added maternal body weight, mostly in extracellular/extravascular fluid and counterbalancing hip and gluteal fat, that the woman will need to lose following pregnancy to return to pre-pregnant weight and shape. Available evidence suggests that women less than 20 years old require additional weight gain beyond the IOM recommendations to reduce the risk of SGA (21).

Physical activity during pregnancy offers benefits to the mother at no cost to the fetus, provided that maternal tolerance is not taxed. Extreme exertion may compromise fetal well-being, though more research is needed to determine this threshold (22). Maintenance of 150 minutes of moderate-intensity aerobic exercise per week during pregnancy is appropriate unless precluded by complications (23). Regular moderate to intense physical activity before pregnancy improves insulin resistance, and regular aerobic activity during pregnancy may reduce risk for GDM (24). Women who were sedentary prior to pregnancy should gradually increase their duration and intensity of exercise while pregnant, whereas women who regularly exercised beforehand and have uncomplicated pregnancies can continue to be physically active during pregnancy and after birth (22,23). Scuba diving, activities performed while lying on the back, and exercises with potential high impact (due to risk of blunt trauma) are to be avoided during pregnancy (22,23). Postpartum exercise coupled with caloric restriction facilitates desired weight loss (23,24).

A total of approximately 925 g of protein is incorporated into the developing fetus and other products of conception. Protein requirements increase with each successive trimester, with average needs of about 79 g/day (14% kcals from protein) during early gestation and 108 g/day (17% kcals from protein) during late gestation (25). Protein intake by women in the United States is typically about 69 g/day, a figure that nearly meets the single recommendation for pregnancy but not the elevated needs during the third trimester. There has been some debate as to whether protein intake should increase during pregnancy, especially since higher protein consumption from food has been associated with a reduction in risk of SGA infants (25). Other research has found an association between dietary protein intake and GDM. Higher intake of animal protein, in particular red meat, was significantly associated with a greater risk of GDM. By contrast, higher intake of vegetable protein, specifically nuts, was associated with a significantly lower risk. Substitution of vegetable protein for animal protein, as well as substitution of some other animal protein sources for red meat, was associated with a lower risk of GDM (26).

The fetus gains approximately 30 g/day during the third trimester. Interventions to ensure term delivery are essential in maintaining this rate of development. Intensive care of premature infants can rarely sustain more than 20 g of growth/day.

The developing fetus uses glucose as its major energy source, and glucose is especially crucial for use by the fetal brain in the third trimester. Carbohydrate requirements therefore may increase to approximately 175 g/day in pregnancy (14).

Overall, the increased micronutrient requirements of pregnancy exceed the increased energy requirements. Therefore, vitamin supplementation during pregnancy is universally indicated, and the nutrient density of foods assumes increased importance.

The teratogenicity of vitamin A in high doses was revealed through the use of the vitamin A analogue isotretinoin for acne. Ingestion of 10,000 IU or more of vitamin A per day via supplements is thought to be potentially teratogenic. Carotenoid precursors of vitamin A provide adequate retinol while avoiding any known toxicity. Therefore, prenatal vitamin supplements typically provide vitamin A at well below the toxic threshold and generally in the form of the precursor beta-carotene. On the other hand, in normal-weight mothers, dietary vitamin A intake during pregnancy below the recommended daily intake is

significantly associated with an increased risk of a child with congenital diaphragmatic hernia (27).

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Immediately following birth for a period of approximately 3 to 5 days, the mother's mammary glands produce colostrum, a fluid rich in sodium, chloride, and immunoglobulins that confer passive immunity to the newborn. Colostrum is replaced by milk, which is rich in lactose and lipids and comparatively low in sodium and chloride. Milk volume consumed by the neonate is about 50 mL/day at birth, 500 mL by day 5, and 750 mL at 3 months, though intake amounts can differ widely by infant (28).

Milk production is maintained by infant suckling, which suppresses hypothalamic dopamine production, thereby disinhibiting prolactin release. The first 4 months of lactation require, and convey to the infant, an amount of energy comparable to that of the entire gestational period. Human milk is both appropriate and optimal as the sole source of infant nutrition for the first 6 months of life, barring contraindication (e.g., human immunodeficiency virus [HIV] infection, untreated brucellosis, human T-cell lymphotropic virus type I or type II). There is uncertainty whether milk meets all the infant's nutritional needs beyond this point (see Chapter 29). Multiple national and international medical and health organizations recommend exclusive breastfeeding as the preferred method of infant feeding for the first 6 months, with continued breastfeeding alongside complementary foods until at least the infant's first birthday (29–31). Increasing the proportion of infants who are ever breastfed, breastfed at 1 year, and exclusively breastfed through 6 months are among the breastfeeding objectives of Healthy People 2020 (32).

The fatty acid composition of human milk varies with maternal dietary intake. With few exceptions, such as choline, iodine, and selenium, there is little evidence that the levels of minerals and trace elements in milk vary with maternal diet (33–36). In contrast, several vitamin levels in milk are responsive to dietary intake, with the strength of the relationship varying by nutrient. The levels of both fat- and water-soluble vitamins in milk vary in proportion to maternal intake (33–35). Calcium and vitamin B_{12}, and possibly other nutrients, are preserved in milk at the expense of maternal stores when maternal intake is less than daily requirements (33).

Recent work has shown that human colostrum and milk, which traditionally have been thought to be sterile, provide a continuous supply of commensal probiotic bacteria to the infant gut such as *Lactobacillus* and *Bifidobacterium* species. Human milk also provides more than 200 different oligosaccharides, which serve not as food for the infant (still lacking the intestinal enzymes to digest them) but as prebiotics for the newly introduced beneficial bacteria (37). There is current interest in the influence these probiotics and prebiotics have on intestinal flora of the infant and their capacity to play a role in the prevention of infection, atopy, allergies, and various other diseases (37–40). Specific probiotic and prebiotic combinations during pregnancy and early feeding, via the mother or incorporated in early formula-feeding, may help shape the intestinal microbiota composition in infants and may be important determinants of later health (37,41,42).

As noted previously, maternal diet influences the fatty acid and vitamin composition of human milk, but it generally exerts a modest influence on minerals. Choline, iodine, and selenium are exceptions, varying substantially in response to maternal intake (33–36). Vitamins D and K are generally present at low levels in human milk, and supplementation is recommended (43–46); however, there is some evidence that lower vitamin D intake in breastfed neonates may not adversely affect bone metabolism (47,48).

Breastfeeding is accompanied by a decline in maternal bone density, regardless of maternal calcium intake; however, studies show that bone mineral density is recovered fully after weaning (49). A study of 52 lactating women in the United States suggested that intake of calcium, zinc, folate, vitamins E and D, and pyridoxine may tend to be deficient in this group (50). Another study of 83 lactating women in the midwestern United States found inadequate consumption of vitamins E and D, potassium, iodine,

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chromium, choline, and fiber (51). A recent study demonstrated that habitual—but not current—fatty fish intake is associated with omega-3 fatty acid concentration in human milk (52).

Breast milk and infant formulas differ substantially in a variety of nutrients (53). The significance of all of the differences has yet to be established. Studies suggest an association between breastfeeding and greater intelligence, whereby infants who are breastfed perform significantly better on intelligence tests in childhood and adolescence even when controlling for maternal intelligence and other potential confounders (54). The lifelong impact of this improved performance remains a topic of debate (see Chapter 29). When evaluating the association between infant feeding and the development of overweight and obesity in late childhood or adolescence, a longitudinal study of siblings in which only one sibling was breastfed found that the breastfed sibling had an adolescent BMI that was 0.39 standard deviations lower than the formula-fed sibling. This difference equates to 13.5 lb for a 14-year-old girl or 14.0 lb for a 14-year-old boy. Likewise, the findings suggest that breastfeeding reduces the risk of reaching the higher end of the BMI distribution (55). A recent meta-analysis of high-quality studies indicates that breastfeeding is associated with a 13% reduction in overweight or obesity later in life (56).

Energy requirements to sustain lactation are based on the caloric density of human milk (approximately 70 kcal/100 mL), the metabolic cost of milk production, and total milk volume, less the amount of energy used from tissue stores. The estimation that lactation requires 450 to 510 kcal/day above the energy required to maintain maternal weight assumes that approximately 170 kcal/day of milk production energy will derive from pregnancy-related fat stores (13). Loss of 0.5 to 1 kg/month is common during lactation, whereas loss in excess of 2 kg/month implies inadequate nutrition. Weight maintenance and weight gain during lactation are not uncommon. Weight loss of up to 2 kg/month appears to be safe during lactation, with preservation of energy transfer to human milk. Prolactin levels rise in response to infant suckling of the breast, which stimulates milk production and mobilization of adipose tissue stores. Prolactin also stimulates appetite and thus increased dietary intake, particularly during the first 2 to 3 months of lactation (57). Evidence suggests that energy restriction beginning 1 month postpartum can facilitate maternal weight loss without adverse effects on milk production or infant growth (58), but dietary restriction may lead to inadequate vitamin D and calcium intake (59). Women who are overweight or obese are less likely to start and continue breastfeeding than normal-weight women due to a number of barriers, including difficulties with infant positioning, nipple issues, delayed onset of lactation, and perceived insufficient milk production, among other challenges (60). Judicious management of diet and weight throughout the gestational and postpartum periods, rather than a focus on energy restriction during lactation, is therefore clearly advisable (61).

Exercise during lactation, independent of energy restriction, is not known to pose any threat to mother or infant, and it offers a range of benefits (62). Lactation may aid in weight loss, though research is conflicting in part due to varying definitions of breastfeeding, data collection time points, and consideration of other maternal characteristics that influence postpartum weight loss. A systematic review of observational studies (37 prospective and 8 retrospective studies) found that the majority reported little or no association between breastfeeding and weight change. Yet, of the five studies with the highest methodological quality, four reported a positive association between breastfeeding and postpartum weight change (63). Studies published since this review continue to provide contradictory results (64,65). Culturally defined mother-care practices probably play a role in weight change patterns among lactating women. This hypothesis should stimulate investigation into gestational weight gain and postpartum losses in different ethnocultural contexts (66).

There is interest in the role breastfeeding may play in preventing the development of atopy in the child, but the data are inconclusive (67) (see Chapter 24). Evidence is convincing that breastfeeding confers

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protection against infections, although the mechanisms by which human milk influences infant immunity remain under study (68–72).

Exclusive breastfeeding promotes an antiinflammatory cytokine milieu, which is maintained throughout infancy. Such an immunological environment limits hyperresponsiveness and promotes tolerization, possibly prohibiting the onset of allergic disease (73). Erythropoietin in human milk is apparently resistant to degradation in the infant gastrointestinal tract and may stimulate the newborn's marrow (74,75).

The amino acid pattern of human milk is species specific, suggesting another way in which human milk might make unique contributions to early development (76). Maternal diet influences the flavor of human milk and thereby serves as a means of introducing the neonate to a variety of taste experiences (77–79).

Strong flavors, and the familiarity or novelty of such flavors, may influence the feeding behaviors of infants. There is evidence to support a transfer of flavors from maternal diet to human milk for alcohol, anise, caraway, carrots, eucalyptus, garlic, and mint; infants can detect these flavors as shown through differential behavioral responses (79). For example, ingestion of garlic by the mother has been shown to lengthen feeding at first but to shorten feeding when exposure is recurrent. The duration of breastfeeding may have an influence on sensory preference at the beginning of complementary feeding (79–81). Alcohol ingested by a breastfeeding woman is conveyed to human milk and generally results in reduced feeding by the infant immediately after exposure to the alcohol, with compensatory increased feeding when alcohol is no longer present in the milk (82). Research by Mennella (83) and Mennella and Beauchamp (84) suggests that this effect is not due to the taste of alcohol per se but to some other effect of alcohol on the feeding experience. Contrary to folklore, maternal alcohol ingestion appears to decrease the sleep of a breastfeeding infant rather than increase it (85,86).

NUTRIENTS, NUTRICEUTICALS, AND FUNCTIONAL FOODS

Alcohol

Heavy alcohol ingestion during pregnancy is associated with fetal alcohol syndrome, a condition of fetal developmental delay and cognitive deficits. Multinational data estimate that 1 in every 67 mothers who consume alcohol during pregnancy give birth to a child with fetal alcohol syndrome (87). A "drink" contains on average 14 g of ethanol. About 11.5% of United States women report drinking alcohol during pregnancy (88), but given that no safe amount has been identified, recommendations in the United States promote complete abstinence.

Caffeine/Coffee

The WHO recommendation and other major guidelines indicate that caffeine intake of up to 300 mg/day—the equivalent of about 3 cups of coffee—is not harmful to mother or fetus. However, studies show that the effects of caffeine on pregnancy outcomes are highly variable from person to person, and daily doses of 100 to 200 mg during pregnancy have been associated with increased risks of miscarriage, fetal growth restriction, low birth weight, and other adverse health outcomes in the infant (89). Recent studies have also suggested that high maternal intake of coffee and cola, but not tea, during pregnancy is associated with increased risk of childhood acute leukemia (90).

Calcium

Although calcium intake recommendations do not increase during pregnancy, some studies suggest that

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calcium supplementation may reduce the risk of pregnancy-induced hypertension and preeclampsia, particularly among women with low dietary calcium intake or high risk of preeclampsia (91). However, calcium supplementation does not appear to reduce the risk of preterm birth or low birthweight and may even increase the risk of preterm birth when combined with vitamin D supplementation (92,93).

Choline

Although choline can be synthesized by the body in small amounts, it is an essential nutrient that must be consumed in the diet to meet metabolic needs. It is estimated that only 10% of the United States population meets recommended intakes, and awareness of choline's importance is low among health professionals and the public alike. Inadequate choline availability during the perinatal period has adverse effects on the development and functioning of the placenta, whereas higher intakes are associated with lasting cognitive benefits (94,95). Choline needs increase during pregnancy and lactation, though most prenatal supplements do not include choline (94). Women following a strict vegetarian or vegan diet are at an even higher risk for inadequate choline intake since animal-derived foods (e.g., eggs, meat, poultry, seafood) often contain more choline than plant sources (e.g., wheat germ, cruciferous vegetables, and certain beans and nuts) (95).

Omega-3 Fatty Acids

Available data suggest that high consumption of marine oils during pregnancy is associated with longer gestation (96,97), and the risk of preterm birth appears lower among women who receive omega-3 supplementation compared to those who do not (98). Maternal plasma docosahexaenoic acid (DHA) levels decrease significantly after delivery (99), and observational studies have found that low maternal DHA status after birth is associated with postpartum depression (100). However, clinical trials show conflicting results and there is not enough evidence to support omega-3 supplementation to prevent or treat perinatal depression (96–98). Additionally, there is evidence that omega-3 fatty acids are important in the normal development of eye and brain function (96,101–103). Yet again, reviews of the research are mixed and are unable to either support or refute the hypothesis that omega-3 fatty acid supplementation in pregnancy or lactation improves visual or cognitive development (96,98,102,104).

The omega-3 content of human milk is mediated by maternal intake. Maternal supplementation with omega-3 fatty acids during pregnancy and lactation has been shown to increase levels of DHA, alpha-linolenic acid (ALA), and/or eicosapentaenoic acid (EPA) in human milk (34). Increased consumption of omega-3 fatty acids may therefore confer health benefits to both mother and baby. Global intake recommendations for pregnant and lactating women range from 200 to 300 mg DHA and 100 to 250 mg EPA/day (105). Relative to the prehistoric dietary pattern, however, the modern diet is deficient in omega-3 fatty acids (105–107), lending the support of an evolutionary context to the hypothesis that increased intake may be beneficial.

Of note, while marine foods provide omega-3 fatty acids and other important nutrients necessary during pregnancy and lactation (such as iodine, iron, protein, selenium, vitamins B_{12} and D, and zinc), several varieties are commonly contaminated with high levels of mercury, a neurotoxin. As a result, the United States Food and Drug Administration (FDA) advises women who are pregnant or may become pregnant and breastfeeding mothers to avoid king mackerel, marlin, orange roughy, shark, swordfish, tilefish, and bigeye tuna. These species are large predators, and they concentrate in their bodies the mercury accumulated by the smaller fish on which they feed. The FDA also recommends limiting intake of albacore/white tuna, yellowfin tuna, and other large predatory fish to no more than 1 serving/week if no other seafood is consumed that week. Smaller fish, such as anchovies, canned light tuna, cod, crab,

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salmon, sardines, shrimp, and tilapia contain much less mercury and can be eaten 2 to 3 times/week. The FDA recommends a total seafood intake during pregnancy and lactation of up to 12 oz, or two to three 4-oz servings/week (108). Non-fish sources of ALA include plant oils (flaxseed, soybean, and canola), chia seeds, flaxseeds, and walnuts. Some brands of eggs, dairy foods, and juices are fortified with DHA and other omega-3 fatty acids. Fish oil supplements can provide omega-3 fatty acids while avoiding the risk of heavy metal contaminants, and algal oil supplements are available for vegetarians (109).

Folate

The link between adequate folic acid intake and reduced risk of NTD is so definitive (110) that mandatory folic acid supplementation of refined grain products was instituted in the United States in 1998; studies show that the incidence of anencephaly and spina bifida declined by 21% to 35% following this public health measure (111). There is some controversy about whether fortification levels should be further increased to reduce NTD risk (112). There is no clear effect of folic acid supplementation on other birth defects, such as cleft palate, cleft lip, congenital cardiovascular defects, miscarriages, or any other birth defects (113). Reviews of the research on maternal folate exposure show inconclusive associations with additional outcomes, such as childhood asthma, autism spectrum disorders, obesity and insulin resistance, and preterm birth (114–117).

Current recommendations suggest that all women capable of becoming pregnant supplement with approximately 400 to 800 mcg of folic acid/day in addition to consuming a folate-rich diet. Pregnant women should increase supplementation to 600 mcg/day. Ingestion of more than 1 mg/day of folate is generally not recommended. However, in women with prior pregnancies leading to NTD, the daily ingestion of up to 4000 mcg/day of folic acid may confer additional benefit (118).

Fluoride

Breast milk does not provide optimal fluoride levels to term infants, and supplementation is generally recommended after 6 months of age if local drinking water contains less than 0.3 parts per million (ppm) of fluoride (119).

Gingerroot

Several studies suggest that ginger reduces nausea and vomiting symptoms in early pregnancy without adverse maternal or fetal outcomes (120). Trials comparing ginger to vitamin B_6 show no significant difference in the reduction of symptoms, (120) though the combination of ginger and vitamin B_6 may be synergistic in the treatment of hyperemesis gravidarum (121).

Iron

Anemia is the most common nutrient-related abnormality of pregnancy and is attributable to iron deficiency at least half of the time, with the remainder due primarily to folate deficiency. Because of the cessation of menses, iron requirements drop during the first trimester. Demands increase over baseline in the second trimester and peak in the third trimester, at 5 to 6 mg/day.

Pregnancy consumes approximately 1,070 mg of iron in total, of which 250 to 350 mg is recaptured after pregnancy from the expanded red cell mass and 720 to 820 mg is permanently lost. The iron is lost to the fetus (245 mg), the placenta (75 mg), basal loss (250 mg), and blood loss at delivery (150–250 mg). Only about 18% of ingested iron is absorbed in the nonpregnant state, but pregnancy may enhance absorption by as much as 25%. Therefore, a median intake of 22 mg/day is required during the third

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trimester. During exclusive breastfeeding and until menstruation resumes, a median intake of 6.5 mg/day is required to account for basal iron losses and iron secretion in human milk (122). Prenatal multivitamin/multimineral supplements generally contain 27 mg of iron, and the diet provides an additional 12 mg, easily meeting the needs of most women without anemia.

Iron supplementation before conception can facilitate meeting the iron needs of pregnancy and lactation and has shown to reduce the risks of maternal anemia, iron deficiency, and iron deficiency anemia at term (123). However, it appears that iron supplementation in women with already adequate iron stores increases the risk of GDM and adverse birth outcomes (124,125). Women with iron-deficiency anemia during pregnancy require increased intake to replenish bone marrow stores and still provide for the metabolic needs of the fetus. In this situation, the WHO recommends daily iron intake of 120 mg until hemoglobin concentrations rise to normal (126). Routine iron supplementation for full-term, healthy breastfed infants does not appear to be necessary until about 4 months of age (44,127).

Iodine

Iodine is an essential nutrient required for thyroid hormone production, and needs increase during pregnancy and lactation as the production of maternal thyroid hormones increase. Iodine deficiency during pregnancy can lead to a number of adverse effects on fetal growth and development, including autism and mental retardation. Similar to choline, there is little public awareness of the importance of iodine during the perinatal period. In the United States, iodine intake has steadily declined since the 1970s and rates of severe iodine deficiency among women of reproductive age have increased from 11.6% to 13.2% between 2001 and 2012, most likely due to decreased dairy, egg, and salt intake (128). Among populations with poor iodine status, supplementation during lactation increases human milk iodine concentration (36). Many commercially available prenatal vitamins contain iodine, though not the full amount needed during pregnancy and lactation.

Magnesium

The evidence that magnesium supplementation may prevent preeclampsia is mixed, and there is not enough high-quality evidence to conclude that magnesium supplementation is beneficial during pregnancy (129). Alternative medicine sources recommend supplements of about 500 mg/day, which exceeds the tolerable upper intake level for supplemental magnesium of 350 mg daily. Conventional prenatal vitamins provide only 45 mg/day; as a result, intake is often below recommended levels. Magnesium supplementation may be a treatment option for women suffering from pregnancy-induced leg cramps or migraines (130).

Selenium

Poor maternal selenium status may be associated with increased risk of NTDs, preeclampsia, preterm delivery, and miscarriage (131,132). The benefits of selenium supplementation may be limited to individuals from areas with selenium-deficient soil. Selenium deficiency in the United States, where soil levels are high, is not generally considered a problem and average intake exceed recommendations. Selenium in human milk is very responsive to maternal intake, which distinguishes it from most other minerals (133).

Vitamin B_6

Other than its role in metabolism, supplemental B_6 is recommended for treatment of pregnancy-induced

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nausea based on the results of small randomized, double-blind trials (120). A dose range of 10 to 25 mg, 3 times/day is advised, and this level well exceeds the content of diet and prenatal vitamins combined (134).

Vitamin B_{12}

The prevalence of vitamin B_{12} insufficiency is estimated to be 13% among United States women of reproductive age and 21% among pregnant women (135). Research suggests that lower maternal B_{12} levels during pregnancy are associated with increased risk of preterm birth (136), as well as a predictor of low offspring B_{12} levels of preschool-age children (137). Vitamin B_{12} content in human milk is strongly correlated with both maternal blood stores and recent maternal intake, as well as with the B_{12} status of exclusively breastfed infants. Supplementation during pregnancy and lactation may be necessary for strict vegetarians, vegans, and women who follow macrobiotic diets, since vitamin B_{12} is found in animal-derived foods (137).

Vitamin C

A review of the literature suggests that vitamin C supplementation may play a role in the prevention of placental abruption, although it is not clear whether this finding is due to vitamin C or vitamin E, as most trials gave women a combination of both (138). Vitamin C supplementation may also reduce the risk of pre-labor rupture of the membranes (138). Maternal intake of vitamin C has been shown to influence the level of vitamin C in human milk (35,139).

Vitamin D

Adequate vitamin D intake is important during pregnancy, as vitamin D deficiency has been associated with increased risks of preeclampsia, GDM, preterm birth, and low birthweight (93). Vitamin D supplementation in pregnancy and lactation has come under scrutiny in the past few years as a result of increased prevalence of vitamin D deficiency in Americans, particularly among those with more darkly pigmented skin or who are veiled or covered. Supplementation of at least 400 IU daily during pregnancy increases maternal circulating 25(OH)D concentrations, while at least 2,000 IU daily has been shown to increase infant circulating 25(OH)D concentrations (140). Although an optimal dose has not been determined, recent reviews of the literature conclude that doses of vitamin D higher than the current recommended intakes may reduce the risk of GDM, but seem to make no difference for outcomes such as preeclampsia and preterm birth (140,141). Since only minimal amounts of maternal 25(OH)D are transferred to human milk, the American Academy of Pediatrics and Academy of Breastfeeding Medicine recommend that breastfed babies be supplemented with 400 IU daily starting in the first few days of life (43,44).

Zinc

Studies of zinc nutriture in relation to pregnancy outcomes have shown mixed results. There is evidence that zinc supplementation reduces preterm birth risk by 14%, though this finding is based primarily on women of low income. Zinc supplementation does not appear to prevent other adverse outcomes, such as low birthweight, stillbirth, or neonatal death (142). Among lactating women, zinc is efficiently conserved by the intestine so that zinc levels in human milk are maintained even when maternal intake is low. Supplementation may be necessary if dietary zinc is inadequate, but consumption above requirements

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does not increase the zinc concentration in human milk (44,143). Zinc deficiency among United States adults is rare, though vegetarians and vegans are at higher risk because meat is a good source of zinc, and beans and grains contain compounds that reduce zinc absorption.

SPECIAL CONSIDERATIONS

Diabetes/Gestational Diabetes

Diabetes during pregnancy should be controlled so that blood sugar is consistently in the normal range to prevent adverse maternal and fetal outcomes. Maternal outcomes related to uncontrolled diabetes during pregnancy include microvascular complications, miscarriage, pregnancy-induced hypertension, and preeclampsia. Adverse fetal outcomes include macrosomia, shoulder dystocia, congenital malformations, and metabolic complications such as hypoglycemia, hyperbilirubinemia, hypocalcemia, and hypomagnesemia (144). Pregnancy itself induces a state of mild insulin resistance and hyperinsulinemia, which predisposes some women to develop GDM. Women with diabetes in pregnancy may also experience delayed onset of lactation due to the impact of metabolic control on lactogenesis (145). The dietary control of diabetes is discussed in Chapter 6.

Phenylketonuria

A history of phenylketonuria (PKU) in the mother requires a return to a phenylalanine-restricted diet prior to conception and throughout pregnancy to prevent related complications in the fetus, such as microcephaly and intellectual or developmental disability (146). Women with PKU are encouraged to continue this diet postpartum and can breastfeed their infant. In the event that the infant has PKU, breastfeeding can still occur under the guidance of the healthcare team (147).

Infectious Diseases

HIV and some other infectious diseases are transmissible in human milk. When alternatives to human milk are acceptable, affordable, feasible, safe, and sustainable, breastfeeding is contraindicated in HIV-positive women (148). Women infected with untreated brucellosis or human T-cell lymphotropic virus type I or type II are also advised not to breastfeed or feed expressed human milk to their infant (149). The Centers for Disease Control and Prevention's (CDC's) website provides additional guidance for breastfeeding with other infections, such as coronavirus, Ebola virus, herpes simplex virus, tuberculosis, and varicella (https://www.cdc.gov/breastfeeding).

Vegetarian and Vegan Diets

Women who follow strict vegetarian and vegan diets are at risk for inadequate intake or absorption of choline, iron, vitamin B_{12}, and zinc. The need for each of these nutrients increases during pregnancy and/or lactation, further raising the risk of deficiency among vegetarian and vegan women. Some research suggests that following a vegan diet as opposed to an omnivore diet during pregnancy increases the risk of SGA and lower birthweight yet decreases the risk for excessive maternal weight gain (150–152). However, other studies have reported no negative effects of a vegan or vegetarian diet, and there is a lack of evidence indicating that these diets lead to severe adverse pregnancy-related events or major birth defects (152,153). In general, so long as a woman is freely choosing to follow a vegan or vegetarian diet, the diet is well balanced and planned, and any nutrients that cannot be met by diet or fortified foods are supplemented (such as vitamins B_{12} and D), a vegetarian or vegan diet can be considered safe for the

mother and child during pregnancy and lactation (152,153).

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CLINICAL HIGHLIGHTS

Dietary recommendations for pregnancy and lactation vary to some extent with the pre-pregnant weight, age, and nutritional status of individual women. Assuming near-optimal pre-pregnancy weight and nutritional status and biologic maturity at conception, most women following a prudent diet during pregnancy would be able to meet their macronutrient recommendations. In such a diet, 20% to 35% of calories come from fat, 45% to 60% from carbohydrate, and 10% to 35% from protein. Energy consumption should be increased approximately 330 to 340 kcal/day in the second trimester and 452 to 540 kcal/day in the third trimester during pregnancy, and 330 to 450 kcal/day during the first 6 months of lactation.

The use of multivitamin/multimineral supplements beginning several months before conception and throughout pregnancy and lactation is indicated. An omega-3 fatty acid supplement, generally in the form of fish oil at 1 to 2 g/day, may be appropriate for women with low dietary intakes. Dairy products should be eaten regularly as a source of calcium (154), and lean red meat, shellfish, sardines, and other food with a high iron content should be eaten as a source of iron, provided that fat and protein intake is in compliance with guidelines. Vegetarian and vegan women may require iron supplementation in addition to a prenatal vitamin; such supplementation is generally not required in omnivorous women. Vegans may require vitamin D supplementation, as is true of other women without regular intake of dairy products, as well as choline, vitamin B_{12}, and zinc (see Chapter 43).

Vitamin B_6 and gingerroot have been used with success in the management of pregnancy-related nausea and appear to be safe. A graded program of exercise and caloric restriction postpartum may be required to restore pre-pregnancy weight. Women in the United States retain an average of 2 to 3 kg after each pregnancy, a factor contributing to the prevalence of obesity among women (155). Management of diet and the degree of weight gain during pregnancy are thought to be preferable to an exclusive focus on postpartum weight loss; obese women should try to lose weight before pregnancy to minimize adverse outcomes but dieting to lose weight is not advised during pregnancy (12). When maternal weight gain is insufficient during pregnancy, the risks of preterm birth and SGA are increased; therefore, diet should be managed to ensure that energy intake is neither excessive nor deficient.

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Diet and the Menstrual Cycle

Brigitta Gehl

INTRODUCTION

Variations in food intake and preference occur throughout the normal menstrual cycle, primarily driven by hormone levels. Hormonal fluctuations during the menstrual cycle induce changes in taste perception, nutrient metabolism, and the thermic effect of food. Such variations are characteristic of normal physiology but may manifest to a greater extreme as symptoms of the premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD). Dietary management and certain nutritional supplementation may alleviate symptoms of PMS/PMDD.

OVERVIEW

The normal menstrual cycle is approximately 28 days in length and consists of three phases: menstruation, the follicular phase, and the luteal phase. During menstruation, levels of the pituitary gonadotropins luteinizing hormone (LH) and follicle-stimulating hormone (FSH) as well as the ovarian hormones estradiol and progesterone are at baseline levels. When the endometrium has sloughed completely, the follicular phase begins and estradiol levels begin to rise. Estradiol levels peak just before the midpoint of the cycle (day 14), inducing a surge in levels of the gonadotropins. This surge, in turn, induces a transient fall in estradiol levels. Progesterone levels rise slowly throughout the follicular phase. Ovulation, induced by the mid-cycle surge in gonadotropins, occurs on or about day 14 and represents the division between the follicular and luteal phases. In the luteal phase, gonadotropin levels return quickly to baseline, as estradiol levels begin to rise again while progesterone levels continue to rise, now at a somewhat accelerated rate. Estradiol peaks for a second time, and progesterone for the first time, at or near the midpoint of the luteal phase. If implantation occurs, progesterone levels are maintained and continue to rise. In the absence of implantation, levels of both estradiol and progesterone fall toward baseline, inducing menstruation approximately 14 days after ovulation. The phases of the menstrual cycle are summarized in Table 28.1.

TABLE 28.1

Phases of the Prototypical Menstrual Cycle[a]

Phase	Approximate Timing	Gonadotropins (LH and FSH)	Estradiol	Progesterone
Menstruation	Days 1–3	Baseline level	Baseline level	Baseline level
Follicular phase	Days 3–14	Baseline level	Gradual rise/peak	Gradual rise
Ovulation	Day 14	Surge	Abrupt fall	Gradual rise

Luteal phase Days 14–28	Baseline level	Gradual rise/second peak followed by a decline to baseline	Faster rise/peak followed by a decline to baseline

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[a]*FSH, follicle-stimulating hormone; LH, luteinizing hormone*.

Diet

The recurrent hormonal fluctuations associated with the menstrual cycle interact with diet in important ways. Variation in eating pattern and appetite is a well-recognized occurrence even in normal menstrual cycles. Basal metabolic rate varies throughout the cycle, increasing by up to 15% during the luteal (premenstrual) phase (1). Appetite, hunger, satiety, cravings, and aversions also vary with the cycle. In healthy eumenorrheic women, caloric intake varies by approximately 200–300 kcal/day, with maximal caloric intake occurring during the luteal phase and minimal intake during the peri-ovulatory phase (2). This variation is thought to be related to the anorexigenic effects of estrogen levels, of which are highest just prior to ovulation (3). The role of progesterone is less understood, but may be associated with increased tendencies for binge eating and emotional eating commonly seen in the luteal phase (2). A recent review of binge eating related to gonadal hormone fluctuation described increases in binge eating to be significantly correlated with progesterone levels, which are highest in the luteal phase of the menstrual cycle (4).

Changes in appetite and intake may also be related to physiologic need. Analysis of menstrual cycle rhythmicity and associated metabolites found the luteal phase to be largely anabolic, marked by low levels of amino and fatty acids. The authors suggest an increase in macronutrient intake may be advantageous to support the greater metabolic need (5). This interpretation is consistent with dietary analysis of healthy women that shows an increase in macronutrient intake, primarily protein, in the mid-luteal phase, compared to other menstrual phases (6). Normal physiologic fluctuations in metabolism may be exaggerated in sex-hormone-related disorders such as PMS and PMDD, highlighting possible opportunities for nutritional therapies (5). Nutrient analysis of dietary intake of women experiencing PMS compared to that of women not meeting PMS criteria has shown that women with PMS significantly increase total energy intake premenstrually, with significant increases in intake of fat and total carbohydrates, particularly simple sugars. This phenomenon could potentially be a contributing factor for women who experience difficulties adhering to suggested dietary modification and should be considered when counseling premenopausal women (7).

There is evidence that with variation in steroid hormone levels, there is corresponding variation in the reward value of foods (8,9). A systematic review of the role of ovarian hormones on palatable food intake found an association between estrogen and dopaminergic reward pathways. In the absence of consistently high estrogen levels, the luteal phase is marked by increased intake of palatable (high-fat, sweet) foods that also activate similar neural pathways (9). Although controversial, some studies have suggested an increase in olfactory sensitivity related to changes in food preference during the luteal phase of the menstrual cycle. For example, one study examining the influence of the menstrual cycle on gustatory thresholds and food preferences found decreased olfaction and an explicit desire for high-fat foods during the mid-luteal phase compared to the follicular and ovulatory phases. However, the two variables appeared to be unrelated to one another, nor were they correlated with estradiol and progesterone levels (8). In contrast, another study found hormonal variations in estrogen and progesterone were associated with gustative and olfactory discrimination, thus influencing eating habits across the cycle (10). It is uncertain at present what mechanism may cause variations in olfactory performance and whether gustatory

thresholds change more profoundly in women with PMS.

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Leptin levels have been shown to vary throughout the menstrual cycle, suggesting a role in the changes in appetite and occurrence of cravings. In an observational study, however, Paolisso et al. (11) found that although both leptin and food intake varied throughout the menstrual cycle in 16 healthy women, no significant correlations between food intake values and fasting plasma leptin concentration were found. One possible reason for the discordant findings may be leptin's role in defending against reductions in body weight rather than causing increases in body weight. More studies are needed to assess the association between leptin and estrogen in women with low body mass index (2).

Isoflavones in soy and other foods are known to exert selective estrogenic effects, generating clinical and popular interest in such foods as a natural means to replace ovarian hormones or modify disease risk. In a randomized crossover study of 14 premenopausal women, Duncan et al. (12) found that even high-level isoflavone supplementation induced no significant changes in menstrual cycle length, endometrial histology, or plasma estrogen levels. A more recent cohort study found total urinary phytoestrogens (isoflavones and lignans) were associated with very modest decreases in menstrual cycle length and improved cycle regularity (13). A double-blind, placebo-controlled, crossover intervention study in women with confirmed PMS found soy protein containing soy isoflavones to significantly reduce specific premenstrual symptoms from baseline compared to placebo (14). Additional randomized controlled trials to assess the influence of isoflavones on premenstrual symptoms are ongoing (15). Phytoestrogens are discussed in more detail in Chapter 33.

SPECIAL CONSIDERATIONS

Premenstrual Syndrome and Premenstrual Dysphoric Disorder

PMS is a constellation of monthly physical and psychological symptoms associated with significant impairment during the luteal phase of the cycle when fluctuations occur in levels of estrogen, progesterone, aldosterone, and prolactin. It has been estimated that up to 80% of women of reproductive age experience some degree of physical or emotional changes premenstrually; about 20% to 30% of women have symptoms that would fit criteria for PMS (16,17). Survey data reported by the American Academy of Family Physicians suggest a high burden of disease. Women with PMS are more likely to report higher healthcare costs and poorer health-related quality of life compared to women without PMS (16). In general, PMS is categorized based on a predominance of somatic symptoms (abdominal bloating, breast tenderness, headache, joint pain), affective symptoms (anxiety, depression, irritability, mood swings, difficulty concentrating), or mixed symptomatology. The pathophysiology of PMS is poorly understood. The cyclic nature of symptoms in premenopausal women and improvement in symptoms through physiologic or pharmacologic ovulation suppression suggests an important role of ovarian hormones in PMS. However, women diagnosed with PMS have not been shown to have consistently higher or lower levels of estrogen or progesterone compared to women who do not experience PMS (16). Rather, it is thought to be a related to a pathological response to normal fluctuations in hormone levels and their downstream effects on various biologic pathways (17). Approximately 1.2% to 6.4% of all menstruating women experience severe psychological symptoms fitting the diagnostic criteria for a variant of PMS called PMDD. The diagnostic criteria for PMDD are more specific than PMS and are outlined in the *DSM-5*. In general, the diagnosis of PMDD requires a minimum number of severe psychological symptoms that correlate with the luteal phase of the menstrual cycle (17).

Etiology of Premenstrual Syndrome/Premenstrual Dysphoric Disorder Symptoms

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A leading theory for the psychological symptoms of PMS and PMDD involves the relationship between ovarian hormones and the neurotransmitter serotonin (16,17). Human and animal studies have shown that sex steroids and their receptors are ubiquitous throughout a number of brain regions involved in emotional regulation, specifically those involved in serotonin transmission. PMS, consequently, has been consistently linked with dysregulated serotonin signaling (17). This is supported by significant research showing the effectiveness of selective serotonin reuptake inhibitors (SSRIs) in the management of PMS and PMDD (18). The benefit of SSRIs apparently is greatest when dysphoric or depressive symptoms are predominant (21). SSRIs are considered a safe and effective therapy for PMDD when administered continuously or intermittently (18–20).

Etiology of the somatic symptoms of PMS is less clear, but appears to be, in part, related to dysfunctional activation of the renin-aldosterone-angiotensin system (RAAS). Elevations in aldosterone levels induce fluid retention and the commonly experienced premenstrual symptoms of abdominal bloating, breast tenderness, and weight gain. Women with PMS are also at higher risk for high blood pressure than women without PMS, putting them at risk for a number of long-term cardiovascular complications (21). As previously discussed, increased appetite and cravings for sugar and other refined carbohydrates during the luteal phase likely also play a role in many of these symptoms. In contrast, caffeine intake has not been shown to be associated with symptoms of PMS (22).

Lastly, chronic inflammation has been implicated in PMS/PMDD. A cross-sectional study by Bertone-Johnsone et al. found levels of inflammatory markers, interleukins and interferon gamma, to be positively associated with menstrual symptom severity among 277 women 18–30 years of age (23). Similarly, Bahrami et al. found elevated inflammatory markers C-reactive protein (CRP) and high pro-oxidant to antioxidant balance to be associated with PMS among 897 adolescent girls. These inflammatory mechanisms may be involved in both the psychologic and physical symptoms of PMS and point to the possible therapeutic role of antioxidants and other fat-soluble vitamins (24).

Understanding of the pathophysiology of the subtypes of PMS is still quite limited. The possibility that the behavioral, emotional, and physical symptoms are mechanistically distinct suggests that intervention trials that failed to target a particular PMS subtype were treating a heterogeneous group and, therefore, subject to type II error (25). Studies of PMS are increasingly focusing on homogenous subject groups with regard to symptom complex.

Macronutrients

Based on the current understanding of PMS, dietary manipulation may be helpful in alleviating symptoms. The majority of evidence for various nutritional strategies and the treatment of PMS is inconclusive. Most consensus recommendations for non-pharmacologic treatment reflect a more general endorsement for positive health habits (17,26). A cross-sectional study by Hashim et al. found high calorie, high fat, high sugar, and high salt intake to be correlated with reports of increased severity of physical symptoms of PMS. However, causation could not be inferred based on the cross-sectional study design (27). High-fat, low-fiber diets, which may contribute to the higher estrogen levels, were thought to be a factor in premenstrual symptoms and are generally discouraged in favor of dietary intake that is lower in fat and high in fiber (28,29). However, more recent prospective cohort studies, as part of the Nurses' Health Study II, found no correlation between PMS symptoms and dietary fat and fiber intake (30,31).

One hypothesis that would account for the carbohydrate craving experienced by some women relates to the proposed association between low serotonin and symptoms of PMS (see Chapter 34). The rate of brain serotonin synthesis normally depends on its concentration of tryptophan, serotonin's essential amino acid precursor. Brain tryptophan concentrations and the flux of tryptophan from blood to brain depend, in

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turn, partly on plasma tryptophan and partly on plasma concentrations of other large neutral amino acids (LNAAs), which compete with tryptophan for blood–brain barrier transport. Carbohydrate stimulation of insulin secretion diminishes plasma levels of other LNAAs, thus increasing tryptophan's flux across the blood–brain barrier and its brain levels, increasing the synthesis of serotonin. Based on this theory, L-tryptophan, a precursor of 5-hydroxytryptophan may be used for the prevention of PMS symptoms (17,32). Similarly, protein intake has been hypothesized to improve both the psychologic and physical symptoms of PMS through amino acid-mediated effects on neurotransmitters, hormone binding globulin levels, and regulation of RAAS. However, carbohydrate and protein intake has not shown any correlation with PMS in prospective cohort studies (21,31). Further studies are needed to assess the possible effectiveness of macronutrient intake and L-tryptophan supplementation.

Micronutrient Supplementation

As a cofactor in the tryptophan-serotonin pathway, vitamin B_6 (pyridoxine) has been hypothesized to improve PMS symptoms (33). The evidence supporting a therapeutic role for vitamin B_6 (pyridoxine), however, has been criticized for its methodologic limitations. Nonetheless, one double-blinded randomized controlled trial found pyridoxine to reduce both overall PMS symptoms and specific psychiatric symptoms compared to baseline and placebo (34). In a systematic review, Wyatt et al. (35) found evidence supporting use of up to 100 mg/day of vitamin B_6 in the treatment of PMS, particularly with depressive symptoms. In the Nurses' Health Study II Cohort, Chocano Bodoya et al. (36) showed a lower risk of PMS in women with higher intakes of other B vitamins (thiamine and riboflavin), but from food sources only. The study found no significant association between PMS and vitamin B_6, niacin, folate, and vitamin B_{12}. Another systematic review by McCabe et al. found the combination of B6 and magnesium to be effective in improving premenstrual anxiety, but neither had an effect as monotherapy (37). A more recent randomized controlled trial by Retallick-Brown et al. reported improvements in PMS symptoms with either vitamin B_6 supplementation or multivitamin supplementation; however, the study was limited by a small sample size and did not include a placebo group for comparison (38).

Evidence appears to be strongest for the role of calcium in PMS. Ovarian hormones, including estrogen, are known to influence calcium and vitamin D metabolism, processes that vary across the menstrual cycle. Measurements of hormone and metabolite levels in eumenorrheic women show decreased levels of 25(OH) vitamin D and calcium during the luteal phase of the menstrual cycle (5). An exaggerated response in women with PMS may result in a more significant hypocalcemia and vitamin D deficiency (39). In 1995, Thys-Jacobs and Alvir (40) demonstrated that although total and ionized calcium levels varied predictably throughout the menstrual cycle in subjects with PMS and in matched controls, only the subjects with PMS experienced a mid-cycle surge in levels of intact parathyroid hormone. The authors interpreted these data to indicate that a transient, secondary hyperparathyroid state was implicated in the pathogenesis of PMS. Interestingly, symptoms of PMS are remarkably similar to those of hypocalcemia (41). Following up on this finding, Thys-Jacobs et al. (42) conducted a randomized trial of calcium supplementation involving more than 450 women. Compared with placebo, supplementation with 1,200 mg/day of elemental calcium resulted in a significant reduction in all symptoms of PMS. This is consistent with a systematic review by Abdi et al. that found calcium supplementation to be consistently associated with the improvement and/or elimination of PMS symptoms. The authors also found improvements in PMS symptoms in women consuming diets rich in vitamin D and calcium (39). While foods rich in calcium appear to decrease risk for symptomatic kidney stones, supplemental calcium may increase the risk (43). Similarly, there is evidence that calcium

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supplementation, but not dietary intake, particularly in excess of 500 mg daily, may increase the risk of cardiovascular events such as myocardial infarction, coronary revascularization, death from coronary heart disease, and stroke (44–46).

In addition to its role in calcium homeostasis, vitamin D interacts with many of the other systems involved in PMS. For example, vitamin D deficiency has been shown to activate the RAAS system, leading to increased volume status and essential hypertension (47). Additionally, vitamin D deficiency has been implicated in stress response and oxidative imbalance associated with PMS. A randomized controlled trial by Heidari et al. found participants given biweekly 50,0000 IU vitamin D_3 supplementation had reduced plasma levels of IL-10, IL-12, and improved total antioxidant capacity and PMS symptomatology compared to placebo (48). Interestingly, a systematic review and meta-analysis of vitamin D and PMS found no association between serum 25(OH) vitamin D levels and PMS; however, vitamin D supplementation was effective in reducing the symptoms of PMS (49).

Although in the aggregate less compelling than the evidence for calcium, there has been suggestion of therapeutic effects of magnesium as well as other minerals, including potassium, iron, and zinc, due to their roles as cofactors in a number of biological pathways (50,51). Facchinetti et al. (52) studied a high-magnesium yeast product (Sillix Donna) in a double-blind, placebo-controlled, randomized trial and found a statistically and clinically significant reduction in PMS symptoms over the 6-month study period. Walker et al. (53) found that a daily dose of 200 mg of magnesium oxide reduced symptoms related to increased volume status by the second month of administration in a randomized, double-blind, crossover trial of 38 women; no significant effect was seen on other symptom categories. A more recent systematic review of 13 observational studies found no association between PMS and serum magnesium or erythrocyte magnesium levels; however, the review did not comment on any effects of supplementation (54). As previously mentioned, there may be a role for combination therapy with magnesium and vitamin B_6; however, there has been little evidence at this point to support the use of magnesium as monotherapy (37). More broadly, a case control study nested within the Nurses' Health Study II evaluating the association between mineral intake and the risk of PMS found high intake of nonheme iron (>20 mg/day), zinc (≥25 mg/day) was associated with a lower risk for PMS, while high potassium intake was associated with a higher risk for PMS. There was no association found between PMS and intake of sodium, magnesium, and manganese (51). Although chocolate cravings were initially attributed to its relatively high concentration of magnesium, more recent research suggests more of a cultural and psychological influence on chocolate cravings during the menstrual cycle (55,56). There is a need for additional clinical trials assessing mineral intake and PMS. There has been interest in the use of essential fatty acids in the treatment of PMS; evening primrose oil (EPO), which is rich in γ-linolenic acid, has been advocated. A review of the role of EPO in menstrual disorders reported two randomized, double-blind, placebo-controlled trials that showed a reduction in PMS severity score in participants treated with EPO compared with placebo, but noted the need for long-term supplementation (57). However, this benefit has not been consistent across clinical trials, and more research is needed to determine the true efficacy (58). Studies on fatty acids are similarly controversial. In a randomized crossover trial, Collins et al. (59) found no benefit of essential fatty acid supplementation in 27 women with PMS. Nevertheless, more recent studies have shown that *omega*-3 fatty acids may improve PMS symptomatology. Rocha Filho et al. (60) showed that the administration of 1 or 2 g of fatty acids (γ-linolenic acid, oleic acid, and linoleic acid) results in a significant reduction of PMS symptoms. Similarly, Sohrabi et al. found omega-3 fatty acid supplementation was associated with statistically significant reductions in psychiatric and physical symptoms of PMS, namely, anxiety, depression, lack of concentration, and bloating (61). Krill oil, rich in

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n-3 (ω-3) polyunsaturated fatty acids incorporated in phosphatidylcholine, has been reported to reduce PMS symptoms and dysmenorrhea (62).

Menstrual Cycle Irregularities

Adolescent Menstruation and the Female Athlete Triad

Competitive athletics in adolescent girls is associated with amenorrhea due to the energy demands of training and, in some, associated eating disorders thought to be induced by the pressure to remain thin. The concurrence of low energy availability (EA), menstrual dysfunction, and low bone mineral density is known as the "female athlete triad" (63,64). Of note, the occurrence of menstrual irregularities in female athletes without disordered eating is also well established; the term "exercise-related menstrual irregularities" has been applied (65). Although it was previously thought that the amenorrhea was primarily due to reduction of body fat from intense training that disrupted the menstrual cycle via effects on estrogen metabolism (66), negative energy balance associated with hypothalamic dysfunction has been identified as the causal factor in the menstrual irregularities seen in the triad (64). It is thought that low levels of circulating leptin, a metabolic signal of low EA, act as a metabolic checkpoint on the hypothalamic-pituitary-ovarian (HPO) axis, leading to slowed pulsation of GnRH and amenorrhea when insufficient energy is available to compensate for exercise-related energy costs (64,67). Although a threshold of <30 kcal/kg fat-free mass (ffm) is commonly cited (64), a recent randomized controlled trial by Lieberman et al. suggested that the relationship between EA and menstrual disruption is linear, with increasing dysfunction as EA decreases, without any identifiable cutoff (68). In addition to low EA, other risk factors for amenorrhea, secondary to the female athlete triad, include psychological stress, genetics, and age. Adolescent athletes appear at particular risk for menstrual irregularities due to their relatively young "gynecologic age" (chronological age- age at menarge) and more susceptible hormonal cycles. A study by Loucks et al. found adolescents with a gynecologic age between 5 and 8 years had decreased LH pulsatility in response to a low EA, while subjects with a gynecological age of 14–18 saw no change in HPO reactivity (69). The nutritional requirements associated with competitive athletics are discussed in Chapter 32; the prevention of osteoporosis is discussed in Chapter 14. In addition to cardiovascular and metabolic consequences of a chronic hypoestrogenic state, amenorrhea in adolescent girls is a clear indication of risk for potentially irreversible osteopenia. Although management should focus on the restoration of adequate nutrition and energy balance, oral contraceptives are indicated when the patient is resistant to such interventions or when primary or secondary amenorrhea persists despite these actions. There is also some evidence for the interplay of iron deficiency with the female athlete triad, suggesting a role for iron supplementation to improve metabolic fuel availability, reproductive function, and bone health (70).

Dysmenorrhea

Dysmenorrhea is the most common gynecologic problem among adolescents and women of reproductive age worldwide. The pathophysiology of dysmenorrhea is thought to be related to increased synthesis of prostaglandins resulting in uterine contractions and disrupted blood flow. This is supported by the use of oral contraceptive pills (OCPs) and nonsteroidal anti-inflammatory drugs as primary treatment modalities (71). A number of vitamins and minerals have been suggested as non-pharmacologic treatment for menstrual pain based on their proposed analgesic and anti-inflammatory properties; however, supporting evidence is inconsistent (72). A Cochrane review by Pattanittum et al. found no high-quality evidence supporting nutritional supplements in the treatment of dysmenorrhea (73). However, a more recent

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double-blind, randomized controlled trial by Sadeghi et al. found omega-3 and vitamin E supplementations, alone and to a greater extent in combination, to be effective in relieving menstrual pain as compared to the placebo (74). Ginger, vitamin D, and calcium have also shown some effectiveness in reducing pain associated with dysmenorrhea in recent randomized studies (72,75,76). More generally, a systematic review by Bajalan et al. found improvements in menstrual pain with increased consumption of fruits, vegetables, fish, and dairy products. However, the authors cited methodologic heterogeneity as a major limitation to drawing more definitive conclusions (77). There is a need for additional large, interventional trials that include the assessment of adverse effects to further evaluate the role of nutritional therapy in dysmenorrhea.

Polycystic Ovarian Syndrome

Perhaps most closely related to diet and nutrition, polycystic ovarian syndrome (PCOS) is one of the most common endocrine disorders characterized by anovulation, hirsutism, polycystic ovaries, and, in many cases, obesity. Although the pathogenesis is still subject to debate, insulin resistance leading to excess ovarian androgen production and disordered folliculogenesis has been identified as a primary pathway. In addition to infertility, the resultant anovulation and unopposed estrogen lead to a number of downstream health effects such as dysfunctional uterine bleeding, endometrial hyperplasia, and breast and endometrial cancer (78,79). Due to the numerous metabolic risk factors and consequences associated with PCOS, lifestyle and dietary management are essential components of the multidisciplinary approach to treatment. Lifestyle interventions among adolescents with PCOS have been shown to reduce levels of LH and free androgens, body mass index, triglyceride levels, and menstrual irregularities (80). However, evidence to support the recommendation of specific nutritional therapies or dietary composition is limited (81). Suggested diets include those with a low-glycemic index, a ketogenic diet, and the Mediterranean diet (81–83). Additionally, vitamin D supplementation has been investigated due to low levels of 25(OH) vitamin D in women with PCOS (84). However, data from randomized controlled trials have not shown any significant effect of vitamin D supplementation on the metabolic hormonal parameters related to PCOS (85). Additional high-quality research is needed to optimize the dietary recommendations for the treatment of PCOS. More information on nutritional approaches to insulin resistance and diabetes can be found in Chapter 6.

Hot Topics in Nutrition and the Menstrual Cycle

Popular literature has shown increased interest in plant-based and anti-inflammatory diets in the treatment of a number of disease processes, including menstrual irregularities. While specific micronutrients have been evaluated for their role as anti-inflammatory agents in the treatment of PMS and dysmenorrhea, currently scientific literature is lacking in evidence to support these more general dietary plans. The evaluation of broader dietary composition in the management of menstrual ailments may warrant future research. Additionally, there has been a significant movement for the investigation of the role of the microbiome on human health. There are a number of ongoing clinical trials to evaluate the relationship between hormonal changes related to the menstrual cycle and alterations in the microbiome and the possible consequences of PMS and dysmenorrhea. To date, no large study data have been published, but this will likely represent a significant area of ongoing investigation.

CLINICAL HIGHLIGHTS

The normal menstrual cycle produces changes in metabolism and taste that result in variations in food

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intake pattern. This tendency becomes extreme in cases of PMS/PMDD. Physical and emotional symptoms triggered by hormonal fluctuations may respond to supplemental micronutrients and vitamins, although in many cases, data are limited. Supplementation with calcium is most supported in the literature and may be beneficial for all patients with PMS. Additional supplementation with vitamin D also appears appropriate given available evidence. Current research suggests that a daily dose of calcium in the range of 1,000 to 1,500 mg along with 600 IU of vitamin D is appropriate for a therapeutic trial, given the safety and other potential benefits associated with these supplements.

If this strategy is ineffective, a trial of pyridoxine (B_6), vitamin E, and fish oil supplementation appears to be justified; whether such interventions should be combined or applied separately has not yet been fully resolved and must rely on clinical judgment. Possible combination therapy is not precluded by any potential toxicity. A diet rich in complex carbohydrates may be beneficial in ameliorating depressive symptoms of PMS through a serotonergic mechanism. When depressive symptoms are pronounced or refractory to dietary interventions, SSRIs should be used as indicated. Physical activity, a diet rich in fruit and vegetables, avoidance of nicotine, and restricted intake of saturated fat and salt may offer benefit in PMS and are indicated on other grounds. By judiciously selecting and combining available therapies, clinicians may hope to alleviate symptoms in the great majority of patients with PMS.

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Chapter 29

Diet and Early Development: Pediatric Nutrition

Rupa Mahadevan

INTRODUCTION

During infancy and childhood, physical and cognitive development is growing rapidly, which can impose extreme metabolic demands on the body. Providing adequate nutrition from birth is fundamental to maintaining normal growth and development. Infants require specific nutrients different from those of adults.

The health benefits of breastfeeding (see Chapter 27) during the first 6 months of life are increasingly clear. Although the principal goal of nutrition management in early childhood is the preservation of optimal growth and development, children in the United States and other developed countries are increasingly susceptible to the adverse effects of dietary excess, particularly obesity (see Chapter 5). As a result, there is intense interest regarding the age at which dietary restrictions might first be safely imposed.

In general, restriction of macronutrients (saturated fat being of particular concern) is discouraged before age 2, with increasing evidence that restrictions comparable to those recommended for adults may be safe and appropriate after age 2. The establishment of health promoting diets and activity patterns in childhood may be of particular importance, as preferences established early in life tend to persist (see Chapters 38 and 44).

OVERVIEW

Diet Nutrient Recommendations

The importance of adequate nutrition to normal growth and development during the neonatal period and early childhood is well established and largely self-evident. Basal metabolic rate is higher in infants and children than in adults; the nutritional needs to support growth are superimposed on the higher basal metabolism, resulting in considerably higher energy and nutrient requirements per unit body weight.

The average-term infant triples in weight and doubles in length during the first year of life. Consequently, energy requirements in early childhood are very high. Newborns require three to four times more energy per unit body weight than do adults: 100 to 110 kcal/kg/day (1) compared to 25 to 30 kcal/kg/day for adults (2). Inefficiency of intestinal absorption contributes to this difference.

As a result of a child's rapid growth, protein requirements are higher in infancy than in adulthood. Total protein requirement is greater than the additive needs for essential amino acids by a factor of two to three. Protein intake of 1.5 g/kg/day is recommended for infants and 1.1 g/kg/day for children 1 to 3 years of age, compared with 0.8 to 1.0 g/kg/day for adults who engage in moderate levels of physical activity (3).

Infants require protein of high biologic value to ensure adequate consumption of essential amino acids (leucine, isoleucine, valine, threonine, methionine, phenylalanine, tryptophan, lysine, and histidine). Cysteine and tyrosine also are recognized as essential dietary proteins in infancy, although not beyond the

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first 6 months of life. The reason is unclear in the case of tyrosine, whereas for cysteine, there is a well-characterized delay in the maturity of the enzymatic pathway that converts methionine to cysteine. The minimal intake necessary to provide the indicated amounts of all essential amino acids would provide half or less of total protein requirements, indicating the importance of both quantity and quality of dietary protein.

The protein composition of human milk is ideal for infants. Breast milk provides on average 1 g of protein/100 mL. Therefore, to achieve the recommended intake of 1.5 g/kg/day, infants need to consume approximately 150 mL of breast milk/ kg/day. This level may exceed the intake of many infants, yet protein deficiency generally does not occur in breast-fed infants. Apparently, any limitations in the quantity of breast milk protein consumed are compensated by the digestibility and quality of protein in breast milk (see Chapter 27). Currently available infant formulas contain all amino acids essential for infants and, therefore, provide protein of comparable quality to that of breast milk. Carbohydrate sources in standard formulas provide approximately 35% to 40% of calories and include lactose, corn syrup solids, sucrose, modified starch, or other complex carbohydrates such as maltodextrins (4,5).

Need for carbohydrate and fat in infancy is restricted to those levels necessary to prevent ketosis and fatty acid deficiency, respectively. Total intake of carbohydrate and fat generally are adequate whenever total energy intake is appropriate.

Recommended dietary allowances (RDAs) have been established for essential nutrients for both the first and second 6-month intervals of life (see Table 29.1). Iron deficiency is one of the most common nutrient deficiencies in early childhood (6). In the United States the prevalence of iron deficiency anemia in children 1 to 5 is estimated to be 1% to 2% (7,8).

Because a majority of iron is accumulated in the third trimester, preterm infants are often a concerning group at risk for iron deficiency. In preterm infants after 2 weeks of age there is a general agreement that they require 2 to 4 mg/kg/day of iron. Iron supplements should start at 2 weeks of age and be continued until 6 to 12 months of age depending on the diet (9). In healthy full-term infants, iron storage from in utero is adequate for the first 4 to 6 months of life.

The AAP recommends that full-term, exclusively breast-fed infants start 1 mg/kg/day of elemental iron supplementation at 4 months of age until appropriate iron-containing foods are introduced. The adequate intake of iron is 0.27 mg/day from birth to 6 months of age and then increases to 11 mg/day from 7 to 12 months of age. Infants born at full-term usually have iron stores until approximately 4 to 6 months. Micronutrient fortified milk and cereal products have been found to reduce iron-deficiency anemia in children up to 3 years of age (10). The iron concentration in human milk is 0.5 mg/L and declines slightly to 0.2 to 0.4 mg/L in mature milk; with infant formula (e.g., 4 mg/L), the amount is tenfold higher. The dietary iron requirement is minimal during the first 3 to 4 months of life and very little exogenous iron is likely absorbed. Caretakers that choose to provide formula for their children should use caution with low-iron formulations, but healthy-term infants who had the benefit of delayed cord clamping may be the least risky group for these formulations (11).

Vitamin D should be supplemented for all exclusively breast-fed infants. In 2008, the American Academy of Pediatrics (AAP) increased their recommended intake of vitamin D for infants <1 year of age from 200 to 400 IU daily with the primary intention of preventing rickets. The recommendations stated that exclusively or partially breastfeeding infants should be supplemented with 400 IU daily and that non-breastfeeding infants should consume at least 1 L of formula daily to get adequate amounts of vitamin D. By federal regulations/standards, 1 L of formula should contain at least 400 IU of vitamin D. For non-breastfeeding infants consuming <1 L a day of formula, the AAP recommended supplementation as well. Currently, less than 40% of infants met the vitamin D recommendations in nearly all demographic

subgroups. These findings suggest that there needs to be continued advocacy in this area (12,13).

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Another important vitamin for infants is vitamin K, which is given to newborns at birth to prevent neonatal hemorrhage. Vitamin K is provided by injection and deficiency is uncommon. In general, vitamin deficiencies are rare in adequately nourished infants. Reference Table 29.1 for the Recommended Dietary Allowances in Infancy/Childhood age Nutrients.

An intake of 75 to 100 mL of breast milk or formula/kg/day is considered adequate for the first years of life, but 150 mL/ kg/day is preferred as a defense against dehydration. A well-nourished infant generally easily meets the recommended intake with either breast milk or formula.

TABLE 29.1

Recommended Dietary Allowances (or Adequate Intakes) in Infancy/Childhood[a]

	Age			
Nutrient	**0–6 Mo**	**7–12 Mo**	**1–3 Yr**	**4–8 Yr**
Protein (g)	9.1	11	13	19
Vitamin A (µg RE)	400	500	300	400
Vitamin D (µg)	10	10	15	15
Vitamin E (mg TE)	4	5	6	7
Vitamin K (µg)	2	2.5	30	55
Vitamin C (mg)	40	50	15	25
Thiamine (mg)	0.2	0.3	0.5	0.6
Riboflavin (mg)	0.3	0.4	0.5	0.6
Niacin (mg NE)	2	4	6	8
Vitamin B_6 (mg)	0.1	0.3	0.5	0.6
Folate (µg)	65	80	150	200
Vitamin B_{12} (µg)	0.4	0.5	0.9	1.2
Calcium (mg)	200	260	700	1,000
Phosphorus (mg)	100	275	460	500
Magnesium (mg)	30	75	80	130
Iron (mg)	0.27	11	7	10
Zinc (mg)	2	3	3	5
Iodine (µg)	110	130	90	90
Selenium (µg)	15	20	20	30
Biotin (µg)	5	6	8	12
Pantothenic acid (mg)	1.7	1.8	2	3
Copper (µg)	200	220	340	440
Manganese (mg)	0.003	0.6	1.2	1.5
Fluoride (mg)	0.01	0.5	0.7	1.0
Chromium (µg)	0.2	5.5	11	15
Molybdenum (µg)	2	3	17	22

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[a]*NE, niacin equivalent, which equals 1 mg of dietary niacin or 60 mg of dietary tryptophan; RE, retinol equivalent; TE, α-tocopherol equivalent.*

Adapted from Dietary Reference Intakes (DRIs): Recommended Dietary Allowances and Adequate Intakes, Vitamins. Food and Nutrition Board, Institute of Medicine, National Academies. Available at: http://iom.edu/Activities/Nutrition/SummaryDRIs/~/media/Files/Activity%20Files/Nutrition/DRIs/RDA%20and%20AIs_Vitamin%20and%20Elements.pdf. Accessed on 6/11/2013.

The nutrient recommendations for infants 6 to 12 months of age are based largely on extrapolation from the first 6-month period; less is known about the nutrient needs of infants 6 to 12 months old. There is currently debate regarding the optimal level of energy intake, with some recommending a reduction to 80 to 85 kcal/kg/day (1). Adequate growth apparently is maintained at the lower-energy-intake level.

By 6 months of age, gastrointestinal physiology is substantially mature, and infants metabolize most nutrients comparably to adults. Nutrient needs can be met with breast milk or formula, but most authorities advocate the gradual introduction of solid foods beginning at or around 6 months. As foods begin to replace breast milk or formula, the nutrient density of the diet is apt to decline, and the introduction of a multivitamin supplement may be indicated only if the child does not have adequate intake of key nutrients (i.e., vitamin D, iron, B_{12}, etc.). Completion of weaning to solid food by 1 year of age is common practice and is appropriate (14).

Fluoride

When starting solids infants can begin to consume water between 3 and 4 oz after 6 months of age and 8 oz by 12 months. Fluoride is a mineral that is often found in drinking water and can reduce the risk that a young child will develop dental caries. Given that not all drinking water contains an adequate amount of fluoride a fluoride supplement is recommended for children between 6 months and 3 years if the fluoride level in the local water supply is low (41). To determine the level of fluoride content in the water supply, it is best to call the water department to arrange to have well water tested.

Breastfeeding

Breast milk is widely considered the optimal means of nourishing newborns, barring contraindications such as communicable disease in the mother. The nutrient content of human milk is complete and serves the nutrient needs of healthy full-term infants as an exclusive feeding for the first 4 to 6 months of life. The AAP recommends that infants be exclusively breastfed until 6 months of age followed by continued breastfeeding as complementary foods are introduced, with continuation of breastfeeding until 1 year or longer as desired by mother and infant (15). WHO and UNICEF recommend breast milk until 24 months. It can provide half or more of a child's energy needs between the ages of 6 and 12 months, and one third of energy needs between 12 and 24 months (16).

The milk of healthy lactating women contains relatively small amounts of vitamin D and 25(OH)D and is usually considered insufficient in exclusively breast-fed infants. As noted earlier, vitamin D supplementation is recommended between 200 and 400 IU/day (17).

The properties of breast milk are discussed in greater detail in Chapter 27. Breast milk has lower calcium and phosphorus than does bovine milk. Bone density during the first several months of life is lower in breast-fed than in formula-fed infants because of the lower calcium and phosphorus of breast milk. Differences in bone density do not persist beyond infancy. Breastfeeding can also be associated with transient hyperbilirubinemia seen in both breast milk jaundice and lactation failure jaundice during

the first few days of life; if extreme, phototherapy is indicated to prevent kernicterus.

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The particular advantages of breastfeeding relate to the development of immune function and resistance to infection, development of the intestinal tract, and psychological bonding between mother and infant (see Chapter 27). More than 98% of the fat in human milk is in the form of triglycerides, made in the mammary glands from medium- and long-chain fatty acids. These fatty acids are constituents of brain and neural tissue that are needed in early life for mental and visual development (18). The prebiotic and antimicrobial roles of human milk oligosaccharides (HMOs) are currently being explored among mother–infant pairs (19). Although before 12 months of life, breast-fed infants and formula-fed infants do not have significantly different diversity, formula-fed infants have been shown to have less phylogenetic diversity, bacterial richness, and biodiversity between 12 and 24 months. After the introduction of solid foods and with an increased portion of formula being consumed, obligate anaerobes increase until a pattern similar to that seen in adults is achieved, normally by the age of 2 to 3 years (4).

There is increasing evidence that breastfeeding reduces the risk of infant and childhood infections (20,21). Secretory IgA is the principal immunoglobulin of human milk and, together with lactoferrin, represents about 30% of all milk protein. The specificity of human milk secretory IgA antibodies reflects the mother's exposure to various antigens and targets commensal microorganisms (22,23). There is evidence that exclusive breastfeeding has been associated with the following benefits: for the first 3 to 4 months it decreases the cumulative incidence of eczema in the first 2 years of life; any duration of breastfeeding beyond 3 to 4 months is protective against wheezing in the first 2 years of life; longer duration of any breastfeeding protects against asthma, even after 5 years of age (24).

As noted, there are countless benefits to breastfeeding infants due to anti-inflammatory and immunological properties that protect against a host of illnesses and diseases for both mothers and children. For instance, the risk associated with some serious infections and diseases, such as severe lower respiratory infections and leukemia, is higher for formula-fed infants (25). A study found that full breastfeeding for 6 months of life was associated with reduced risk of hospital admission for infections in the first year of life (26). Breastfeeding also likely protects against food allergy and intolerance as well, as discussed in Chapter 24.

An increasing body of evidence points to prolonged breastfeeding is a significant protective factor against overweight/obesity in children (27). It is thought that higher protein and fat levels found in bovine-based formula leads to increased secretion of insulin growth factor (IGF-1) and stimulates the overproduction of adipocytes (28).

The meta-analysis of several observational studies determined the risk of obesity for school-aged children was reduced by 15% to 25% in children who were breastfed compared to children that were formula fed (29). Other studies have had similar results (30,31). One hypothesized mechanism for this is that mothers who breastfeed develop less restrictive feeding behavior and are more responsive to infant cues of hunger and satiety (32). A relationship has also been found between children who were breastfed with improved appetite regulation during early childhood (33). The duration of breastfeeding has also been associated with a reduced risk of overweight dose-dependently. It was found that 1 month of breastfeeding was associated with a 4% decrease in overweight risk (OR, 0.96/month of breastfeeding; 95% CI: 0.94, 0.98) (34).

The principal hazard of breastfeeding is the issue of maternal exhaustion and supply issues; infants must be followed closely during the first few days to weeks of life to ensure normal growth. The adequacy of breastfeeding can be assessed by preprandial and postprandial weights; every milliliter of milk consumed should add 1 g of weight. Average weight gain per day in the first few weeks is 35 to 40 g/day with infants expected to be back to birth weight by 10 to 14 days of life. Those delivered by cesarean on

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average take longer to regain their birth weight than those delivered vaginally and can be anywhere between 14 and 21 days. This is important to note as this may reduce clinicians from recommending formula when infants have not gained back birth weight by 10 to 14 days and also provide reassurance to parents of infants who are still below birth weight at 10 to 14 days, which may cause breast feeding cessation (35).

Inclusion of cow's milk in the diets of infants 6 to 12 months old appears to be fairly common practice in the United States. There are concerns about converting from breast milk to bovine milk, rather than formula, as the principal source of nutrition after 6 months as this can result in protein and sodium intake well above recommendations. The substitution of bovine milk for formula also tends to reduce the iron level in the diet, and skim milk will reduce the intake of linoleic acid below recommended levels. Deficiency of essential fatty acids is the most significant concern regarding the use of bovine milk (whole or reduced fat) as the staple after 6 months. A negative correlation has been well established between iron status and cow's milk ingestion in infancy and later in childhood. In toddlers, excessive cow's milk consumption is the most common risk factor for severe anemia. Bovine milk interferes with the absorption of iron as the proteins in milk negatively affect iron bioavailability. Iron balance is a delicate dance between consumption, absorption, and excretion. Certain nutrients in cow's milk such as phosphorus and calcium are well-known inhibitors of iron; greater amounts of calcium yields poorer iron absorption. GI losses are also associated with cow's milk ingestion in the first 6 months of life; the role of cow's milk causing GI blood loss remains unclear (36).

The substitution of skim or reduced-fat milk for whole milk in this age group does not confer any known benefit, nor does it appear to reduce total energy intake as a result of compensation for the missing calories (37,38).

Formulas are generally based on either unmodified or modified bovine milk protein. Bovine milk can be modified so that the whey-to-casein ratio approximates that of human milk. There is no clear evidence that either is superior. For infants intolerant of bovine milk protein, the protein can be hydrolyzed, or soy protein can be substituted. Soy-based formulas are appropriate for infants with lactose intolerance (see Chapter 18).

Formulas based on bovine milk protein typically provide 1.5 g of protein/100 mL, or 50% more protein than breast milk. The nutrient composition of commercial formulas is otherwise very comparable to that of breast milk. Provided that a sanitary water supply is available, the safety of formula generally is not of concern. Properly nourished, a healthy infant should double in weight by 4 to 5 months of age and triple in weight by 12 months. Demand feeding is the preferred method of ensuring adequate energy intake.

Parental Feeding Practices in Infants

For most infants, nutrient intake from human milk is sufficient through 4 months of age and becomes increasingly insufficient at about 6 months of age and complementary foods need to be added to the diet. Typically most parents start offering solids between 4 and 6 months of age as this is safe time developmentally, although as noted earlier, there are increased benefits with breastfeeding exclusively until 6 months of age.

Children's eating habits and behavior are formed in the first few years of life. Birth weight is quadrupled around 2 years of age, and birth length is doubled around 4 years of age. On average, children from 2 years of age to puberty gain 2 to 3 kg and grow 5 to 8 cm in height/year (39). Frequent concerns at the beginning of solid food introduction include questions about baby-led weaning (BLW), picky eating, and confusion regarding limited variety and consumption of protein, fruits, and vegetables in a child's

diet.
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Healthy eating behaviors should start with the maternal diet. Amniotic fluid that surrounds the fetus is a rich source of sensory exposure for infants. Many flavors in the maternal diet appear to be present in amniotic fluid. Recent findings reveal that experience with dietary flavors begins as the fetus is exposed to flavors from the maternal diet in utero, and that this early experience can provide a "flavor bridge" that can begin to familiarize the infant with flavors of the maternal diet (40).

In general infants should be offered a variety of colors and textures. Habits established during infancy track into later childhood and adolescence (41); early experiences with nutritious foods and flavor variety should maximize the chance that, as infants grow, they will enjoy a more healthy diet because they like the taste. Sensory experiences with food flavors in mother's milk in children whose mothers eat a varied diet may explain why children who were breastfed tend to be less picky and more willing to try new foods during childhood.

Parents should offer a variety of nutritious foods with structured eating times. Parents should model good behavior themselves and provide appropriate portion sizes for the infant. Traditionally, complementary feeding usually starts with pureed foods that are spoon-fed to infants (42). An alternative approach called BLW is also growing in popularity where infants feed themselves all their foods in graspable pieces (42). The thought behind BLW is that it may encourage improved energy self-regulation as opposed to the traditional spoon-feeding approach where the parent has much more control and is likely to encourage the child to eat an amount of food a parent deems appropriate instead of following the satiety cues of the child (43). In both techniques, infants should be seated in an upright position with solids introduced once the child has appropriate head control. Recent studies also demonstrate no further concerns for choking with BLW than with traditional spoon-feeding methods (42).

The AAP guidelines recommend early, "purposeful" introduction of allergens to help reduce a baby's food allergy risk. This includes introducing foods like peanut, egg, and milk when babies are 4 to 11 months old, regardless of the food allergy risks (44).

The learning early about peanut (LEAP) study demonstrated early introduction to peanut products from 4 to 11 months was associated with a substantial and significant decrease in the development of peanut allergy in high-risk infants (45,46). It is important to note that the LEAP study did not target infants with mild to moderate eczema. Therefore, following the study an additional addendum was made that children with severe eczema strongly consider evaluation by IgE testing or oral food challenge and those with mild to moderate eczema strongly consider early introduction with peanut containing foods given that the benefits outweigh the risks but to also be evaluated by a healthcare professional (47).

Parental Feeding Practices in Toddlers and Children

In general families should eat mealtimes together and children should be offered the same foods as the family with no special alternatives. Parents are encouraged to expose children to a variety of tastes and flavors. Guidance from the AAP recommends children be offered certain foods 10 to 12 times to develop a taste for it (48, 49).

Most toddlers between 12 and 24 months of age should be consuming three meals and two snacks daily with balanced meals consisting of vegetables, fruits, whole grains, and protein. The feeding experience strongly affects an infant's, child's, and adolescent's physical, social, emotional, and cognitive development overtime (50). Children should express hunger and age-appropriate food should be offered at mealtimes. There are many factors shaping the development of children's food preferences and eating behaviors during the first years of life. Food habits of children are influenced strongly by the knowledge, attitude, and eating behavior of their parents as they are the ones selecting the food in the home and their

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feeding practices serve as role models for children. Research indicates that the extent to which fruits and vegetables are present and readily available and accessible in the home correlates positively with the level of consumption in school-aged children (40).

Recent evidence shows decreasing quality of a child's diet with advancing age (50). Many nutrient requirements depend on energy needs and intake. Micronutrients that are most likely to be low or deficient in the diets of young children are vitamin D, calcium, vitamin E, and potassium. Table 29.2 demonstrates recommended feeding practices from childhood to adolescence to provide a framework for nutrition balanced meals.

Eating Recommendations

Healthcare professionals must learn to respect and appreciate the variety of cultural traditions related to food and the wide variation in food practices within, among, and across cultural groups. Parents must not only model good behavior, but they must provide a variety of textures and flavors to children as stated earlier. Just like adults, toddlers and school-aged children are more likely to consume fruits and vegetables when they taste good and are flavored with herbs and spices. Children do not need to be supplemented with a multivitamin if they are consuming an adequate amount of fruits, whole grains, and vegetables daily. Latest united states department of agriculture (USDA) Dietary Guidelines from 2020 demonstrate five major food groups that complete a balanced diet:

- Fruits, i.e., apples, oranges, pears, pineapples, bananas, plums, peaches
- Vegetables, i.e., broccoli, spinach, cauliflowers, red and orange peppers, beans and peas
- Dairy, i.e., unflavored including milk, yogurt, and cheese, including calcium-fortified soy beverages
- Grains, i.e., whole grains and refined grains such as whole grain oats, pasta, bread, buckwheat, quinoa
- Protein Foods, i.e., meats, beans, poultry, and eggs; seafood; nuts, seeds, and soy products

Children over the age of 1 year tend to eat an appropriate variety of foods and nutrients when provided access to them. Parents should be reassured that a balanced diet need not be measured on a per-meal or even per-day basis. A reasonable approach is to avoid any major distinction between snacks and meals so that healthy food can be eaten when the child is hungry, and meal size can be adjusted to account for snacking (51). In general, vegetarian diets also support growth and good health, despite concerns about their adequacy.

Food Environment

The food environment parents provide during childhood may have an effect on eating behaviors and weight later in the child's life. The foods provided during mealtime as well as parents eating style can both have an influence on the child's intake. Restriction and pressure can eventually lead to overeating, food dislikes, or disordered eating (52). One study analyzed four different parenting styles (authoritative, authoritarian, permissive, and neglectful), with the risk of having an overweight child. The authoritarian (strict disciplinarian) parenting style was determined to have the highest prevalence of overweight children (17.1%). Neglectful (emotionally uninvolved) and permissive (indulgent, without discipline) parenting had a 9.8% to 9.9% rate of overweight children. The authoritative parents (respectful of child's opinion, but maintain clear boundaries) were found to have the lowest prevalence of overweight children (3.9%) (56). This study as well as several others demonstrate the relationship between feeding styles and children's weight (57,58).

TABLE 29.2

Recommended Feeding Practices from Childhood to Adolescence

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Nutrients:

- Consume nutrient dense foods including at least five servings of fruits and vegetables daily.
- Limit highly processed foods, fast foods, and sugars
- Children younger than 2 y/o should not consume sugar-sweetened beverages

Intake of fruit juice should be limited to 4 oz/day for children 1 through 3 years of age and to 46 oz for children 4 to 6 years of age. For children 7 through 17 years old, juice intake should be limited to 8 oz/day (53).
The American Academy of Pediatrics recommends sports drinks can be ingested when there is a need for rapid replenishment of carbohydrates and/or electrolytes in combination with water during prolonged, vigorous physical activity but should not be consumed after participating in short training or competition sessions (54)

- Limit sodium, refined and added sugars, trans fats
- Recommend foods rich in fiber, potassium, vitamin D, calcium for age

Factors that influence eating behaviors:

- Picky eating: often reflects lack of hunger than a change in taste preferences.
- Introduce a variety foods multiple times and in multiple ways with different textures (i.e., steamed carrots vs. roasted carrots vs. mashed carrots)
- Allow the child to choose 1–2 options for healthy snacks provided by the caregiver for a sense of autonomy (i.e., choice of an apple or an orange)
- Advertising and Marketing: Companies pay for shelf space in the grocery stores with the least healthy options at a childs eye level; therefore, look low and look high for nutritious alternatives

Feeding Recommendations:

- Promote a healthy feeding environment
- Caregivers should model good behavior and consume fruits and vegetables in the diet
- Offer culturally appropriate foods to expand the palate
- Use planned meals and snacks timed throughout the day to help manage hunger and achieve portion control.
- Healthy eating habits should be based on balance and moderation (55)
- Avoid letting a child eat while watching TV as this promotes unhealthy eating patterns
- Mindful eating is key to promoting a healthy relationship with food, which in essence is eating with intention and attention.
- Take the time to eat at the table as a family (55)

Food Insecurity

Food insecurity is the uncertain availability nutritionally adequate and safe foods or uncertain ability to acquire appropriate foods in socially acceptable ways. Lack of adequate healthy food can impair a child's ability to concentrate and perform well in school which is linked to higher levels of behavioral and emotional problems from preschool through adolescence. Food insecurity shapes individual behaviors and health outcomes. Food insecurity can affect children in any community, not only marginalized populations.

In 2015, AAP recommended that pediatricians screen children and youth for food insecurity with the "hunger vital sign." The "Hunger Vital Sign" is a validated two-question food insecurity screening tool

based on the US Household Food Security Survey Module used by the USDA to identify households at risk of food insecurity (59).

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Childhood Overweight and Obesity

Obesity in children continues to be a worldwide epidemic requiring the focus of health professionals (60). The factors that predispose an individual child to excess weight gain are complex, Extrinsic factors that may lead to overweight or obesity in children include newborn feeding practices and parenting styles mentioned earlier, as well as the timing of the introduction of solid foods, increased portion sizes, medications such as steroids, increased intake of calories from sugar-sweetened beverages and high energy-dense foods, and lack of physical activity (61–65) (see Chapter 5). Other environmental influences such as food deserts, food swamps, and lack of green space are all thought to contribute to weight gain (66). Intrinsic factors that lead a child to gain excess weight gain are also complex, as weight gain is the result of burning fewer calories than are consumed. Genetic predisposition, energy metabolism, and the inability to self-regulate are all biologic factors that contribute to obesity (67). Children with obesity suffer from psychosocial concerns such as depression, being bullied, and poor school performance and physical complications such as hypertension, nonalcoholic fatty liver disease, type 2 diabetes, and hyperlipidemia (67).

The Institute of Medicine's (IOM) Committee on Obesity Prevention for Young Children recommends following the Dietary Guidelines for Americans for children 2 years of age and older and the AAP for children younger than 2. The IOM also suggests using "responsive feeding" practices in which parents provide healthy foods and children control the amount they eat using hunger and fullness cues. To further prevent obesity, the IOM also recommends limiting screen time to less than 2 hours/day for children ages 2 to 5, advises appropriate sleep duration for age, and promotes increasing physical activity (68). The Dietary Guidelines for Americans and USDA MyPlate recommend a healthy diet focusing on fruits, vegetables, whole grains, fat-free or lowfat milk and dairy products, and lean meats; low saturated fat, trans fat, cholesterol, salt, and added sugars; and increased water consumption (69). Guidance to promote healthful eating patterns in the overweight child should be directed toward modifying the dietary intake patterns and behaviors of the family rather than focusing just on the overweight child. Exercise also plays a critical role. Increased physical activity is an important component of childhood obesity prevention/management and should be encouraged by parents and care givers.

A growing trend with weight loss is the timed restricted feeding approach known as intermittent fasting (see Chapters 5 and 32 for more information). There are minimal data to date on children, and most researchers conclude that intermittent fasting is not recommended for those in periods of rapid growth, such as children and adolescents. However, there are newer studies demonstrating that time-limited eating can be effective to reduce BMI in children but short- and long-term data are needed to see if this is a sustainable weight management technique for the future (70).

Food Marketing on children

Media companies spend billions of dollars marketing to children. Among US children 8 through 10 years of age, the average amount of time spent in a variety of media is nearly 8 hours/day and even more in teenagers (>11 hours/day). Disparities are also seen through targeted marketing campaigns from food companies designed to appeal specifically to Hispanic and Black consumers that may further contribute to the diet-related health disparities affecting communities of color (71). There must be corporate responsibility and public health interventions to make healthier choices more accessible and affordable for children (71). Empowered with this knowledge clinicians may provide knowledge to parents to

provide awareness and ideally counteract these messages in their households and communities.

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The World Health Organization has asked governments to implement policies that promote the intake of healthy foods and reduce the intake of unhealthy foods by children and adolescents, given the worldwide obesity crises. Food advertising and product placement on shelves effect children's eating behaviors (72,73). With the internet now a major source of food marketing, and with children spending a larger amount of time on social media, it is prudent that caregivers and parents monitor screen content and limit time spent on electronic devices to no more than 2 hours/day. One study demonstrated that children who observed (social media) influencers with unhealthy snacks had a significantly increased overall intake of food, especially unhealthy snacks (73). In fact, young children prefer and often select foods that have been associated with popular food brands and cartoon characters. Future research should explore strategies to encourage fruit, vegetable, and whole-grain consumption in children.

Cardiovascular Disease

Studies show that children today are consuming a significantly greater volume of unhealthy food and beverages than children did decades ago (62,74), as well as large amounts of soft drinks and fast foods contributing to the obesogenic environment (63,75,76). Recent data demonstrate prehypertension or hypertension in 19.2% of adolescent-age boys and 12.6% of girls, an estimated 38% increase compared to the early 1990s (77). Blood pressure percentiles should be looked at closely at every well visit as blood pressure values vary by age. Primary hypertension due to kidney issues should be evaluated in those children whose blood pressure is not well controlled.

Most children still consume saturated and trans fat in excess of recommendations and fail to consume the recommended quantities of fruits and vegetables. National surveys have revealed excessive intake of both total and saturated fat in children over the age of 1 year (78,79). Forty percent of the energy consumed by 2- to 18-year-olds comes in the form of solid fats and added sugars in just six sources: soda, fruit drinks, dairy desserts, grain desserts, pizza, and whole milk (80). The increased prevalence of overweight and hypertension has also been observed to be disproportionately great among ethnic minority children (81).

A pathology study of adolescents and young adults who died of trauma demonstrated that elevated serum lipids, as well as smoking, influence the development of early signs of atherosclerosis in adolescents; the Bogalusa Heart Study found that childhood measures of low-density lipoprotein (LDL) cholesterol and body mass index (BMI) were predictive of carotid intima-media thickness, an important predictive measure of future atherosclerotic events (82). Elevated serum lipids probably contribute to early lesions of atherosclerosis in children 10 to 14 years old and may begin to do so in children between the ages of 3 and 9 years (83). Dietary intervention has been shown to lower the high cholesterol levels common among children in Finland, with levels rising again on resumption of the habitual diet (84). The Special Turku Coronary Risk Factor Intervention Project (STRIP) was used to determine the possibility of reducing the effects of coronary risk factors using dietary counseling from 7 months to 19 years of age. Families met with a nutritionist who recommended an intake of fat between 30% and 35%, with a ratio of 1:2 of saturated to monounsaturated/polyunsaturated fat and cholesterol intake less than 200 mg/day. Individualized counseling was also provided based on the children's food records, and recommendations were made for improved consumption. Study findings showed that low-fat dietary counseling started during infancy was found to have a positive effect on serum LDL-cholesterol levels and various lipoprotein measures, especially among boys, without negatively effecting children's growth (85,86). Therefore, from a population perspective, there appears to be little potential harm and considerable potential gain in promoting the dietary pattern recommended for adults to school-aged children as well

(87).
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The prudence of advocating the same diet for adults and children is challenging. Over the past decade, there has been controversy over the safety and efficacy of fat restriction after age 2 (88); proponents of the restriction of dietary fat beginning at age 2 cite evidence that atherosclerosis begins in childhood and that a diet with not more than 30% of calories from fat beginning at age 2 is compatible with optimal growth (89); others argue for a gradual transition to lower-fat intake and attention to the type and distribution of dietary fat, as has been recommended in Canada (90).

Further support for advocating dietary fat restriction in particular for young children comes from epidemiological data in Italy. A rise in the consumption of saturated fat has been noted in a population with a traditionally health-promoting "Mediterranean" diet (91). A study of 100 Finnish school-aged children demonstrated that the intake of several important nutrients tended to be lower among the children with the highest fat intake (92). Further, this study suggested that the diets of young children are quite diverse, so offering dietary recommendations was unlikely to "disrupt" a traditional dietary pattern chosen by families for their young children.

Efforts to resolve the debate regarding the safety of fat restriction in early childhood have resulted in controlled intervention studies (93,94). One earlier intervention trial (the Child and Adolescent Trial for Cardiovascular Health [CATCH]) examined the effects of a multidisciplinary program emphasizing change in school nutrition on cardiac risk factors in children beginning in third grade (95). The study lowered fat intake significantly and lowered serum cholesterol minimally. Growth and development were unaffected. Another study using the CATCH program also showed a significant effect in slowing the increased risk of overweight/obesity in low-income elementary schools serving primarily Hispanic students (96).

The Dietary Intervention Study in Children (DISC) randomly assigned 8- to 10-year-old children with LDL cholesterol above the 80th percentile to either usual care or a dietary intervention with 28% of energy from total fat, less than 8% from saturated fat, up to 9% from polyunsaturated fat, and less than 75 mg/1,000 kcal cholesterol/day. After approximately 7 years of follow-up, children in the intervention group were found to have greater reductions in LDL-cholesterol levels compared to the usual care group, and they had no adverse effects on growth and development (97). Results of a long-term follow-up study, 9 years after the end of the original DISC study, showed that the consumption of a low-fat diet in childhood may contribute to significant blood pressure and glycemic control in adulthood (98). In children, it is well known that trans fats must be limited/eliminated from the diet. Recent research found lower BMI with total fat intake at 30% of total energy (30% TE) or less has beneficial effects on total cholesterol and low-density lipoprotein (LDL) cholesterol, with no meaningful effects on any of the other outcomes. High-quality longer-term trials and prospective cohort studies are needed to better assess guidelines (99).

In addition to the Dietary Guidelines for Americans and MyPlate recommendations mentioned earlier by the USDA, the American Heart Association (AHA) guidelines for promoting cardiovascular health includes the DASH diet (Dietary Approaches to Stop Hypertension) with the goal of eating a variety of fruits and vegetables while limiting juice intake, choosing whole grain/high-fiber bread and cereals, and keeping fat intake between 30% and 35% of calories for children 2 to 3 years of age and between 25% and 35% above 3 years of age. Dairy products should include fat-free and low-fat; children ages 1 to 8 need two cups of milk or its equivalent per day and three cups per day for children from 9 to 18 years of age (100). DASH diet also recommends limiting daily sodium intake while increasing daily potassium intake. It is hoped that these dietary modifications will not only constitute primary prevention, limiting the development of cardiovascular disease, but also act as primordial prevention, a term now used to

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describe the prevention of the development of cardiovascular risk factors (101). Furthermore, data from studies encourage a common eating pattern for families, with the implication that the fat content in the diets of children might decline, and all sources encourage the promotion of regular physical activity and fruit and vegetable consumption during childhood (102).

Data from the Bogalusa Heart Study and the Muscatine Study demonstrate that there is tracking through early childhood and adolescence of dietary pattern, physical fitness, and cardiovascular risk factors (103,104).

In light of these considerations, it appears that the recommendation in the United States to advocate a similar diet for everyone over the age of 2 years is reasonable and safe, and it may offer long-term benefits (105). Although there is some evidence that a comparable diet may be safe even before age 2 (106), consensus opinion in the United States and prudence argue against the imposition of macronutrient restrictions in this age group. Conclusive evidence of benefit from early dietary modification efforts will accrue very slowly.

Prediabetes and Type 2 Diabetes

The prevalence of prediabetes (A1c > or = 5.7%) and type 2 diabetes (A1c > or = 6.5%), formerly considered to be an adult-onset disease, among children and adolescents has been rising (see Chapter 6). Impaired fasting glucose (fasting glucose of 100–125 mg/dL) and impaired glucose tolerance (IGT) (2-hour glucose of 140–199 mg/dL on an oral glucose tolerance test [OGTT]) are associated with increased risk of developing diabetes. Individuals with impaired fasting glucose, IGT, or both are included under the broad definition of prediabetes (107).

Prediabetes is a precursor to T2DM, and the cause of this disease in children is similar to adults as it includes factors such as obesity, metabolic syndrome, physical inactivity, and inflammation (108). Children at greatest risk for type 2 diabetes include children with BMI >85th percentile, family history of DM, signs of insulin resistance such as dyslipidemia, hypertension, acanthosis nigricans, and polycystic ovary syndrome (109). Nutritional management is an important aspect of treatment in children with type 2 diabetes. The International Society for Pediatric and Adolescent Diabetes recommendations include eliminating sugar-sweetened beverages, reducing total and saturated fat intake, increasing fiber intake, portion control, and increased physical activity (109). Parents should make sure children have an optimal sleep environment as research is emerging that there is metabolic and glycemic sequelae effecting insulin dysregulation if there is sleep disturbance (110). Additional care with a pediatric dietitian and endocrinologist are also strongly recommended for comprehensive management and further guidance (107).

NUTRIENTS, NUTRICEUTICALS, AND FUNCTIONAL FOODS

n-3 Fatty Acids

Long-chain polyunsaturated fatty acids are particularly concentrated in the brain and retina. Eicosapentaenoic acid and docosahexaenoic acid (DHA) are relatively abundant in human breast milk and prominently incorporated into the developing brain (111,112). DHA in particular is considered essential to healthy brain development (113). Impaired cognitive development in premature infants may be related in part to insufficient availability of DHA during a critical period of brain development (114,115).

Breastfeeding has been associated with enhancement of IQ and visual acuity in infants (116,117),

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though recent evidence suggests that the evidence for an effect on intelligence may have been confounded by maternal IQ (118). The apparent health benefits of breastfeeding relative to formula feeding may be related in part to the DHA content of breast milk. Increasingly, long-chain polyunsaturated fatty acids, including DHA, are being added to commercial formulas (119). Although there is no regulatory requirement for the inclusion of arachidonic acid (ARA) and DHA in infant formulas, formulas in the United States now provide them. Most US term infant formulas provide 0.15% to 0.35% fatty acids from DHA and 0.35% to 0.64% fatty acids from arachidonic acid 99. One recent double-blind, randomized trial compared DHA and arachidonic acid supplementation of infant formula to breast milk; at 4 years of age, children who had been fed either the DHA- and AHA-supplemented formula had visual acuity and verbal IQ scores similar to those who were breast-fed, while the control group had poorer visual acuity and poorer verbal IQ scores (120). Although the essential fatty acid a-linolenic acid is a precursor to DHA as well as to eicosapentaenoic acid, conversion to DHA in particular appears to be limited and variable. The putative benefits of DHA apparently require that it be administered directly in the diet (121). Although health benefits of DHA supplementation are likely on the basis of confluent lines of evidence, the benefits are not yet conclusive (122).

Relevant Nutrigenomic Considerations

An association between children's environment and its effect on overweight and obesity has been found, but there may also be a genetic connection. A variant in the FTO (fat mass and obesity-associated) gene has been linked to obesity and BMI in several studies (123–125). Research has revealed that the FTO gene may play a role in the regulation of feeding and energy homeostasis (126). A study also determined that children with the A allele had a significantly higher weight, greater BMI, and consumed more energy-dense food at meals when compared to the noncarriers (127). As this nutrient-gene interaction research advances, future studies will be able to shed more light in its influence on health promotion and disease prevention.

CLINICAL HIGHLIGHTS

Nutrition for pregnant women and young children is essential for growth and healthy physical and mental development. The provision of optimal nutrition during infancy and early childhood is of vital importance to growth and is likely related to a wide array of health outcomes later in life. The establishment of good nutriture for an infant begins while in utero, during which time maternal dietary practices may influence fetal metabolism (see Chapter 27).

The most reliable way to ensure optimal nutrition for a newborn is breastfeeding. Therefore, clinicians should routinely encourage breastfeeding for a period of 6 months unless the practice is contraindicated by communicable disease. This advice is based on the confluence of multiple lines of evidence.

The maintenance of salutary maternal nutrition during lactation is of importance to the health of both mother and baby (see Chapter 27). As evidence of the importance of DHA and other essential fatty acids continues to accrue, the composition of most commercial formulas has been revised to mimic levels found in breast milk.

Weaning to solid food generally should begin at approximately 6 months (see Chapter 24). Weaning from breast milk or formula is generally complete by around 12 months, although such practices are culturally determined; medically, weaning at 12 months is appropriate.

Children generally will self-select foods that meet micronutrient requirements when provided with an array of healthy food choices; this practice is to be encouraged. Children also reliably meet their energy

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needs, although energy intake may vary considerably by meal and even day. In addition, parental feeding practices have been associated with a child's eating behavior and weight status. Parents who use authoritative approach (respectful of child's opinion, but maintain clear boundaries) were found to have the lowest prevalence of overweight children.

Controversy persists regarding the optimal timing for approximating adult dietary guidelines in children. There is evidence that adult dietary recommendations are safe for children as young as 7 months of age, although few in the United States would endorse such a practice. Evidence is more definitive that the imposition of such guidelines beginning at age 2 is safe and reasonable. Taking this approach provides the added benefit of unifying family dietary practices earlier. There is evidence that dietary preferences established in childhood tend to persist (see Chapter 38), highlighting the importance of establishing a prudent dietary pattern early. Therefore, the diet that should be advocated to adults and older children to promote health (see Chapter 45) may be provided promptly, or approximated gradually, in children beginning at age 2. Micronutrient supplementation with a multivitamin/multimineral tailored for children is a reasonable practice when children are not consuming a balanced diet. The consistent intake of DHA through omega-3s may offer considerable health benefits, which is supported by preliminary, but accumulating, evidence. There are many influences on feeding practices, and caregivers should be aware of the relationship advertising has on children. With diet-related chronic diseases rising, healthcare professionals should be adequately trained in nutrition and lifestyle counseling for improvement management. Good nutrition beginning in early life significantly pays off in childhood and in later life. Investing in maternal and childhood nutrition has both short- and long-term benefits, which may play a significant economic and social role down the road.

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Chapter 30

Diet and Adolescence

Qadira Ali Huff

INTRODUCTION

The nutritional requirements of adolescence differ from those of childhood by virtue of the adolescent's larger body size and the advent of sexual maturation. They differ as well from those of adulthood because of the metabolic demands of rapid growth. During normal puberty, height and body weight increase rapidly, with 50% of adult body weight gained during adolescence (1). As a result, the recommended dietary allowances (RDAs) for adolescence differ from those of other periods of the life cycle (see Table 30.1). Nutrients of particular importance to all adolescents appear to be magnesium, zinc, and calcium. With the advent of menses, adolescent girls become particularly subject to iron deficiency.

While dietary quality has gradually improved for adolescents over the past two decades, based on National Health and Nutrition Examination Survey (NHANES) data from 1999 to 2016, more than two-thirds of adolescents currently consume diets rated as poor quality as defined by the American Heart Association (2). Adolescent diets are lacking in fruits, vegetables, legumes, whole grains, and fish, all the while containing excess amounts of sugar-sweetened beverages, sodium, processed meat, and saturated fat. Despite these dietary challenges, trends demonstrate modest improvements, such as reductions in sugar-sweetened beverages, juice, and processed meat, and increases in nut, seed, and whole fruit consumption (2).

Specific aspects of diet, health, and adolescence relate to physical activity patterns and issues of body image. Relatively sedentary adolescents are at risk of obesity because nutrient energy intake exceeds need. Adolescent obesity anticipates adult obesity. Similarly, the combination of inactivity and a diet excessive in processed and fast food—high in saturated fat, sugar, salt, and calories—predisposes to elevations of cholesterol, insulin, and blood pressure. Adolescence brings more independence and food selection autonomy that is additionally impacted by peers and marketing (3). Gaps in knowledge about nutrition and its numerous health effects contribute to suboptimal food selections (4).

Many adolescents participate in competitive sports and, therefore, are at potential risk of inadequate nutrient intake. Inadequate nutrients and energy are particularly problematic in those participating in sports requiring low body weight, such as wrestling, crew, gymnastics, and ballet. Adolescents are at higher risk for disordered eating that may emerge in the context of competitive, body image-conscious sports.

In addition to the pressure from competitive sports participation, adolescents often feel the need to excel in the classroom in the midst of increasingly competitive college admissions. Teens may stay up late and consume poor diets and unregulated supplements, like energy drinks, with the goal of better concentration, performance, and stamina.

Body image is of particular importance to adolescents and may result in extreme efforts to control or modify diet. Eating disorders, considered psychiatric rather than truly nutritional disorders, typically manifest during adolescence; they will be discussed further in Chapter 25. The adoption of vegetarianism

by an adolescent may mask an intentional weight-loss effort and, if so, may increase the risk of a nutritionally unbalanced diet due to restrictive eating (5). As the vegetarian diet grows in popularity in the context of amassing evidence supporting its health benefits, it is critical to assess and counsel adolescents adhering to plant-based diets to ensure nutritional adequacy.

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TABLE 30.1

Dietary Reference Intakes: Recommended Dietary Allowances or Adequate Intake for Adolescents[a]

	Ages 9–13 Yr		Ages 14–18 Yr		Ages 19–30 Yr	
Nutrient Energy[b]	Female	Male	Female	Male	Female	Male
kcal (Sedentary lifestyle)	1,400–1,600	1,600–2,000	1,800	2,000–2,400	1,800–2,000	2,400–2,600
kcal (Moderately active)	1,600–2,000	1,800–2,200	2,000	2,400–2,800	2,000–2,200	2,600–2,800
Protein (g)	34	34	46	52	46	56
Sodium[c] (mg) (AI)	<1,500	<1,500	<1,500	<1,500	<1,500	<1,500
Vitamin A[d] (µg RAE)	600	600	700	900	700	900
Vitamin D (IU)	600	600	600	600	600	600
Vitamin E (mg TE)	11	11	15	15	15	15
Vitamin K (µg AI)	60	60	75	75	90	120
Vitamin C[d,e] (mg)	45	45	65	75	75	90
Thiamine (mg)	0.9	0.9	1.0	1.2	1.1	1.2
Riboflavin (mg)	0.9	0.9	1.0	1.3	1.1	1.3
Niacin (mg NE)	12	12	14	16	14	16
Vitamin B_6 (mg)	1.0	1.0	1.2	1.3	1.3	1.3
Folate[f] (µg)	300	300	400	400	400	400
Vitamin B_{12} (µg)	1.8	1.8	2.4	2.4	2.4	2.4
Calcium[d,g] (mg)	1,300	1,300	1,300	1,300	1,000	1,000
Phosphorus (mg)	1,250	1,250	1,250	1,250	700	700
Magnesium (mg)	240	240	360	410	310	400
Iron[d,h] (mg)	8	8	15	11	18	8
Zinc[d] (mg)	8	8	9	11	8	11
Iodine (µg)	120	120	150	150	150	150
Selenium (µg)	40	40	55	55	55	55
Copper (µg)	700	700	890	890	900	900

[a]NE, niacin equivalent, which equals 1 mg of dietary niacin or 60 mg of dietary tryptophan; RAE, retinol activity equivalent; TE, α-tocopherol equivalent.

[b]Energy intake is expressed based on activity levels and requirement needed to maintain calorie balance, using average height and weight.

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[c]*These values represent adequate intake (AI) for sodium. The upper limit is 2,200–2,300. But recent guidelines have recommended further reducing intake of all African Americans, those with hypertension, diabetes, or chronic kidney disease to <1,500 mg. Also are believed to cover the needs of healthy individuals, but lack data to define the percentage of individuals covered by this intake*.

[d]*Nutrients for which adolescent intake is most likely to fall short of recommendations*.

[e]*The recommended intake of vitamin C has been increased for adults from 60 to 200 mg/day*.

[f]*Daily intake of about 400 μg is recommended before conception to prevent neural tube defects. This intake is advisable in adolescent girls planning on becoming, or at risk of becoming, pregnant*.

[g]*Calcium supplementation may be particularly important in adolescent girls unless the diet is very calcium dense. An intake of 1,500 mg/day may be better than the Recommended Dietary Allowances (RDA) of 1,200 mg. During pregnancy and lactation, the calcium requirements of adolescent girls are even higher*.

[h]*Iron supplementation in adolescent girls may be indicated. Monitoring of the complete blood count after menarche is indicated but has low sensitivity for early iron deficiency. If an individual adolescent is believed to be at risk of deficiency, serum ferritin should be assayed*.

Adapted from Institute of Medicine. Dietary reference intakes: Recommended intakes for individuals. National Academy of Sciences, recently updated 2010. http://www.iom.edu/Activities/Nutrition/SummaryDRIs/~/media/Files/Activity%20Files/Nutrition/Summary%20Table%20Tables%201-4.pdf& accessed 4/10/13& U.S. Department of Agriculture and US. Department of Health and Human Services. Dietary guidelines for Americans, 7th ed. Washington, DC: U.S. Government Printing Office, 2010

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OVERVIEW

Factors influencing changes in dietary pattern for adolescence are both physiologic and social. Physiologically, energy and nutrient requirements are driven up by increasing body size and the advent of sexual maturation, including menarche in girls. Socially, adolescence affords opportunity for food selection independent of parental guidance, often for the first time. Food choices are often made on the basis of prevailing patterns in peer groups. Adolescents are particularly resistant to health promotion messages, likely secondary to a drive for autonomy and less focus on long-term health. Typical dietary

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patterns in adolescents are influenced by targeted advertising and, therefore, emphasize commercial products, such as sodas and fast foods, rather than unprocessed foods. Of note, food companies excessively market their lines of unhealthy products (candy, sugar-sweetened beverages, fast food, and snacks) to Black and Hispanic communities. Given that Black and Hispanic youth tend to view more of these television advertisements, racially targeted marketing contributes an important factor in the propagation of health disparities, many of which have dietary dimensions (6).

Adolescents also manifest their newfound food-related autonomy through increased meal skipping behavior. Adolescents may skip any meal of the day& however, the most commonly skipped meal is breakfast. Likely related to an evening chronotype associated with a delayed sleep onset and subsequently later natural awakening, adolescents display a tendency to sleep beyond the typical breakfast time or to have a poor appetite if forced to awaken too early in the morning (7). Adolescents cite running out of time to eat breakfast and trying to limit weight gain by avoiding "excess calories" as common reasons for skipping meals. The process of skipping breakfast may contribute to a reflex overcompensation of calories at later meals, but also limit important nutrients into the adolescent diet that are often associated with the first meal of the day such as vitamins A, B_6, B_{12}, iron, and calcium. Notably, these missed nutrients are typically not filled in at subsequent meals (8,9). The mechanism by which skipping breakfast impacts risk for overweight and obesity requires more research as hypotheses vary from insulin resistance to higher caloric consumption through compensatory overeating at later meals (10,11). Intermittent fasting under medical guidance and extreme caution has been considered as a tool for weight loss and to reverse insulin resistance for older adolescents (12). Overall, eating breakfast seems to be associated with healthier body weight and improved school performance—inclusive of learning and behavior (13).

Although adolescents sometimes voluntarily skip sources of good nutrition, the problem of food insecurity cannot be overlooked. The WHO defines food security to be "when all people at all times have access to sufficient, safe, nutritious food to maintain a healthy and active life." In 2019, 6.5% of US households with children under age 18 years experienced food insecurity (14). Children and adolescents spend a large majority of their time in the school setting, so with the passing of the Healthy Hunger-Free Kids Act of 2010, school districts that receive federal funding for specific meal programs are increasing the standards for nutrient-rich school foods and allowing students to access these foods in the comfort of their school (15).

When families are food secure and thus able to prepare home-cooked meals, adolescents may benefit through the consumption of healthier meals and the observation of modeled parental food habits. The home food environment and at-home meal preparation are associated with maintaining a healthier weight. Children who eat meals at home with family tend to have healthier diets, including less fried food and sugar-sweetened beverages and more fruits, vegetables, and whole grains (16).

Topics of importance in the dietary management of health during adolescence include obesity, hypertension, metabolic syndrome, diabetes, vegetarian diets, athletic activity, school performance, and eating disorders (see Chapters 5, 6, 8, 14, 25, 32, and 43), as well as the nutritional demands of rapid growth. Although adolescents' energy requirements are high because of their rapid growth, the recommended dietary pattern is the same as that for adults. Recommendations call for calories predominantly from complex carbohydrates, but adolescents in developed countries tend to have diets particularly high in fat and sugar, a phenomenon that has led to markedly increased prevalence of overweight and obesity in recent years (17) (see Chapter 5). The short-term risks of such a dietary pattern are modest, but the persistence of this pattern beyond adolescence is common and clearly associated with the prevailing chronic diseases of adulthood.

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In the United States, there continues to be a gradual decline in the age of puberty for children and adolescents. While a variety of dietary factors have been associated with earlier puberty, childhood adiposity and rapid weight gain during early childhood have been most consistently linked to a younger puberty age in girls (18–20). Additional factors have been hypothesized as contributors to early puberty, including higher meat consumption, increased dairy intake, and less vegetable consumption (21–23). Findings have been less consistent, perhaps related to the age at food exposure assessment, method of dietary assessment, body composition variability, and frequency of dietary exposure (21). One study evaluated female food consumption using food frequency questionnaires at 3, 7, and 10 years of age. Increased total and animal protein consumption weekly was associated with 49% of girls starting earlier puberty compared to 35% of girls with lower meat consumptions (23). The maximal rate of growth in height for girls occurs between the ages of 10 and 13, whereas for boys it is between the ages of 12 and 15 (24). In girls, peak height velocity usually occurs 0.5 years prior to menarche, with African American and Hispanic girls more commonly reaching these milestones earlier than Caucasian girls (25,26). The adolescent growth spurt contributes approximately 15% to 20% to adult height and 45% to 50% to adult weight. The growth during adolescence reduces the proportion of total body mass contributed by adipose tissue in boys but increases it in girls. Body fat in girls rises during adolescence from 10% to between 20% and 24%. A divergence in adiposity at adolescence contributes to the diverging nutritional requirements of males and females at this stage of life. By the end of adolescence, lean body mass in males on average is double that of females.

In girls, peak calorie intake typically occurs in the year of menarche. In boys, calorie intake continues to rise throughout the growth spurt, generally peaking near 3,400 kcal at about age 16. The divergence in lean body mass results in a marked divergence in macronutrient needs. The average daily caloric requirement per unit height rises during adolescence for boys, and it falls for girls because of the increasing proportion and lower metabolic demand of body fat.

The adequacy of energy intake in adolescents can be assessed through the determination of body mass index (BMI) and comparison to age-appropriate reference ranges (27). Inadequate energy intake in adolescents, if mild, tends to delay the growth spurt rather than prevent attainment of normal height. While Dietary Reference Intakes are developed, in part, on the basis of chronologic age, the developmental stage of the child is a more reliable index of actual needs. The Tanner scale of sexual maturity is widely used and can guide nutritional recommendations to adolescents.

While the protein intake for most adolescents in the United States falls above the threshold for adequate intake, more than one in ten adolescent girls may fall short of the Estimated Average Requirement (EARs) for protein as noted in the 2004–2010 NHANES results (28). However, if protein deficiency is suspected because of dietary restrictions, prealbumin and retinol-binding proteins are useful laboratory assays that provide high sensitivity for subclinical protein malnutrition.

National data suggest that in the United States, the average adolescent consumes a diet deficient in several key vitamins and minerals, most prominently calcium, iron, folate, vitamins A and E, zinc, and magnesium (29). Inadequate calcium intake is both common and of great concern in adolescents, as it contributes to the risk of osteoporosis and fractures in later life (see Chapter 14) (30). Adequate calcium is necessary for bone mineral density, but high dairy intake (>2.6–2.8 g/day) may be associated with reduced bone mineral density in females, Black children, and early adolescents (30). Nondairy sources of calcium include fortified plant-based milks, and “beans and greens,” like spinach, collard greens, soybeans, and calcium-set tofu. Rapid growth and expansion of both blood volume and muscle mass lead to increased iron requirements in adolescence; with the onset of menarche, girls become further susceptible to iron deficiency. Serum ferritin is the most reliable measure of iron stores. Iron deficiency

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commonly leads to anemia, defined in adolescents as a hemoglobin level below 11.8 g/dL at ages 12 to 14.9 years and below 12.0 g/dL at 15 years and older. Adolescents have increased requirements for folate; supplementation may therefore be warranted. This is especially true for sexually active young women, given the demonstrated benefits of folate supplementation in reducing the risk of neural tube defects if taken early in pregnancy (31) (see Chapter 27). Nominal zinc and magnesium deficiency is common in US adolescents, and inclusion in the diet of foods rich in these minerals (see Appendix E) or supplementation (in a multivitamin or multimineral) is appropriate.

In general, the dietary fiber intake of the US population is well below recommendations, including children and adolescents (32). Although there has been concern that high fiber intake could interfere with micronutrient absorption and adequate caloric intake among growing children and adolescents, the current recommendation of "age+5"–that is, fiber intake equal to age plus 5 to 10 g/day-is both safe and sufficient for disease prevention (33,34). A plant-predominant eating pattern may fill this fiber deficiency through its emphasis on legumes, fruits, vegetables, nuts, and seeds.

Excess energy and fat intake is common in children and adolescents in the United States, contributing to obesity, type 2 diabetes, and adult risk of cardiac events (35–37). Consumption of sugar-sweetened drinks such as soda (38) and increased sedentary activities—particularly television/video and computer use—have also been found to be associated with increased risk of obesity (39). An individual's polygenic risk has been investigated as an independent predictor of obesity later in life, in addition to the parental history of overweight, cardiorespiratory fitness, and activity level. A 2020 study of the coronary artery risk development in young adults (CARDIA) data set found that while polygenic risk score was modestly associated with BMI in young adulthood and midlife; fitness, activity, and parental history of overweight had similar associations with BMI at both time points. Lifestyle habits, dietary pattern plus level of fitness and physical activity, still appear to be more useful targets of intervention and prevention (40).

For severe cases of obesity in adolescents, bariatric surgery presents an effective treatment option. Currently, 7% of girls and 9.7% of boys 12 to 19 years old in the United States have severe obesity as defined by BMI ≥120% of 95th percentile or ≥35 kg/m2, whichever is lower (17). Adolescents with severe obesity are at risk for developing comorbidities, including obstructive sleep apnea, diabetes, hypertension, dyslipidemia, nonalcoholic fatty liver disease, and idiopathic intracranial hypertension, and reduced life expectancy (41). The mental health toll of severe obesity may also be significant, including bullying, depression, anxiety, and weight-related stigma (42). Given the serious health consequences of severe obesity, it is important to evaluate bariatric surgery as a viable option (43). Vertical sleeve gastrectomy has replaced Roux-en-Y gastric bypass (RYGB) as the most commonly performed procedure, accounting for 80% of all adolescent bariatric surgeries (44). Sleeve gastrectomy surgeries have lower short- and long-term complication rates than RYGB; the most common short-term complications include staple line leaks, protracted nausea, and infection. Long-term complications are the risk of nutritional deficiencies, particularly vitamin B_{12}, iron, thiamine, and vitamin D (45).

Mirroring the rise in obesity, the incidence of metabolic syndrome has risen precipitously over the past 20 years (46,47). While no consensus definition exists for adolescents, the syndrome has a constellation of symptoms including abnormalities in waist circumference, body weight, triglycerides, high-density lipoprotein, blood pressure, and glucose levels. In adults, these risk factors have been linked with obesity, cardiac disease, hypertension, and type 2 diabetes (46–48). Although the long-term outcomes are less firmly established when associated with the cluster of risk factors, it is clear that the prevalence of metabolic syndrome is higher among adolescents with obesity (48–51). Data from National Heart Lung and Blood Institute Lipid Research Clinics Princeton Prevalence Study and Princeton Follow-Up Study demonstrated that children with metabolic syndrome (pediatric metabolic syndrome definition: age-

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specific BMI >90th percentile on centers for disease control & prevention (CDC) 2000 growth chart, pediatric standards for blood pressure, high-density lipoprotein-cholesterol (HDL-C) ≤50 mg/dL, triglycerides ≥100 mg/dL, and glucose ≥110 mg/dL) were 9.4 times more likely to develop adult metabolic syndrome (adult metabolic syndrome definition: HDL-C ≤50 mg/dL [females] and 40 mg/dL [males], triglycerides ≥150 mg/dL, blood pressure ≥130 [systolic] or 85 [diastolic] mm Hg, and glucose ≥110 mg/dL) and 11.5 times more likely to develop type 2 diabetes 20 to 30 years after childhood (50).

The past three decades have witnessed a dramatic increase in the incidence of type 2 diabetes among children and adolescents with obesity. Now, approximately one in three new cases of diabetes mellitus in children <18 years old is type 2 diabetes mellitus (DM), and as a result, primary care clinicians are being forced to provide care for many adult complications at an earlier age (52). Although medicines such as metformin are being attempted earlier to quell some of these complications of hyperinsulinemia and impaired glucose tolerance, most of these medications have not been tested for safety and efficacy in adolescents <18 years old (53,54). Cardiac risk factors established in adolescence or earlier are known to track into adulthood. Diabetes screenings, as well as assessment of tobacco use and serum lipids, BMI, blood pressure, physical activity level, and habitual diet, are indicated in adolescence to reverse or prevent developing risk for cardiovascular disease in adulthood (55).

Hypertension in adolescents poses increased long-term health risks; thus, prompt identification and management are warranted (56). Dietary sodium has steadily increased and exceeded the upper-limit reference intake of 2,300 mg/day from the National Academy of Sciences. The increase in sodium intake correlates with increasing consumption of processed foods and foods eaten outside of the home (57). A 2006 meta-analysis of controlled trials assessing the effects of salt restriction on blood pressure in children found that modest reductions in dietary salt intake resulted in significant reduction in systolic blood pressure (58) (see Chapter 8).

As concerns regarding the rise of lifestyle-related chronic disease among adolescents grow, so does understanding the role of a well-planned, unprocessed plant–based diet in being a potential mitigator. Clinicians should begin with clarifying the degree of animal product exclusion from diet as basis for nutritional counseling (59). While an association with eating disorders has been identified for some adolescents whose restrictive eating manifests through vegetarianism, a plant-based diet may present long-term health benefits, including lower incidence of obesity, coronary heart disease, hypertension, and type 2 diabetes as compared with an omnivore diet (59–61). Additionally, vegetarian children and adolescents tend to be leaner while maintaining normal growth and development parameters (62). Carefully planned plant-based diets can meet nutritional needs for both growth and development with special attention to overall calories, protein, iron, calcium, vitamin D, and vitamin B_{12}. The more restrictive a plant-based diet, the more critical it is to plan meals deliberately (60). Universal vitamin B_{12} supplementation is indicated for those on vegan diets. Lab monitoring for particular nutritional deficiencies may be warranted, including iron, vitamin D, and possibly vitamin B_{12} if concern exists for deficiency. In balancing the documented health benefits of a vegetarian diet with the potential masking of restrictive eating disorders, careful dietary history and nutritional counseling are warranted (59).

On average, adolescents typically sleep about 7 hours nightly, while recommendations range from 8 to 10 hours for adolescents 14 to 17 years old (63). The decreased sleep duration has been attributed to many factors, including social and school obligations and early school time. With adolescents staying up later at night, they are increasingly exposed to the toxic obesogenic environment and increased snacking (64). In addition, the hormone dysregulation associated with short sleep duration includes decreased leptin and increased ghrelin levels leading to increased hunger and overconsumption of calories

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throughout the day. Research into Circadian Locomotor Output Cycles Kaput (CLOCK) gene variants expands another dimension of the short sleep duration–obesity association. Further research into CLOCK single-nucleotide variants may help to identify those at higher risk of overeating and gaining weight when exposed to short sleep durations (65). Overall, short sleep duration in adolescents is strongly correlated with etiology and maintenance of obesity (66).

Another method adolescents use to alter sleep is through consumption of energy drinks. These drinks are marketed heavily toward youth for improving energy, athletic performance and concentration using catchy slogans, and compelling adolescent risk-taking behavior (67). Energy drink consumption has increased over the past decade, with the range of reported adverse reactions related to excessive caffeine consumption (68). Energy drinks not only contain a variety of "secret" ingredients that tend to include caffeine and sugar most importantly, but also contain some combination of taurine, B vitamins, sugars, guarana, ginseng, ginkgo biloba, and l-carnitine (69). Because energy drinks are considered "natural dietary supplements," the regulations are quite limited (68,69). The most potent ingredient in these drinks is caffeine, and the lack of regulation poses a poignant danger. Small amounts of caffeine can have some clear benefits such as improving physical performance, reaction time, slowing fatigue, and increasing auditory vigilance; however, these effects are dose- dependent, variable, and usually generated by adult studies. Given documented risks of caffeine intoxication, including anxiety, headache, and palpitations, adolescents and children should minimize consumption to not exceed 100 mg/day of caffeine or 2.5 mg/kg/day, respectively (70); one energy drink bottle may often contain 160 mg caffeine (71). Another pediatric policy affirmed that stimulant-containing energy drinks have no place in the diets of children and adolescents (72). Adolescents who consume energy drinks have been shown to be more likely to use tobacco, alcohol, and marijuana (73).

Translating recommendations into practice may be particularly difficult with adolescent patients (see Chapter 47). Dietary counseling in adolescence is most likely to be influential if it emphasizes current health, current activities, and/or appearance rather than long-term health effects, to which adolescents generally feel relatively invulnerable. Dietary health promotion in the school setting remains promising as an intervention point (74–77). Nutrition-focused program characteristics associated with positive outcomes include parental engagement through in-person sessions, clearly defined behavior outcomes, program consistency through trained teachers or experts, use of age-appropriate activities, and an intervention duration of at least 6 months (78). Home environment also plays a role: An association has been shown between adolescents who eat dinner with their families and more healthful dietary intake patterns, illustrating the importance of parental involvement as well (16,79).

In general, physical activity is beneficial to health and complementary to the health-promoting effects of prudent diet. Competitive athletics in adolescent girls, however, can lead to a syndrome known as the female athlete triad, which consists of osteoporosis, disordered eating, and menstrual disorders (80). Though initially thought to stem from low adiposity, menstrual disturbances in female adolescents are now believed to result principally from inadequate energy availability, which causes hypothalamic-pituitary hormone dysfunction (81,82) (see Chapters 29 and 34). Amenorrhea in particular is associated with reduced peak bone mass, stress fractures, and increased risk of osteoporosis in later years. In the treatment of adolescent amenorrhea, reductions in training or increases in energy intake or both and use of oral contraceptives may be indicated to restore menses and maintain normal bone mineralization (81,82).

Another potential risk related to athletics in adolescents is overconsumption of sports drinks, which can worsen overweight or obesity and dental erosion. In general, water is the most effective choice for hydration during sports unless there is a need for more rapid replenishment for prolonged periods (>1 hr) of vigorous physical activity, at which time sports drinks are perfectly appropriate (72).

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Acne vulgaris, the most common skin condition affecting late adolescents, has been shown to have dietary and lifestyle associations with severity. Di Landro et al. noted strong associations between moderate to severe acne cases and family history of acne in a first-degree relative–with reduced risk among those with lower BMIs (effect greater in males than females). As milk consumption rose above three servings per week, acne worsened in severity. The effect was greater for skim milk than whole milk (83). There may be an association between obesity and insulin resistance—conditions potentially modifiable through diet—with hyperandrogenism and risk of acne (58).

CLINICAL HIGHLIGHTS

In the United States, adolescents are at greater risk of nutritional excess and obesity than of macronutrient deficiencies. But even in the context of overnutrition, deficiencies of select micronutrients appear to be common. Deficiencies of iron, calcium, zinc, and vitamins A and C are particularly common, although other nutrients probably are not consumed at truly optimal levels. *Omega*-3 fatty acids tend to be deficient in the diets of children and adults alike.

Although a balanced diet built upon fruits, vegetables, legumes, and whole grains provides the needed nutrients to support the dynamic growth of adolescence, social, environmental, and developmental dimensions contribute to a pattern of dietary imbalance characterized by excessive intake of processed foods high in sugar, salt, and saturated fat. A multivitamin or multimineral supplement is an appropriate recommendation, although clearly not compensatory for a suboptimal dietary pattern.

Energy requirements of athletes may not be met. This caloric shortfall is particularly problematic for girls, who as a result may develop endocrinological disturbances and even amenorrhea. The resultant disruption of bone mineralization may be irreversible. Calcium supplementation, control of energy expenditure, and supplemental energy intake are all indicated to maintain menses and protect the bones of female athletes. In extreme cases, oral contraceptives should be used as well. Screening for iron-deficiency anemia is also recommended for menstruating girls.

Eating disorders often emerge at adolescence, and a high level of suspicion facilitates early detection. Management is specialized, often relying on multidisciplinary psychiatric care.

Risk factors for cardiovascular disease often develop during adolescence and, when they do, continue into adulthood. Therefore, efforts to identify and modify risk factors for cardiovascular and other chronic diseases in adolescents are clearly indicated, as are screening for hypertension, lipid disorders, and diabetes.

Modification of adolescent dietary patterns to promote health will be most effective if environmental as well as behavioral factors are addressed. Clinicians should educate their patients on proper dietary habits, such as avoiding meal skipping, and good sleep hygiene to decrease their dependence on “stimulant-seeking behaviors.” Clinicians should be aware of the potential dangers of energy drink consumption. They should also include screening for episodic/chronic energy drink consumption. Children with cardiac conditions should be especially counseled on the risk of consuming caffeine-containing beverages, including arrhythmias, syncope, and sudden death.

The same overall dietary pattern recommended for health promotion in adults (see Chapter 45) is appropriate for adolescents, but translating such recommendations into practice represents a challenge with this age group. Utilizing a multitiered approach that addresses the levels of home, school, and broader community will most effectively empower adolescents to transition into adulthood with well-informed, health-promoting nutritional habits.

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Chapter 31

Diet and Senescence

Karen Glover

INTRODUCTION

Nutritional factors play important roles in the process of aging. Requirements for energy and specific nutrients change as a result of altered metabolism, diminished energy expenditure, and changes in behavioral patterns. Besides diet, factors such as lifestyle and environmental exposures, as well as physical activity, influence the aging process. New findings regarding the effects of chronic inflammation, epigenetics, and the microbiome have added to the query of what is optimal nutrition as one ages. The basic recommendations for protein, carbohydrate, fat, vitamin, and mineral needs for adults over 65 years of age have also evolved over decades as scientific findings are outpacing written recommendations (e.g., the Dietary Guidelines for Americans).

The current trend of the "over 65" population is that chronological age and mental age are disconnected. However, physical aging is burdened by chronic disease. The underlying finding that is contiguous through most disease burdens is chronic inflammation. Macro- and micronutrients play direct roles in either promoting or reducing inflammatory cascades that affect the basic function of cells, including the mitochondria. Oxidation is emerging as an important aspect of cellular aging; therefore, dietary pro-oxidant and antioxidants may influence the nature and pace of the aging process itself.

Slowing and reversing the aging process is the impetus for much research as well as treatment motivated by "anti-aging" companies promoting supplements and health programs that appeal to the desire to keep a youthful physique and appearance. However, aging is inevitable.

OVERVIEW

Physiology of Aging

Life expectancy is steadily increasing and may soon reach 85 to 90 years (1). The aged population of the world has increased due to increased life expectancy or longevity. A United Nations report indicated that the worldwide population of those over 60 years will increase from one in eight people (2017) to one in five by the middle of this century (2). The US population of adults 65 years of age and older stands at 15.2% of the total population (49.2 million), with projections to double by 2060 to 98 million (3).

Age-related physical and mental changes impact function and quality of life. Physiological cellular and organ alterations due to the aging process can manifest in decreased muscle mass and increased body fat, and increase the risk of chronic and debilitating illnesses. Several mechanisms that have been highly studied involve chronic inflammation and deterioration of the immune system. Additionally, alteration in taste and smell, along with difficulty in chewing and swallowing, affects nutrient intake—which in turn may further impact organ and cellular functioning.

Immunosenescence—the deterioration of the immune system—plays a key role in the aging process (4). Chronic low-grade inflammation is mediated by cellular stress and genetic factors (single-nucleotide

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polymorphisms, or SNPs). Mechanisms of action include increased expression of cytokines like interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α) and transcription factors like nuclear factor-kappa B (NF-κB). This process of "Inflammaging" is thought to be the prodrome for age-related diseases, such as atherosclerosis, heart disease, type 2 diabetes mellitus, cancer, Alzheimer's disease, and Parkinson's disease (4,5). Poor nutritional status is one contributor to immunosenescence; and, as described later in this chapter, focused dietary supplementation may be protective (6).

Many other factors can contribute to the inflammatory process. Environmental factors, such as smoking, air pollution, and daily toxin exposure, burden the body's detoxification system. Infections and obesity stress the immune system. Additional cellular processes such as overproduction of reactive oxygen species (ROS), advanced glycation end-products, mitochondrial dysfunction, renin–angiotensin deregulation, and accumulation of cellular debris due to defective autophagy are additional potential triggers of chronic low-grade inflammation (7,8).

Chronic stress is another insult to the process of aging. Typical stressors include chronic illnesses, memory loss, finances, loss of independence, isolation, and loss of friends and family, particularly due to death. Aging can undermine the process of maintaining homeostasis through changes in the endocrine, nervous (specifically, autonomic), and immune systems. These systems usually work together to maintain allostasis, adapting to the challenges of life (9). This is more well known as the Hypothalamus–Pituitary–Adrenal (HPA) axis. Cortisol is the primary stress hormone in this pathway and is elevated in response to physiologic and psychological stress. Levels increase with aging and are associated with higher levels of psychosocial stress, poorer cognitive performance, and atrophy of memory-related structures in the brain (9). There is more evidence that the HPA axis is influenced by inflammatory mediators and perpetuates the stress response.

There are numerous factors that can lead to changes in the composition of the body in relation to muscle mass as people age. Skeletal muscle comprises over half of total body protein in healthy adults; however, muscle mass decreases with age. As overall life expectancy increases, sarcopenia, the age-related degenerative loss of muscle size and strength, is emerging as a major health concern (10). Muscle protein breakdown occurs at a higher rate than synthesis, and adipose cells infiltrate muscle tissue, which leads to decreased muscle strength (11). Causes of sarcopenia can be a combination of many factors, including low-grade chronic inflammation, mitochondrial dysfunction, oxidative stress, malnutrition, inactivity, chronic diseases, hormonal changes, and anabolic resistance (2,11). It is associated with functional decline, poor quality of life, and increased mortality (2). While physical activity certainly plays some role, specific nutrients and dietary patterns are emerging as potentially modifiable factors in the development or prevention of sarcopenia (12).

Aging affects all functions of the gastrointestinal system. Since this is the primary system involved in obtaining nutrients to keep the body functioning, it is important to give it some attention. There are alterations in taste (dysgeusia), swallowing (dysphagia), changes in esophageal peristalsis, dysfunctions of the stomach, intestines, and the colon, including digestion and absorption, as well as enzyme and hormone secretion (13). Salivary secretion and quality change as one ages. Because the digestive process starts in the oral cavity, alterations in saliva can affect chewing and swallowing in addition to the initial breakdown of proteins and carbohydrates. Physiological age-related gastric changes such as decreased gastric blood flow, reduced mucosal protective mechanisms, and vagal stimulation can make older people susceptible to diseases such as atrophic gastritis, peptic ulcers, and gastroesophageal reflux (13). The partial loss of certain gastric mucosa glands can lead to hypochlorhydria or achlorhydria and result in chronic atrophic gastritis and the inability to break down macronutrients. Peptic ulcer disease can be caused by certain medications and *Helicobacter pylori* infection. Because the gastrointestinal system

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plays an essential role in the metabolism of medications, older adults are more likely to experience medication-related gastrointestinal side effects, like decreased small intestine motility. Any medication side effect, including "polypharmacy," can decrease medication adherence and further contribute to morbidity and mortality (13).

Secretion of some gastrointestinal enzymes appears to decrease with advancing age. However, the utility of those enzymes to break down proteins, carbohydrates, and fats is assumed to be sufficient for proper digestion—the process cannot be measured in studies (11). Hormonal secretion, absorptive function, and motility of the small intestine in older adults do not appear to be related to age as much as to chronic disease manifestations (e.g., diabetic gastroparesis). Disorders of the large intestine that affect older adults are diverticulosis, Irritable bowel syndrome, *Clostridium difficile* (*C. diff*) colitis, and constipation. However, motility and transit time of the large intestine seem to be related more to cognitive impairment, limits of physical mobility, dietary changes, anticholinergic and opioid medications, and chronic medical problems (13).

Another important change that occurs with the process of aging is the change in the human gut microbiome. Intestinal microbes have been at the forefront of research as it has been determined that humans have a symbiotic relationship with microorganisms that live on and inside the body. The human microbiome enhances metabolism, modulates inflammation and the immune system, enhances endocrine signaling, modulates brain function through neurotransmitter synthesis and mediation, and increases resilience to autoimmunity and cancer (14). The age-related changes of the intestinal flora depend on the individual's genetic characteristics and environmental influences, as well as lifestyle and diet (4,15). As one ages, there is a decrease in diversity and reduced abundance of bacterial species that produce butyrate, a prominent short-chain fatty acid that is considered primary for intestinal health. Butyrate, along with acetate and propionate (other short-chain fatty acids), reduces intestinal pH to keep bacterial colonies in check, protects against overgrowth of harmful bacteria, and stimulates growth of helpful bacteria (4). Certain beneficial microbes can break down protein molecules to their component amino acids and participate in the luminal conversion of amino acids to biological compounds that modulate the immune system, participate in signaling, and produce antimicrobial peptides (14). The decrease in microbial diversity correlates not only with diet but also with increased antibiotic use, and underlying diseases, which lead to frailty, pro-inflammatory markers, and impaired health parameters (4,14,16).

Older adults are also at risk of harboring potential pathogenic bacterial species because of overgrowth in the large intestine (i.e., dysbiosis). This is caused by an imbalance between beneficial and commensal bacteria. An additional impairment of the gastrointestinal system is small intestinal bacterial overgrowth (SIBO). This is displaced, excessive bacteria in the small intestine, which is not the appropriate environment for microorganisms. SIBO is common in older adults and is associated with chronic diarrhea, malabsorption, weight loss, and secondary nutritional deficiencies (13).

Nutritional Factors of Morbidity and Mortality

There are a number of causes of physical debility in aging, such as chronic disease, acute illness and hospitalization, and accidents. However, the most impactful factors of debility and quality of life are nutrition-related: anorexia of aging, malnutrition, unintentional weight loss, and frailty. Interestingly, these geriatric "syndromes" each have multifactorial causes, which overlap with each other and appear interrelated.

The anorexia of aging, which is aging-associated changes in the regulation of appetite and the lack of hunger, leads to reduced food intake and weight loss. This can even occur in healthy older individuals and despite adequate access to food. The sequelae following a decreased appetite and food intake can include

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protein–energy malnutrition, poor wound healing, functional decline, and slow recovery from illness or surgery (17). There is a combination of various influences on the anorexia of aging, including physiological, pathological, and social factors. However, the physiological mechanisms that seem to underlie the initiation of this anorexia are reduced hunger and inhibitory satiety signals (17). Changes in smell and taste, reduced central and peripheral drives to eat, and delayed gastric emptying leading to a feeling of fullness also play an integral role. Reduced energy intake follows from reduced energy needs and expenditures leading to changes in body composition. The reduced intake is greater than the reduction in energy expenditure, and it leads to weight loss. The cycle further continues and can lead to sarcopenia, malnutrition, frailty, and increased mortality (17).

Other contributors to the anorexia of aging are poor oral health, depression, chronic low-grade inflammation, and gastrointestinal bacterial overgrowth. The ability to chew food is influenced by the quality of a person's dentition. Poor dentition can affect food choices resulting in limitations of type and quantity of foods, thus reducing intake (17). Chronic inflammation and bacterial overgrowth can perpetuate gastrointestinal discomforts, leading to reduced food intake as well as malabsorption and reduced nutrient absorption from the disruption of the intestinal lining. Older people suffering from depression show a higher degree of dysregulation of the HPA axis and consequently eat less when depressed (17). However, if depression is managed in this age group, anorexia and weight loss can be reversed (17).

Frailty is associated with decreased physiological functioning. Although frailty is not particularly the domain of older adults, it is commonly related to aging. It affects mobility, balance, muscle strength, gait, motor processing, physical activity, and nutrition (18). Frailty syndrome is associated with an increased risk of "catastrophic declines in health and function" (17). Although frailty leads to higher morbidity and mortality, it can be prevented, postponed, or reversed with early intervention (18). Nutritional status is an important determinant in the development of frailty due to a decrease in overall food intake. In one study, low intake of certain micronutrients such as vitamins D, E, and C, and folate was related to being frail independent of energy intake (18).

Getting adequate nutrition to support continued function is of primary importance. In general, malnutrition is considered to be a state of undernutrition. This state of undernutrition, directly influenced by food intake, influences the body's ability to maintain and repair itself. For older adults, food intake is affected by physical issues like dental problems, dry mouth, and decreased sensory perception of food. Changes in hypothalamic control of hunger and satiety and alterations in intestinal-related hormones like cholecystokinin, leptin, and ghrelin can cause individuals to feel less hungry, have less food cravings, and reduce the number of times they eat in a day (11). Malnourished individuals are more susceptible to infections and tend to have longer hospitalizations and recovery times.

There are also psychological and social factors that contribute to alteration of food intake during aging. Depression, apathy, and mood fluctuations are some psychological causes, while social isolation, poverty, and change in environment have negative impacts on eating habits. Furthermore, income, education, attitudes and beliefs, decreased mobility, and ability to prepare meals are additional factors that can contribute to malnutrition (11) (see Table 31.1).

TABLE 31.1

Causes of Malnutrition

Social Factors
Lack of knowledge about food, cooking, and nutrition

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Isolation or loneliness
Poverty
Inability to shop and/or prepare food
Inability to prepare food
Physiological Factors
Gastrointestinal dysfunction, e.g., malabsorption
Poor appetite and poor diet
Oral problems such as teeth loss and dysphagia
Loss of taste and smell
Respiratory disorders
Endocrine disorders, e.g., diabetes mellitus type 2
Neurological disorders, e.g., Parkinson disease
Infections, e.g., urinary tract infections
Physical disability to feed self
Drug interactions
Nausea and vomiting
Altered or increased metabolic demands
Other diseases, e.g., cancer
Psychological Factors
Dementia
Depression
Confusion
Anxiety

Reprinted from Rémond D, Shahar DR, Gille D, et al. Understanding the gastrointestinal tract of the elderly to develop dietary solutions that prevent malnutrition. Oncotarget. 2015;6(16):13858–13898.

One comorbidity of malnutrition in older adults is unintentional weight loss, which is more than a 5% reduction in body weight within 6 to 12 months. Unintentional weight loss occurs in 15% to 20% of older adults (19). Consequences of significant and progressive weight loss include decline in activities of daily living, falls leading to hip fractures, and poor recovery from illnesses, especially those requiring hospitalization. The causes of unintentional weight loss can be either physiologic or psychosocial. The most common causes are malignancies, gastrointestinal diseases, depression, and dementia (19). Decreased intake can also be attributed to polypharmacy, which can alter taste and affect appetite. Social factors associated with weight loss include poverty, isolation, financial burdens, substance abuse, and barriers to obtaining and preparing food (19).

Nutritional Perspective on Aging Theory

Senescence has been defined as the progressive deterioration of bodily functions over time (20). Aging is characterized by a loss of homeostasis and accumulation of molecular damage, leading to various pathologies. Biological pathways, both chemical and biochemical, are at the core of the aging process,

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and there are multiple pathways. There are several theories of aging, but most fall under three categories: programmed aging, error or damage, or combination theories (20). Programmed aging is considered a simple “wear and tear” process, whereas damage theory is related to normal metabolic processes in the body. The leading mechanism of this theory is oxidative cellular damage due to ROS. Mitochondria are the major producers of ROS in human cells, and their DNAs are particularly susceptible to oxidative damage (20). Genome (DNA) instability is also a part of damage theory, mostly due to replication errors. Part of translational errors is due to shortening of telomeres, which are the end sequences of DNA. Telomeres shorten with each cell division if not replicated and are influenced by oxidation and inflammation. This can cause major cell dysfunction, which can lead to chronic diseases. Since shorter telomeres are associated with increased rates of age-related chronic diseases and a decreased life expectancy, telomere length is considered a biomarker of aging (21). Recent evidence supports the correlation between telomere length and consumption of specific foods and nutrients, including legumes, nuts, fruit, and coffee (22,23). Conversely, shorter telomere lengths have been measured in people with high intake of sugary beverages, red meat, and processed meats (22,24). Studies suggest that high antioxidant diets, as well as Mediterranean-style anti-inflammatory diets, may be protective against telomere shortening; further investigation is warranted to identify mechanisms and to distinguish the extent to which cultural or genetic factors may influence efficacy (21,25,26).

Whereas the maintenance of adequate nutritional intake in older adults is a priority, caloric restriction (CR) over time is associated with longevity in most species studied (27). CR, defined as the reduction in total calories consumed without compromising the nutritional status of the diet, appears to affect longevity via multiple signaling pathways involving modulation of inflammation, cellular survival, stress defense, autophagy, and protein synthesis (28). CR may inhibit the rapamycin (mTOR) pathway, a known mechanism for increasing longevity and postponing the onset of age-associated diseases in animal models; however, studies are limited at this time and further research is needed (29). CR appears to lower body temperature, reduce basal metabolic rate, and reduce signs of oxidative injury to cells, organelles, and DNA in animal models studied (27). For example, the insulin and Insulin-like Growth Factor-1 (IGF1) signaling pathway, which monitors and regulates the compartmentalization of nutrients, appears to be deregulated in aging, as well as in metabolic disorders (25). Studies also suggest that intermittent fasting—also known as time-restricted eating—may play an important role in stimulating cellular responses to increase insulin sensitivity and suppress inflammation, key mechanisms proposed in CR (29). Both calorie restriction and intermittent fasting have been shown to suppress the insulin/IGF1 signaling pathway. Several studies have shown that metabolic regulation influences longevity and has the promise of extending the lifespan (30). Given the difficulties of maintaining adequate nutritional intake in older adults, advising time-restricted eating rather than overall caloric reduction may be more advisable.

Study of the so-called Blue Zones also offers insight into important lifestyle factors and dietary patterns for increasing longevity. Dan Buettner coined the phrase *Blue Zones* to reference the five places around the world where people consistently lived over the age of 100 years (31). After extensively studying the lifestyle habits and behaviors of the people living in these communities, Buettner concluded there were nine specific behaviors that he hypothesized contribute most to the slowed aging and advanced lifespan in the Blue Zones. Of these, three are diet-related: mindful eating (no food after early evening and eating small meals), eating mostly plant-based diets, and moderate alcohol intake (usually a glass of wine daily). These dietary patterns were exhibited consistently in all Blue Zone communities, despite differences in race, nationality, and regional characteristics; furthermore, in most cases they began early in life and were not begun as aging set in (32). Current research is now exploring how the lifestyle factors present in the Blue Zones may be effectively replicated in other communities throughout the world.

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NUTRITIONAL REQUIREMENTS OF OLDER ADULTS

The nutritional status of older adults is dependent on a variety of factors and a bidirectional relationship to health status. Keeping such individuals healthy, independent, and "community-dwelling" requires a balanced diet with all the specific nutrient requirements as well as being physically active, maintaining a healthy body weight, having social supports, and practicing behaviors that reduce disease risk (11). Many of the physiologic changes of aging are nutrient responsive. Changes in physiology (as seen earlier) and behavior have a direct impact on the ability to meet and manage nutritional needs. In the United States, guidelines for nutrition recommendations for all age groups are routinely developed and, in the last two decades, reflect an emphasis on health promotion and disease prevention. The Department of Health and Human Services and the US Department of Agriculture updated the Dietary Guidelines for Americans 2015 to 2020 (33). Included are age-specific caloric recommendations for older adults in four age categories: 61 to 65, 66 to 70, 71 to 75, and above 76 years of age. However, there are no older-age breakdowns for macro- and micronutrients recommended dietary allowance (RDA), except for calcium and vitamin D (footnoted for 71 + years). Recommendations only fall in the 51+ age category. The dearth of data appears to be motivating research interests in specific nutrient needs of older individuals, including investigating the nutritional needs of the very old (34). The RDAs for older adults are shown in Table 31.2.

TABLE 31.2

Recommended Dietary Allowance (in Bold) or Adequate Intake (in Regular Font) for Certain Vitamins and Minerals for Males and Females Aged 51 to 70 and Over Age 70[a]

	Females			Males		
Nutrient	**Age 31–50**	**Age 51–70**	**Age 70**	**Age 31–50**	**Age 51–70**	**Age 70**
Vitamin A (mcg/d)	**700**	**700**	**700**	**900**	**900**	**900**
Vitamin C (mg/d)	**75**	**75**	**75**	**90**	**90**	**90**
Vitamin D (mg/d*b*)	15	15	20	15	15	20
Vitamin E (mg/d)	**15**	**15**	**15**	**15**	**15**	**15**
Vitamin B_6 (mg/d)	**1.3**	**1.5**	**1.5**	**1.3**	**1.7**	**1.7**
Vitamin B_{12} (mcg/d)	**2.4**	**2.4**	**2.4**	**2.4**	**2.4**	**2.4**
Folate (mcg/d)	**400**	**400**	**400**	**400**	**400**	**400**
Calcium (mg/d)	1,000	1,200	1,200	1,000	1,000	1,200
Chromium (mcg/d)	25	20	20	35	30	30
Selenium (mcg/d)	**55**	**55**	**55**	**55**	**55**	**55**
Zinc (mg/d)	**8**	**8**	**8**	**11**	**11**	**11**

[a]*The RDA for younger adults is shown for comparison.*

[b]*Each mcg of cholecalciferol = 40 IU of vitamin D.*

Data from Otten JJ, Hellwig JP, Meyers LD, eds. Dietary reference intakes. The essential guide to nutrient requirements. Washington, DC: National Academies Press; 2006; Institute of

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Medicine. Dietary reference intakes for calcium and vitamin D. Washington, DC: National Academy Press, 2011.

Dietary Patterns

While considering individual macro- and micronutrient requirements, most times the whole diet gets overlooked. Source of nutrients are listed to encourage adequate intake, but little emphasis is placed on food patterns, particularly in relation to older persons. One familiar food pattern is the Mediterranean diet. It has been emphasized as a heart-healthy, low-inflammatory diet. The diet is characterized by high consumption of plant foods (fruits, vegetables, whole grains, legumes, and nuts), moderate intake of fish, poultry, and dairy, and with low intake of red and processed meats. Olive oil is the main sourced of added fat, and red wine is encouraged in small amounts (35). High adherence to a Mediterranean diet pattern has been shown to improve physical functioning and mobility in older adults while reducing overall incidence of chronic diseases and premature mortality (36). Studies have looked at the effect of such a diet on aging muscle. It appears that the benefit is more associated with lower extremity function than upper extremity. A Westernized diet in comparison seemed to increase the risk of decline in physical functioning (2). Whole food diets bring together macro- and micronutrients with other beneficial food components and may be more important to physical functioning, strength, and maintenance of muscle mass of older adults. Additionally, nutrient combinations may help to preserve the quality and quantity of muscle and counteract the effects of sarcopenia (2).

The anti-inflammatory properties of the Mediterranean Diet have been observed and directly studied. Reports have shown a link between following the diet and protection against neurodegeneration in midlife and old age (37). Key components of the diet, such as omega-3 fatty acids in fish and polyphenols found in fruits, vegetables, red wine, and olive oil, have been shown to reduce pro-inflammatory markers (37). The emphasis, though, is adherence to the diet pattern for the most favorable benefits life-long. The dietary approaches to stop hypertension (DASH) diet has also been seen as a strategy for reducing inflammation and cardiovascular risk. It emphasizes foods high in potassium, calcium, and magnesium, such as fruits, vegetables, and whole grains, along with fat-free or low-fat dairy products. Additionally, the diet recommends fish, poultry, beans, nuts, and vegetable oils while limiting foods that are high in saturated fat as well as sugar-sweetened beverages and sweets (38). A meta-analysis of six random control trials showed significantly decreased serum high-sensitivity C-reactive protein concentration on the DASH diet compared to the typical Western diet (37). The same study group did a prospective cohort meta-analysis of DASH and determined that even the modest adherence to the diet was associated with a lower risk of all-cause mortality, including cardiovascular disease, stroke, and cancer which are the chronic diseases of aging (39). These findings seem to be related to the emphasis of the DASH pattern on greater intake of plant foods just like the Mediterranean Diet.

Energy

Energy needs of older people are influenced by body composition, health status, medication use, and cognitive status (40). Additionally, the requirements vary within the broad age range of 60 to 100 + years. The most recent US Dietary Guidelines do not divide by age group the energy needs of adults past 76 years (33). Although in general, energy requirements decline with age, in part or whole because of diminished physical activity and consequent loss of lean body mass, there is evidence that energy intake goes down disproportionately. Daily energy consumption is driven largely by resting metabolic rate (RMR), which accounts for 60% to 75% of the total (41). An additional 10% is accounted for by postprandial thermogenesis, the thermic effect of food. Resting Energy Expenditure, same as resting

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metabolic rate, is lower in older adults due to the loss of muscle mass. Aging-associated metabolic changes and physical activity also affect the energy requirements of these individuals.

Studies to assess the estimated energy requirements of adults have been based on data collected over the past 100 years. Multiple equations have been developed to determine resting metabolic rate and total energy expenditure. Estimations of the energy needs of older adults have been extrapolated from evaluations of middle-aged individuals (40). The gold standard of measuring total energy expenditure (TEE) is through the method of doubly labeled water. However, few studies have been conducted on individuals over 65 years. Porter et al., determined that several equations effectively predicted TEE or RMR for older adults through analysis of data from 31 studies, which compared known predictive equations with the reference method of doubly labeled water (40). Ndahimana et al. evaluated the accuracy of the Dietary Reference Intakes (DRIs) for estimating the energy requirements for older adults for a cohort of older men and women using the doubly labeled water method. They found that the DRI equations previously developed had acceptable accuracy when applied to older adults (42). As people get older, they are somewhat predisposed to weight gain and obesity because they tend to maintain the energy intake of their younger years and reduce their activity. However, as individuals approach ages over 80, they are increasingly subject to weight loss and the sequelae of malnutrition as a result of reduced food and energy intake as well as reduced adipose and muscle body mass.

Protein

The main stimuli for the development and maintenance of skeletal muscle are exercise and protein intake. Dietary protein intake should be in sufficient amounts to preserve muscle mass. Besides preventing sarcopenia, adequate protein intake provides amino acids that maintain cellular functions. In their review, Traylor et al. presented evidence that older individuals may have a greater requirement for protein based on the preservation of muscle mass as they age (43). They reasoned that older adults could benefit from protein intakes higher than the current RDA through looking at evidence, which indicates older individuals experience “age-related anabolic resistance” after dietary protein intake. This anabolic resistance is one postulate of the development of sarcopenia (43). Additionally, there is some speculation that the gut microbiome may play a role in this resistance (44).

Does the protein source (animal versus plant) affect the health of older adults? M. Kitada et al. reviewed the impact of protein and amino acid composition of diets on aging and longevity. They noted that the source of protein, whether animal or plant, might be more important than the level of protein intake (high vs. low), especially on mortality risk (45). Red meat consumption is associated with the development of some chronic diseases, which increases mortality risk, while plant proteins seem to have a protective effect (45). A prospective cohort study by Song et al further found that animal protein intake, particularly red meat, was associated with a higher risk of mortality than with plant-based protein sources; they also concluded that protein source is important for long-term health and those plant proteins have a protective effect (46).

Besides intact proteins, several essential amino acids, methionine, and the branched-chain amino acids have a role in the aging process. They activate certain chemical and regulatory pathways that affect cell physiology, signaling, synthesis, and even autophagy. So, the quality of dietary proteins also appears to be strongly associated with longevity and metabolic health (45).

Carbohydrates

Metabolism of carbohydrates is based on changes in insulin levels, energy needs—including that which is required to preserve skeletal muscle—and, to an extent, the microbiome. The quality and quantity of

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carbohydrates in the diet in general can be reviewed in Chapter 1. More simple carbohydrates are preferred as a person gets older due to changes in taste and effects of gastrointestinal symptoms from digestion of dietary fiber. However, there have been a few studies on the type of carbohydrate that seems to have a beneficial influence on aging. Whole grains are intact dried plant seeds containing fiber, resistant starch, and oligosaccharides, all of which are thought to be beneficial for health. Refined grains are those that have been through processing (milling), removing the outer hull of the seed, and reducing it to the endodermic product, which is then further refined to flour, with a loss of micronutrients (47). An observational study by Foscolou et al. evaluated the association between the consumption of whole grains on successful aging (48). They determined that because most whole grains have significant vitamins, minerals, and antioxidants, increased consumption contributed to the reduction of certain chronic diseases, particularly cardiovascular disease (48). Whole grains may also have a positive effect on cell-mediated immunity, in comparison to refined grains (49).

Another analysis of the effect of carbohydrate type compared dietary glycemic measures of sugar (simple carbohydrate) and refined carbohydrate. The glycemic index of a food is a relative ranking of carbohydrates in foods according to how they affect blood glucose levels. Diets high in glycemic load have been strongly linked to impaired glucose metabolism. Studies have shown that there is some relationship between impaired glucose metabolism and increased risk of dementia (50). Taylor et al assessed the association of dietary glycemic measures with cerebral amyloid burden and cognitive performance in cognitively normal older adults. Amyloid is a protein that can abnormally accumulate in high levels in the brain and is associated with Alzheimer's disease. They examined four dietary glycemic measures: high glycemic load diet (pattern was characterized by intakes of high-glycemic-load foods, such as total grains, refined grains, potatoes, starchy vegetables, and added sugars), daily individual sugar intake, daily carbohydrate intake, and glycemic load. Amyloid burden was measured through PET scan and participants completed a standard battery of neuropsychological tests. The researchers found evidence that a high-glycemic diet was associated with increased cerebral amyloid burden in older adults with normal cognition. Poor global cognitive performance was associated with high daily sugar consumption. Because of this association, they suggested that diet modification could reduce amyloid burden and decrease Alzheimer's disease risk (50). See Chapter 35, Diet and Cognitive Function, for more detailed attention to this topic.

As mentioned, complex carbohydrates are a source of fiber, both soluble and insoluble, micronutrients, and some antioxidants. Dietary fiber intake in the United States is approximately 12 g/day among adults, whereas the recommended amount is 25 to 30 g/day. Reductions in energy consumption by older patients are likely to result in low fiber intake as well. Older adults are particularly susceptible to constipation and are apt to benefit from increased consumption of dietary fiber. The more rapid intestinal transit time that comes with increased fiber consumption, however, may reduce mineral absorption, increasing the risk of deficiencies in older adults. Therefore, increased nutrient density or supplementation is indicated when fiber intake is augmented (44). Another benefit of fiber has been shown in the support of the gut microbiome. Certain bacteria use fiber as a fuel source and produce short-chain fatty acids that themselves are beneficial for health. But with aging, poor dentition may reduce the ability to eat fruit and vegetables (51). Reduced intake of these complex carbohydrates leads to alterations in the balance of the gut microbiome (4).

Fats

There are debates over the types of dietary fats that seem to be beneficial versus harmful. Differences in saturation of fatty acids can stimulate or reduce inflammation in the body. Essential fatty acids (alpha-

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linolenic acid and linoleic acid) are significant for cell structure and function. Polyunsaturated fatty acids (PUFA) are incorporated into phospholipids, which contribute to the structure of neuronal and glial cell membranes. They regulate cytokine production, which plays a key role in depression and neurodegenerative diseases related to aging and is involved in the regulation of gene expression (11). Dietary omega-3 polyunsaturated fatty acids are considered beneficial at reducing inflammation, but dietary omega-6 polyunsaturated fatty acids are seen as contributors to inflammatory processes. The healthy ratio of dietary intake of omega-3 to omega-6 fatty acids appears to be 1:1, but typical Western diets are higher in omega-6 PUFA and increase the ratio, ranging from 1:10 to 1:30 (11). The higher ratios may increase susceptibility to neuronal damage and some chronic diseases that stem from inflammation. Intake of omega-3 PUFA has also been shown to have a positive effect on memory, better cognitive performance, and higher brain integrity (52).

In their investigation, Olesona et al. found that intake of dietary saturated fatty acids was significantly associated with poorer overall memory performance (52). Saturated fatty acid intake has been linked to elevated cholesterol, insulin resistance, and beta-amyloid production and deposition in the brain. Although the study subjects were middle-aged, this could have a significant impact over time as individuals become older.

The general health implications of dietary fats can be reviewed in Chapter 2.

Hydration

Older patients are particularly subject to dehydration and its sequelae because of reduced body water, diminished renal concentrating ability, diminished thirst, insensitivity to antidiuretic hormone, and susceptibility to orthostatic hypotension due to reduced autonomic tone. Thirst is not a very reliable index of hydration status among older adults. A study examining the prevalence of dehydration in community-dwelling older adults reported virtually no evidence of dehydration in those subjects ingesting six or more glasses of fluid per day (53). Kerstetter et al. (54) offer a practical approach that does not require patients to measure their fluid intake so precisely. Maximal concentration of urine at age 90 is estimated at 800 mosmol/L, down from 1,200 mosmol/L at younger age. Therefore, in older adults, fluid intake should be maintained at a level that allows for the excretion of approximately 1,200 mosmol of solute waste/day. This amount would require at least 1.5 liters of urine produced per day for the very old adults. At this concentration, the urine appears light yellow. Therefore, a level of fluid intake that results in urine that is consistently light yellow implies adequate hydration status.

Micronutrients

Aging is associated with a decline in immune function, as well as greater susceptibility to an array of micronutrient deficiencies. The challenge of diet adequacy is not only related to energy, protein, carbohydrates, and fats but also intimately dependent on the various nutrients in ever so small amounts that act as co-factors, building materials, and even hormones. Deficiencies of micronutrients are more the norm than the exception because of diet quality, food access, and the physiological ability to digest and absorb. Nutrient density is of particular importance in the diets of older adults, given reduced energy intake, which affects micronutrient and protein requirements (55,56).

Bioavailability of nutrients is based on the body's ability to break down food components, cell receptor competition, and levels of nutrients in foods. Adequate nutrient intake is competing with adequate nutrient uptake. Membrane proteins act as carriers for the absorption of some vitamins and minerals; however, the effect of aging on the expression of carriers is not known (11). Certain nutrients such as calcium have both passive and active absorption mechanisms, although the ability to absorb it

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decreases with age. Intestinal pH can be important for the absorption of other minerals, like iron. However, decreased pH due to hypochlorhydria can decrease bioavailability (11). Additionally, increased intestinal transit times due to gastrointestinal disorders or therapeutic fiber intake may reduce mineral absorption.

Food availability and access can put older adults at risk of mineral deficiencies. The trace minerals zinc, copper, and selenium are found in protein foods, mostly of animal origin, which can be cost-prohibitive for some older adults (11). Some food sources are enriched or fortified with nutrients; however, these tend to be refined grain products, which although are of low cost may not support a more healthy diet plan.

As mentioned previously, frailty appears related to insufficient intakes of certain vitamins. Low-serum vitamin D levels were associated with increased mortality risk across all levels of frailty (57). Low levels of vitamin A precursors (carotenoids) were also seen to have a greater effect on frailty in women (58), as well as increased risk of overall mortality (57). High levels of carotenoids were associated with lower levels of frailty (57).

There is evidence that deficiencies of vitamins C, B_6, and B_{12} are prevalent among older adults in the United States. Living situations appear to have a direct effect on the nutrient status of older adults. Older people in congregate living appear to have more compromised nutrient intake and nutritional status. In a study of institutionalized older individuals with evidence of micronutrient deficiencies, multivitamin supplementation (B complex, vitamins C and E, and beta-carotene) for a period of 10 weeks significantly enhanced immune function, as gauged by cutaneous hypersensitivity reactions to injected antigens (59). While multivitamins have not been shown to decrease rates of infection (60), they have been shown to decrease the length of infection (61).

A few micronutrients that have a significant impact on older individuals are vitamin D, vitamins B_{12}, folic acid, vitamin B_6, calcium, zinc, and magnesium. Vitamin D plays an important role in bone metabolism. Deficiency of vitamin D leads to impaired calcium absorption, compounding the generally inadequate calcium intake in older adults. Furthermore, inadequate levels cause impaired bone mineralization and increased bone resorption (11). Serum levels decline with age because of decreased consumption, decreased sun exposure, and decreased efficiency of the body's ability to convert provitamin D to the active form (11,58). The skin's ability to manufacture vitamin D with exposure to sunlight becomes less efficient with age, and older adults tend to reduce their amount of sun exposure. Therefore, vitamin D deficiency appears to be fairly widespread among the older population. Low levels of vitamin D may also be associated with increased diabetes, hypertension, hyperlipidemia, and peripheral vascular disease (62).

Vitamin B_{12} deficiency can be a concern for older persons because of inadequate intrinsic factor or insufficient dietary intake. Atrophic gastritis is a primary cause of inadequate intrinsic factor. Vitamin B_{12} deficiency may contribute to cognitive impairment, anemia, or elevated homocysteine levels in older adults. Besides vitamin B_{12}, insufficient levels of vitamin B_6 and folate can contribute to elevated homocysteine levels. Decreased intake of folate and B_6 occurs if the diet is low in leafy green vegetables and animal protein foods, respectively.

Calcium intake throughout life tends to be lower than recommended, especially for women (see Chapter 14). In older adults, the discrepancy between recommended and actual intake is more pronounced with calcium than perhaps any other micronutrient. Calcium absorption declines with age, particularly after age 60 (11,63). This decline in absorption is compounded by vitamin D deficiency, as mentioned

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earlier. Older adults are particularly susceptible to osteoporosis and related fracture. Adequate calcium intake may forestall osteoporotic fracture (64), but it cannot restore bone density already lost. Calcium intake is also associated with reduced risk of colon cancer (see Chapter 12) and reduction in blood pressure (see Chapter 8). Given recent concerns over possible associations between calcium supplementation and risk of cardiovascular disease, current recommendations support achieving calcium requirements primarily through dietary sources, with modest supplementation as needed (65).

Zinc intake is below the recommended level for adults in the United States, and the gap is greater for older adults. Zinc is essential for the function of the immune system. As immune dysfunction is characteristic of aging and may result in life-threatening infections, efforts to maintain optimal immune function are important. Consumption of less than 10 mg/day by older individuals may impair immunity, wound healing, and the acuity of taste and smell (54). A randomized controlled trial found that daily supplementation of 45 mg of zinc in older subjects reduced incidence of infections and levels of oxidative stress markers compared to placebo (66).

Magnesium intake in developed countries is often marginal in all age groups. Deficiency is particularly likely among older adults due to reduced intake, serum depletion associated with chronic disease states, and impaired GI absorption (67,68). Clinical consequences may include inflammatory disorders, sleep disturbance, neurological and cognitive impairment, myalgias, and musculoskeletal disorders (68,69). Hypermagnesemia, on the other hand, is a serious consequence of use of magnesium-containing laxatives among older adults. Monitoring use is advised.

Food–Drug Interactions

Older patients are more likely to be taking medications and are typically more susceptible to adverse effects related to food–drug interactions. In the population over 65 years old, 80% have one or more chronic medical conditions requiring use of prescription drugs. Coumarin-based anticoagulants are commonly taken to prevent life-threatening clot formation. It is important to note that foods rich in vitamin K such as spinach, kale, or other greens can render such anticoagulants inactive (70). Likewise, tetracycline antibiotics should not be taken with dairy products or foods rich in divalent cations calcium, magnesium, iron, or zinc, as they can decrease bioavailability through physicochemical binding (71). Certain food–drug interactions can also make medications too effective. For example, monoamine oxidase inhibitors, medications used to treat depression and Parkinson's symptoms, may be associated with increased adverse effects when taken with tyramine-containing foods like cheese or aged wines. Food intake, especially foods high in fat content, can slow the rate of gastric emptying. Medication bioavailability can often vary in response to whether the stomach is empty or full. Both the disease state and the pharmacotherapy may influence metabolism (72), and polypharmacy is associated with increased risk of malnutrition (73).

CLINICAL HIGHLIGHTS

Age-related physical decline is intimately connected to nutritional status. The cellular building blocks and cellular function are dependent on the nutrients that need to be consumed regularly. As seen earlier, limitations of intake, synthesis, and excess production of inflammatory chemicals all transpire to create stress on the aging process. Recommendations for nutrition screening of older adults to detect risks of nutrient deficiencies, malnutrition, and frailty are the first step in correcting risk factors. Implementing interventions such as comprehensive assessments, exercise programs, and focus on adequate nutrition have been shown in studies to be effective in reducing age-related decline (11).

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Energy deficiency in older adults results in negative nitrogen balance with accelerated muscle loss. Deficiencies of micronutrients, particularly of B vitamins, vitamin D, and certain minerals, such as zinc, are very common. Use of prescription medications may compound age-related changes in olfaction, taste, and GI motility, contributing to poor dietary intake.

Emphasis in primary care should be on the maintenance of weight and especially preservation of lean body mass, whether through nutrient-dense diet, through nutritional supplementation, or by exercise. The decrease in all-cause mortality evidenced by the obesity paradox likely supports the avoidance of malnourishment and the maintenance of lean body mass more than the promotion of obesity per se. Older people should be encouraged to become or remain physically active as their functional status permits. Periodic assessment of dietary intake, informally or via referral to a dietitian, may help ensure maintenance of adequate nutriture. A multivitamin/multimineral supplement is a low-cost and safe means of protecting older patients against several common micronutrient deficiencies, although specific evidence of benefit from such a practice is lacking.

An effort to increase the nutrient density of the diet is a valid, although more difficult, alternative, and the two practices are complementary rather than mutually exclusive. Common sequelae of aging, such as cognitive and immunologic deficits, may be due in part to nutrient deficiencies and, therefore, are potentially preventable or reversible. There is convincing evidence to support supplementing the diets of older patients with zinc, chromium, magnesium, calcium, and possibly copper, along with vitamins. There is some suggestive evidence that nutrients not traditionally included on the RDA lists, such as ubiquinone (coenzyme Q_{10}) and lipoic acid, may offer benefits for older patients.

As patients age, the short-term functional benefits of adequate nutrition may need to be compared with any long-term consequences of specific dietary practices. For example, whereas the cholesterol content of eggs may be a relevant consideration in younger adults at long-term risk for coronary disease, the nutrient density of eggs may provide benefits in excess of any risks for older patients. A diet rich in a variety of fruits and vegetables offers the same array of benefits to older adults as to younger age groups.

Specific nutraceutical practices to confer longevity are of tantalizing interest, and our understanding of the basic science behind how such supplements could work continues to develop. Evidence guiding clinical practice, however, is still in progress.

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Ergogenic Effects of Foods and Nutrients: Diet and Athletic Performance and Sports Nutrition

Leigh A. Frame

INTRODUCTION

The role of diet in optimizing athletic performance has long been a topic of considerable interest, a natural extrapolation of efforts to optimize dietary health. Diet provides the fuel to sustain physical activity, and it seems reasonable that alterations in the fuel will influence the efficiency of that combustion. Optimal nutrition plays a direct role in optimizing physical activity, athletic performance, and recovery from exercise. In other words, diet is ergogenic, meaning it enhances performance, endurance, or recovery. Macronutrient composition of meals, selection of foods and fluids, timing of intake, and use of ergogenic substances and micronutrient supplements are all variables, albeit with varying degrees of scientific support, relevant to achieving peak physical performance.

Ideally, the well-established link between diet and physical prowess in athletes would foster a general appreciation for the importance of diet to vitality. Indeed, the optimal diet of an "athlete" is quite similar to the well-balanced diet of any physically active person. Instead, all too often, this link is misused to develop marketing schemes, misleading messages, and misguided practices, such as the consumption of sports drinks and energy bars by masses of consumers far more subject to obesity and nutritional excesses than to dehydration and depletion. The clinician has a role to play both in guiding the athlete toward optimal nutrition and guiding the more typical and sedentary patient away from eating like an athlete without acting like one.

OVERVIEW

Macronutrients and Meal Timing

In general, the US population engages in too little physical activity and consumes too many calories. Therefore, sufficient calorie intake is not a concern for the majority of patients, though a fundamental requirement to maintain physical activity. It is helpful for both patients and providers to understand the activity level of the patient in order to gauge caloric needs. The resting metabolic rate (RMR) is an estimate of the caloric expenditure with no physical activity, meaning the energy required by an animal to stay alive with no activity. Key determinants of RMR include age, sex, weight, height, and fat-free body mass, also known as lean body mass. Calculating RMR is the first step in calculating real metabolic rate. RMR can then be combined with caloric expenditure through physical activity to provide a working estimate of total daily energy expenditure/requirements.

- Your Metabolic Rate = Your RMR + Estimated
- Energy Consumed by Your Daily Activities

Numerous tools exist online to assist in performing this calculation and determining a working estimate

of metabolic rate. Table 32.1 provides a list of common physical activities and corresponding caloric expenditures that may be useful for estimating activity-related energy consumption. For comparison, the average number of calories burned per hour is compared to the equivalent number of calories in a popular fast food choice for means of a common reference. The healthcare provider can use this as a benchmark and a resource to educate patients about caloric intake versus caloric expenditure.

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TABLE 32.1

Energy Expenditure of Some Representative Physical Activities[a] and Representative Food Equivalents[b]

Activity	Mets (Multiples of RMR)[c]	KCAL (Calories) Burned Per Minute	Maximum KCAL (Calories) Burned Per Hour (Approximate)	Common Fast Food Equivalent in Number of Calories (Approximate)
Resting (sitting or lying down)	1.0	1.2–1.7	100	Two pieces Wendy's spicy chicken nuggets
Sweeping	1.5	1.8–2.6	150	Jack in the Box egg roll
Driving a car	2.0	2.4–3.4	200	32 oz Gatorade
Walking slowly (2 mph)	2.0–3.5	2.8–4.0	240	20 oz Coke
Cycling slowly (6 mph)	2.0–3.5	2.8–4.0	240	16 oz Starbucks vanilla latte
Horseback riding (at a walk)	2.5	3.0–4.2	250	McDonald's hamburger
Volleyball	3.0	3.5	210	Krispy Kreme original glazed doughnut
Mopping	3.5	4.2–6.0	360	Arby's 5 piece jalapeno bites
Golf	4.0–5.0	4.2–5.8	350	Dunkin Donuts medium strawberry Coolatta
Swimming slowly	4.0–5.0	4.2–5.8	350	IHOP pork sausage links (4 pieces)
Walking moderately fast (3 mph)	4.0–5.0	4.2–5.8	350	Dairy Queen hot dog
Baseball	4.5	5.4–7.6	450	Panera Caesar salad with chicken
Cycling moderately fast (12 mph)	4.5–9.0	6.0–8.3	500	Au Bon Pain blueberry muffin
Dancing	4.5–9.0	6.0–8.3	500	Sweetgreen spicy Thai salad

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Skiing	4.5–9.0	6.0–8.3	500	Coldstone “Love it” chocolate dipped strawberry ice cream
Skating	4.5–9.0	6.0–8.3	500	Panda Express Chow Mein
Walking fast (4.5 mph)	4.5–9.0	6.0–8.3	500	1/2 Cinnabon caramel Pecanbon
Swimming moderately fast	4.5–9.0	6.0–8.3	500	Chick-fil-A deluxe sandwich with American cheese
Tennis (singles)	6.0	7.7	500	1/2 Chipotle burrito with chicken, white rice, black beans, salsa, sour cream, and cheese
Chopping wood	6.5	7.8–11.0	660	Sonic small caramel shake
Shoveling	7.0	8.4–12.0	720	Pizza Hut 6" personal pepperoni lover’s pizza
Digging	7.5	9.0–12.8	770	Taco Bell fiesta taco salad with beef
Cross-country skiing	7.5–12.0	8.5–12.5	750	Popeye’s chicken breast, biscuit, and Coleslaw (regular)
Jogging	7.5–12.0	8.5–12.5	750	Subway footlong Italian biggest, meatiest, tastiest (B.M.T)
Football	9.0	9.1	550	Burger King chicken nuggets and French fries
Basketball	9.0	9.8	590	Two slices Domino’s medium cheese pizza
Running	15.0	12.7–16.7	1000	McDonald’s quarter pounder with cheese, medium fries, and large sweet tea
Running at 4-min mile pace	30.0	36.0–51.0	3060	Chili’s full rack of ribs with awesome blossom petals and roasted street corn plus 2–22 oz light beers
Swimming (crawl) fast	30.0	36.0–51.0	3060	1/2 large order Baja Fresh nachos with soft taco combo, 4 margaritas, and 32-oz root beer float

[a]*All values are estimates and based on a prototypical 70-kg male. Energy expenditure generally is lower in women and higher in larger individuals. MET and kilocalorie values derived from different sources may not correspond exactly*.

[b]*Calorie values for the recommended serving size of common food items were ascertained from the company’s website, and this value was then used to calculate the amount of food equal to the maximum number of calories burned per hour doing the corresponding physical activity*

[c]*A MET is the rate of energy expenditure at rest, attributable to the resting (or basal)*

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metabolic rate (RMR). Whereas resting energy expenditure varies with body size and habitus, a MET generally is accepted to equal approximately 3.5 mL/kg/min of oxygen consumption. The energy expenditure at 1 MET generally varies over the range of 1.2 to 1.7 kcal/min. The intensity of exercise can be measured relative to the RMR in METs.

Adapted from Ensminger AH, Ensminger M, Konlande J, et al. The concise encyclopedia of foods and nutrition. Boca Raton, FL: CRC Press; 1995; Wilmore JH, Costill DL. Physiology of sport and exercise. Human kinetics. Champaign, IL; 1994; American College of Sports Medicine. Resource manual for guidelines for exercise testing and prescription, 2nd ed. Philadelphia, PA: Williams & Wilkins; 1993; Burke L, Deakin V, eds. Clinical sports nutrition. Sydney, AU: McGraw-Hill Book Company; 1994; and McArdle WD, Katch FI, Katch VL. Sports exercise nutrition. Baltimore, MD: Lippincott Williams & Wilkins; 1999.

For the most part, little evidence exists that the dietary pattern for physically active individuals should be altered from that generally recommended for health promotion (see Chapter 45). However, there is evidence that certain deviations from and additions to current dietary recommendations may be beneficial in cases of intense physical activity and caloric expenditure. Individuals engaging in extremely intense physical activity for extended periods, particularly competitive endurance athletes, may actually need to make an effort to meet energy requirements. There is also the potential for dangerous and even life-threatening dehydration and nutrient depletion when protracted and arduous exertion is combined with stressful environmental conditions. Under such conditions, specialized dehydration formulas, sports drinks, and energy bars offer potentially important advantages (1,2). However, undue reliance on such products by patients at modest levels of exertion is apt to contribute to a disadvantageous excess of calories and sugar.

Macronutrient composition of meals may need to be adjusted to meet caloric needs and to accelerate recovery in athletes. The role of increasing dietary protein in augmenting muscle mass and supporting recovery remains controversial (3). The current recommended dietary allowance remains at 0.8 g/kg of protein of body weight (BW) due to a lack of evidence that additional protein is beneficial for strength and endurance athletes (4). For years, however, sports enthusiasts and competitive athletes have perceived a need for increased protein intake, and studies have demonstrated benefits with protein intake three or more times this recommended dietary allowance.

Consensus is emerging that a moderate increase in protein intake may be indicated for some athletes (5). Intake in the range 1.2 to 1.4 g/kg/day is recommended for endurance training and 1.3 to 1.5 g/kg/day for resistance training (6). The US and Canadian dietetic associations and the American College of Sports Medicine recommended 1.2 to 2.0 g/kg/day of protein intake for active adults and competitive athletes in their 2016 joint position statement (5). What seems to be more important than total protein intake is intake of sufficient essential amino acids (EAAs) in the early recovery phase (≤2 hours postexercise) to support muscle protein synthesis (MPS); the joint position statement recommends 0.25 to 0.3 g/kg of protein for the average athlete not attempting weight loss (5). This range has been shown to maximize MPS (6); however, more recent research suggests that maximal MPS occurs at 30 g of protein (around 0.49 g/kg) when ingested with 45 g of carbohydrate with no benefit beyond this limit (7).

These levels of intake may be optimal in terms of the athletic effort, but the long-term effects of such a diet on specific health outcomes and chronic disease risk have not been adequately studied. Therefore, an athlete should prepare to modify dietary intake to meet prevailing recommendations whenever he or she tapers the level of physical activity. The use of amino acid beverages and supplementation with specific

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classes of amino acids are popular practices, but the evidence of beneficial effects and long-term safety is equivocal, and the joint statement recommends using them conservatively and focused on recovery and adaptation (5).

The acceptable macronutrient distribution range for fat is 20% to 35% of energy intake (4). In general, those who engage in strenuous physical activity should follow these general recommendations even if total caloric intake must increase to meet energy demand, and athletes should be counseled against maintaining intake below 20% (5). Fat is the most calorically dense macronutrient, and fat restriction may be untenable in athletes with high energy expenditure. High fat intake is the most efficient means for meeting very high energy requirements associated with extreme exertion, such as endurance training or mountain-climbing expeditions. Such intense exercise can burn 600 to 1,200 kcal/hour in 50 to 100 kg (110–220 lbs) athletes, making their daily requirements on the order of 2,000 to 7,000 kcal, even more in elite athletes (8). The health hazards to the general public of excessive dietary fat intake should be borne in mind, and recommendations for individual athletes to increase dietary fat intake should be made judiciously, with a clear emphasis on the distinctions among fatty acid classes.

Evidence in other areas suggests the virtue of prioritizing intake of monounsaturated fatty acids and a mixture of omega-3 and -6 polyunsaturates in a ratio of 1:1 to 1:4. Saturated and trans-fatty acid intake should be kept proportionately low, with the joint statement recommending <10% of energy intake (see Chapters 2, 7, and 45) (5). The evidence for the ideal profile of fatty acids in a high-fat diet and the proper timing of fat intake for optimal athletic performance and for a role of high-fat diets in influencing athletic performance other than by meeting high energy requirements is equivocal (6,9). When energy requirements are high and increased fat intake is desirable, nuts, seeds, nut butters, avocados, fatty fish such as salmon, and olives all represent salutary means to the desired ends.

There is also the issue of timing—when to eat certain macronutrients in relation to exercise/competition or time of day, spurring the new field of chrononutrition—a combination of nutrition and chronobiology. Eating both impacts and is impacted by circadian rhythms, which can be optimized in any individual but may be more important in athletes. This emerging field has shown that eating at biological night, the circadian dark phase, is highly detrimental to metabolism, potentially increasing risk of dysregulation of blood glucose and lipids (10,11). Further, insulin sensitivity is highest in the morning, the beginning of the light phase, and declines over the course of a day—in other words, glycemic control is best first thing in the morning and worsens as the day progresses (12,13). This means it may be better to decrease carbohydrate intake over the course of the day or perhaps limit intake outside of workout preparation and recovery.

The majority of research on nutrient timing in athletes looks at the ingestion of carbohydrates after exercise to optimize recovery and glycogen replenishment. Exercise induces greater insulin sensitivity and responsiveness of glycemic control with in vitro and in vivo studies showing increased insulin-mediated glucose uptake with muscle contraction (6,14–17). Rigorous physical training catabolizes glycogen and diverts amino acids away from protein synthesis; hence, proper nutrient timing for recovery involves utilizing the insulin response from exercise to optimize postexercise glycogen repletion and muscle repair. Immediate carbohydrate consumption (up to 1–1.2 g/kg/hour), particularly those that are easily digestible (higher glycemic), accelerates glycogen repletion compared to consumption 2+ hours postexercise (6,18). Combining a rapidly digesting protein source with the carbohydrate immediately after exercise may enhance accretion of whole-body protein and promote muscle repair via the exercise-induced insulin response (19–22); however, for rapid recovery between bouts ≤4 hours apart, carbohydrate intake and hydration may need to be prioritized (23). The need for protein to be delivered immediately before or after training is in question and is certainly less time sensitive than carbohydrate

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for recovery (6,24,25). Intake of protein every 3 to 5 hours may be a better approach (5,26). Further, the body conducts most repairs during the dark phase while we sleep, and, thus, consuming up to 0.6 g/kg before sleep may improve muscle protein synthesis and adaptation (6,27,28).

Many athletes use chocolate milk for their postexercise recovery. There is an obvious issue with this in those lactose intolerant even to some extent, but it could be beneficial in those who persistently produce enough lactase. In 2019, a systematic review and meta-analysis was published in the European Journal of Clinical Nutrition, addressing whether the components of chocolate milk could function to improve recovery (29). One cup of chocolate milk contains 27 g carbohydrate (26 g sugar), 8 g protein (80% casein, 20% whey protein), 8 g fat (2/3 saturated, 1/3 monounsaturated, some polyunsaturated), and electrolytes, which will be discussed under the section Hydration (30). In short, the literature does not have sufficiently robust studies to say definitively; however, it appears from the 12 studies in the systematic review that chocolate milk may perform similarly or better than placebo and other recovery drinks (29). The literature also suggests that whey protein may be superior for MPS in part due to branched-chain amino acids (BCAAs) (31–33). With this preliminary data in mind, chocolate milk may be an option for the right athlete.

Intermittent fasting is an attempt to gain the benefits of caloric restriction without the arduous protocol and negative side effects. Instead of chronic low-calorie intake (30%–50% of caloric requirements), fasting is maintained for 12 to 20 hours each day (time-restricted feeding) or for some days each week (intermittent calorie restriction, e.g., 5 fed:2 fasted or alternate day), which leads to periodic ketogenesis and mimics the regenerative effects of caloric restriction, for example, autophagy and mitophagy. Intermittent fasting has been shown to improve blood glucose regulation, resiliency to stress, inflammation, and cognition and may decrease risk of diabetes, cardiovascular disease, obesity, neurodegenerative diseases, and cancer (34,35). While intermittent fasting shows obvious promise for increased health span, its role as an ergogenic tool has only recently been explored. Time-restricted feeding may allow reduction in fat mass while maintaining fat-free mass without full-day fasting, making it more pragmatic (36). In a 2020 systematic review and meta-analysis, time-restricted feeding was found to significantly improve maximal oxygen uptake, while the opposite was true of fasting for Ramadan, perhaps due to dehydration (36). Therefore, time-restricted eating may be beneficial in athletes if intake of necessary nutrition and hydration is maintained, which has been shown to be feasible in several studies (36–39). However, more research is needed to establish the effects of time-restricted feeding and what the optimum protocol(s) may be. For instance, how long does fasting need to be maintained to see benefits? The body of evidence is elucidating that 14 hours fasted may be the minimum for metabolic benefits (40) and 16 hours seems to be used most frequently, but there is no consensus in general, let alone for ergogenic benefits.

But what are the benefits of fasting and caloric restriction? Much of the fanfare focuses on mitophagy and mitochondrial function. Mitochondria are the powerhouses of our cells and, thus, our bodies, so there is a natural connection with athletic performance. Energy metabolism (i.e., production of adenosine triphosphate (ATP), fatty acids, and amino acids) is just part of their role. Mitochondria are involved in the production of heme- and other iron-related proteins, calcium buffering, apoptosis, and immunity—all potentially ergogenic. Much of this relates directly to the quality control of mitochondria and therefore their function and the function of the organism as a whole (41,42). Mitophagy, mitochondrial degradation through autophagy balanced with biogenesis, is a key component in this maintenance process and is often triggered during times of stress, for example, starvation and hypoxia (41,42). Many factors determine the efficiency of mitophagy, including nutrition and disease status. Mitophagy has been associated with the pathogenesis of numerous diseases (e.g., neurodegenerative diseases, cancer, aging, cardiovascular

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disease), with reduced quality control and subsequent decline in mitochondrial function being the primary driver (43). Therefore, many hypothesize that increasing mitophagy may mitigate or reverse these disease processes, which in turn may also offer an ergogenic benefit in healthy athletes. Or is there enough gain to be had in healthy athletes? The magnitude of this effect is unclear and likely small, at least in terms of athletic performance. Part of this reason is that physical activity, particularly athletic training, stimulates mitophagy by inducing stress (44–46). Therefore, mitophagy in athletes may already be close to optimal (44,45).

Competing Dietary Claims Pertaining to Athletic Performance

Carbohydrate is generally the predominant energy source in the human diet and is readily oxidized to support physical activity. Studies generally suggest that monosaccharides and polysaccharides are comparable energy sources, although glucose is metabolized somewhat more efficiently than are other sugars. Preliminary studies suggest that carbohydrate sources with a low glycemic index/load, such as lentils, may support endurance better than foods with a high glycemic index, such as potatoes, when consumed prior to exercise (see Chapter 6). Low-glycemic-index foods are absorbed more slowly into the bloodstream, potentially providing a steady and gradual energy supply to support prolonged exercise. In contrast, high-glycemic-index carbohydrates immediately after exercise may promote glycogen storage, greater glucose and insulin responses, and enhanced recovery (47). However, the relationship of the glycemic index of pre-exercise meals has yet to become clear in the literature (48,49).

More than 90 minutes of high-intensity exercise typically depletes muscle glycogen, and, thus, high muscle glycogen stores may benefit endurance athletes (50). However, this does not need to be achieved through intensive carbohydrate loading, a practice that seems less beneficial in women in particular (51–53). The benefit of carbohydrate loading to endurance athletes may be in avoiding the need to consume carbohydrates during exercise, which often is in the form of hyperosmotic solutions that may lead to gastrointestinal discomfort (53). Interestingly, low muscle glycogen does not seem to impede muscle protein synthesis or athletic performance, which is good news since most competitive athletes do not replenish their glycogen stores between training sessions (54,55). However, performance seems to improve on moderate to high carbohydrate diets (54).

Controversy persists regarding optimal alterations of diet for the enhancement of sustained, high-intensity exercise and fast recovery. Over recent years, different diet theories, supplementation regimens, and fueling strategies have arisen, purporting to optimize athletic performance. These trends range from excess consumption of certain macronutrients while completely avoiding others to only consuming foods that are cultivated in certain ways. Patients, whether competitive athletes or not, will undoubtedly hear about these trends and will seek expert advice regarding dietary experimentation strategies.

Dietary protein is of particular interest to bodybuilders and other athletes involved in strength training. A high-protein diet is often recommended by bodybuilders and nutritionists to repair muscle damage after anaerobic training and to aid in muscle growth and fat loss. While there is evidence that high protein intake may better support muscle protein synthesis when compared to moderate protein intake, this has failed to translate in human studies. The joint statement reports that higher protein intakes “may be indicated for short periods during intensified training or when reducing energy intake,” and, thus, a high-protein diet is not a long-term solution (5). It is clear that consistent underconsumption of protein causes a decline in lean muscle mass even with adequate caloric intake (39). Therefore, it seems reasonable to prescribe current dietary guidelines of protein intake (0.8 g/kg/day) for sedentary individuals with the recommendation of boosting protein intake to 1.2 to 1.8 g/kg/day for those who are physically active, particularly those engaging in strength training who may benefit from protein intake up to 2.0 g/kg/day

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(5,6). Again, recent research suggests that maximal MPS occurs at 30 g of protein (around 0.49 g/kg) when ingested with 45 g of carbohydrate with no benefit beyond this limit (7).

With respect to athletic performance, there have been reports and observations that consuming a carbohydrate-restricted diet may improve performance. There is some suggestion that a short period of high fat intake may enhance fat oxidation, spare carbohydrate, and delay fatigue (56,57). Original theories explaining the purported benefits centered on the fact that fat oxidation increases, thereby sparing muscle glycogen. While endurance training enhances fatty acid utilization in muscle, there is little evidence that high fat intake actually enhances performance outside of ultra-endurance events (e.g., ironman triathlons and ultramarathons) and may actually harm performance in explosive events like sprinting (9,58,59). While low-carbohydrate, high-fat diets (ketogenic or not) may elicit changes in body composition, these diets compromise the ability to maintain high-intensity training when compared with consumption of more carbohydrates (9,60,61). Concern has been raised about fat loading, both on the basis of limited and contrary evidence and because the practice is potentially at odds with dietary practices for health promotion, although that depends in part on the type of fat ingested (9).

Some athletes are moving to a periodized nutrition approach—meaning they are on different diets at different points, also known as nutritional training (8,9,62). This may include “train low” periods where the athlete trains while on a low or no carbohydrate diet between two sessions or trains fasted. These are alternated with “train high” periods where carbohydrates are introduced to support glycogen-intensive training sessions. A less extreme version of this is “train for the work at hand,” which attempts to tailor the diet to the training session or competitive event each day. This approach, while likely beneficial due to its personalization, is not easy to design or implement due to its complexity.

The Paleolithic or “Paleo” diet has gained widespread following; though, Paleo is now overshadowed by the very low carb, very high fat ketogenic or “keto” diet, for which there is limited and mixed findings in athletes (8). Paleo has been popularized as a viable strategy for athletes and those engaging in intense physical training. While there is no one Paleo diet but rather a group of diets under the Paleo heading, a Paleo nutrition plan is based on the presumed ancient diet of wild plants and animals that hominid species consumed during the Paleolithic era, before the development of agriculture and grain-based diets. Paleo is generally a higher protein, lower carbohydrate diet. In the book *The Paleo Diet for Athletes: A Nutritional Formula for Peak Athletic Performance*, Loren Cordain and Joe Friel study the diets of our ancestors and today’s top athletes to provide meticulous evidence that this nutrition plan can improve and sustain optimal performance (63). While the diet may lead to short-term improvements in metabolic biomarkers, more research is needed to elucidate this relationship (64). No controlled studies have yet to show a demonstrable improvement in athletic performance using Paleo. However, the emphasis on whole foods with minimal processing is good dietary advice for anyone.

Vegan diets have become increasingly popular among athletes. Emerging evidence from those working with elite vegan athletes provides evidence that the vegan athlete can compete effectively at a high level by focusing the diet on micronutrient-rich whole plant foods and avoiding potential deficiencies. This requires careful construction of a varied diet, paying attention to higher protein plant foods (soy, lentils, beans, nuts, and seeds including quinoa) and, perhaps, aiming for the higher range of recommended intakes—1.4 to 2.0 kg/day—to limit the potential for deficiency in any individual EAA (65). Many plant foods contain smaller amounts of protein as well: a 100 g broccoli stalk has 3 g protein and 100 g of mushrooms or kale has 3 g protein. Use of vegan protein powders, for example, soy or pea protein, can assist in meeting the protein needs of the vegan athlete, especially for leucine and creatine. Dietary sources of the EAAs leucine include soybeans, hemp seeds, beans, and legumes. Iron should be monitored in the vegan athlete, and calcium may also be a concern (5,65). Supplementing zinc, iodine (or sea

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vegetables), vitamin B_{12}, and vitamin D are typically necessary (5,65). Supplementation with docosahexaenoic acid (DHA) and, to a lesser extent, eicosapentaenoic acid (EPA) omega-3 fatty acids from algal sources as well as riboflavin is likely beneficial, and there may also be a role for supplemental creatine, carnosine, and taurine (5,65).

Hydration

One realm in which a general consensus exists is that hydration is essential. Replenishment of water and electrolytes before, during, and after exercise is vital for maintaining homeostasis and health (5). Dehydration can degrade aerobic performance and lead to cognitive impairment with as little as >2% BW fluid loss (i.e., 1.4 kg BW loss in a 70-kg athlete), especially in hot environments, and are typically seen with 3% to 5% BW deficit (5,66). Sweat losses vary by individual (fitness, acclimatization), type of activity (intensity, duration), and other environmental variables (heat, humidity), ranging from 0.3 to 2.4 L/hour of activity (5); sodium sweat losses have been shown to be lower in endurance athletes (67). Excessive drinking of hypotonic solutions (water, sports drinks) during prolonged or strenuous activity may lead to exercise-associated hyponatremia (EAH), perhaps especially during menstruation, and has been reported with marathons, hiking, swimming, yoga, weightlifting, tennis, etc. (67). Consumption of isotonic fluids with electrolytes according to thirst (≤sweat loss) can help prevent EAH (67). The effectiveness of sodium supplementation is still under debate; for instance, no relationship between sodium intake and EAH and related symptoms was found in ultramarathoners in a number of studies (67–70). It may be that long-term sodium depletion is the key, with one study showing 10 days of reduced sodium intake potentially setting the body up to develop EAH (67,71). The role of sodium supplementation in performance cannot be supported by the literature at this time (66).

It was recommended that fluid replacement beverages contain 20 to 30 mEq/L sodium chloride (replace electrolyte losses, stimulate thirst, promote fluid retention); 2 to 5 mEq/L potassium (electrolyte losses); and 5% to 10% carbohydrate (energy) (72). The sports drink market used this formula to grow into a multibillion-dollar industry with numerous products available that claim to optimize athletic performance. Most sports drinks contain a combination of simple carbohydrates (glucose, fructose, maltodextrins) and electrolytes (sodium, potassium), with little evidence to suggest advantages of one over another (66). More recently, companies are promoting a series of drinks designed to “optimize” pre-workout priming, mid-workout performance and endurance, and post-workout recovery. This is based on recommendations from sports nutritionists that team-sport athletes participating in intermittent high-intensity exercise for >1 hour consume 1 to 4 g carbohydrate/kg 1 to 4 hours before, 30 to 60 g carbohydrate/hour during, and 1 to 1.2 g carbohydrate/kg/hour with 20 to 25 g protein as soon as possible after exercise (73). To date, there have been no studies demonstrating clear performance advantages with these recipes, and, more importantly, this prescription applies to elite athletes exercising in oppressive conditions for over an hour per day. Although these drinks may help replenish nutrient and fluid loss and prevent excess muscle breakdown during strenuous training, they are high-calorie sugared drinks—virtually indistinguishable from other obesogenic sugary beverages when consumed in large quantity by non-exercising individuals. The aggressive marketing of sports drinks to the general population, particularly children, is dubious at best and may contribute to overweight and obesity (74). Sports drinks may also contribute to tooth erosion and decay (75).

Coconut water has enjoyed increasing popularity under the premise that it is low in calories, high in potassium, and effective as a super rehydrating fluid with industry claims like improved circulation, slowed aging, increased immunity, and reduced risk of stroke, heart disease, and cancer. Coconut water does contain easily digestible carbohydrates (sugar) and electrolytes. It has fewer calories, less sodium,

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and more potassium than a sports drink, see Table 32.2 (30). Anecdotally, the ample potassium in coconut water may help prevent cramping during prolonged, rigorous exercise in excessive heat, but equivocal evidence is lacking (8). Since sweating makes people lose more sodium than potassium, coconut water alone may not be able to replace this lost sodium. Sweating can also lead to magnesium loss, which is only contained in coconut water, though in small amounts. Summing up the evidence to date, coconut water may be a valid way to hydrate, reduce sodium, and add potassium to the diet. Beyond this, there is a paucity of supportive evidence in the scientific literature to substantiate claims about coconut water (76–79). The same holds true for the multitude of new drinks containing vitamin and other health-promoting supplements, many of which are loaded with excess sugar.

TABLE 32.2

Comparison of Coconut Water, Gatorade, and Chocolate Milk for Hydration

Nutrition in 1 fl oz	Coconut Water, Unsweetened	Gatorade G	Chocolate Milk
Calories (kcal)	5–6	8	26
Sugar (g)	1	1.6	3
Magnesium (mg)	2	0	4
Potassium (mg)	50–80	5	52
Sodium (mg)	2–10	12	18

Data from U.S. Department of Agriculture ARS. FoodData Central. 2020.

The reality is that for the average exerciser in a temperate environment for an hour or less, water is an adequate source of rehydration when taken to thirst. It is important that healthcare professionals educate consumers about the composition and appropriate use of sports drinks, gels, and bars, empowering the consumer to make appropriate health choices. For athletes, pre- versus post-workout BW can estimate sweat losses (% BW) and help evaluate hydration regimens (80).

When carbohydrates are needed, as in intense training in elite athletes, a popular post-workout recovery drink is chocolate milk. Ounce for ounce, chocolate milk contains more magnesium and potassium than coconut water and more sodium than Gatorade, making it a potentially better hydrator than either one. Since chocolate milk contains about four times as many calories and three times the sugar, there is still some concern with this product if it is used on a regular basis, especially in those overconsuming sugar and calories.

NUTRIENTS, NUTRACEUTICALS, AND FUNCTIONAL FOODS

That the overall quality of diet can influence physical performance in an athlete and beyond is undisputable. The desire to enhance performance beyond this with dietary supplements has existed since ancient times. In antiquity, such practices were rooted in superstition, such as the belief that eating the heart of an enemy would impart courage (81). Whereas modern practices are more likely to derive from science than superstition, interest in performance-enhancing dietary regimens consistently runs ahead of available evidence.

Micronutrients: Vitamins and Minerals

A variety of micronutrients that play defined roles in energy metabolism have received attention as

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potential enhancers of athletic performance, and, although evidence of enhanced athletic performance with supplementation is accumulating for some of these substances, the research is generally of marginal quality and the findings inconsistent. These so-called ergogenic aids are often promoted on the basis of animal or in vitro data before human interventions are conducted (8,82). The financial imperative and limited regulation driving the promotion of such products warrant cautious skepticism; however, the trend has been toward increased research to support claims and potentially increase sales (8).

A varied diet of predominantly whole, unprocessed, plant-based foods can supply sufficient micronutrients for general health, and additional supplementation has not generally proven effective for athletic performance (8). There is some support for the use of vitamin E at high altitudes (83) and that vitamin C supplementation (200 mg + recommended dietary allowance (RDA)) after training may reduce the risk for upper respiratory tract infections (82,84–86). However, supplementation with niacin (B_3) may decrease free fatty acids, potentially limiting exercise capacity (87). Since vitamins B_6 and B_{12} are important for the production of serotonin, supplementation could potentially reduce anxiety and improve skill in target sports, for example, archery (8). Magnesium may also have a calming effect, but this potential has not been shown in athletes to date.

Magnesium may support muscle mass and power, potentially even in non-deficient individuals (88). Zinc supplementation may reduce exercise-induced immunosuppression (85,89,90). Prolonged zinc intake above 40 mg/day may reduce copper and should be monitored (91). Sodium phosphate, but not other forms of phosphorous, may support endurance through the oxygen energy system (92–94). In athletes with iron deficiency, iron supplementation has shown improvements in exercise capacity and performance with relatively high-quality evidence (88). In general, more research is needed to determine the optimum intake of micronutrients as ergogenic aids.

Creatine

Creatine phosphate serves as an immediate energy reserve in muscle by donating phosphate to adenosine diphosphate to reconstitute adenosine triphosphate. The intent of creatine supplementation is to increase energy storage in muscle to enhance performance (95). There is general consensus that creatine supplementation enhances athletic performance in high-intensity exercises, particular those requiring strength and/or power, regardless of age with more limited evidence in women (96). Creatine may decrease risk of injury and support recovery and rehabilitation and is being investigated in neurodegenerative diseases, for example, muscular dystrophy and Huntington's disease, and to support fetal development (96). Adverse effects with common doses are minimal and limited to weight gain (likely water retention) and perhaps gastrointestinal upset (95,96). The safest, effective method may be to ensure regular intake of creatine at lower levels such as 3 g/day (vs. typical intake 1–2 g/day) rather than supplementing for short- or long-term bouts with larger doses (5–10 g/day or up to 0.8 g/kg/day); though, this will require time to build up stores, about 3 to 4 weeks (96). Taking creatine with carbohydrate (and protein) may improve its effectiveness; while the form does not seem to matter, creatine monohydrate is the typical form (96). Long-term use of larger doses has not been studied. While there is concern that kidney function could be affected, research in type II diabetes (a state of impaired kidney function) did not bear this out with 12 weeks of 5 g/day creatine (97). Further, taking more is not beneficial as muscle quickly becomes saturated with creatine (96) (see Appendix E).

Carnitine

Carnitine participates in the transport of long-chain fatty acids into mitochondria. As this is a crucial role,

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both the liver and kidneys endogenously produce creatine. The body of evidence shows a lack of effect of carnitine supplementation on the concentration of carnitine in muscle; likewise, altered fatty acid metabolism or subsequent improved athletic performance has not been shown with carnitine supplementation (8). While it has been suggested that combining carnitine with carbohydrate may increase the concentration of creatine in muscle, studies using this approach have not found an improvement in power or output but suggest a possible improvement in endurance (8,95). Further, these carbohydrate protocols are not pragmatic (95) (see Appendix E).

Dehydroepiandrosterone

Dehydroepiandrosterone (DHEA) is a prohormone that appears to be stimulated with higher intensity or power exercise, which may not change with training (98). Levels of DHEA decline significantly over the course of adulthood, suggesting theoretical benefit for supplementation in seniors. A systematic review assessed DHEA supplementation for muscle mass, based on four randomized controlled trials (RCTs), and muscle strength (3 RCTs) in subjects aged 60 years and older (99). Duration of supplementation ranged from 3 to 23 months, with dosage ranging from 50 to 100 mg/day; no significant effects were found (99). More research is needed in this population, but what about in athletes? DHEA is on the World Anti-Doping Agency list of prohibited substances. The assumption leading to this prohibition is that DHEA is readily converted into testosterone; however, any conversion appears to be small and fleeting (98). In fact, anti-doping measurements for testosterone are not affected even immediately following high-dose DHEA supplementation, 250 mg (98). This is likely why the small body of literature to date has not found an ergogenic effect of DHEA supplementation.

Caffeine

Caffeine is a stimulant found in many natural sources, supplements, and drugs. It has been established that supplementation with caffeine prior to exercise improves endurance by sparing carbohydrates, resulting in improved performance (8,95). Effective dosages range from 3 to 6 mg/kg (not higher than 9 mg/kg) about 60 minutes (30–90 minutes) before exercise, and habituation does not appear to affect outcomes significantly (8,95). Some of the endurance benefits may come from an improvement in mood (8). There are also benefits in higher intensity or power exercises using the same supplementation protocol; however, the research on maximal strength and fatigue from repetitions is mixed (8,95). Recent research has turned to lower doses (<3 mg/kg or about 200 mg), studying the timing of intake (before and during) and showing no need for withdrawal (95). One potential concern has been dehydration, but the research has not substantiated this (8).

Caffeine is the main component of virtually all energy drinks, performance enhancers, and weight-loss supplements. These products are targeted at individuals interested in athletics and an active lifestyle and have been one of the fastest-growing sectors in the fitness industry. Most of these supplements feature caffeine and a combination of other components, including taurine, sucrose, guarana, ginseng, niacin, and cyanocobalamin. Ergogenic benefits are likely due to caffeine and glucose content. As with any pharmacoactive substance, however, these products are associated with adverse effects, most notably insomnia, nervousness, headache, tachycardia, and increased blood pressure. These products often contain excess sugar and thus may contribute to obesity and insulin resistance. Further, caffeine abuse and intoxication pose serious threats to physical and mental health. Practitioners should beware of the adverse effects of these loosely regulated products and help to educate and monitor those most likely to consume them, most of which are consumed by men aged 18 to 34 years (100).

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Medium Chain Triglycerides

Medium Chain Triglycerides (MCT) oil is a popular supplement and found in everything from coffee and smoothies to salad dressings. MCTs are highly digestible due to their shorter length. MCTs have been shown to enter the mitochondria easily, where they are readily metabolized to produce energy (101). The idea is that they serve as a source of energy through fat metabolism instead of utilizing carbohydrates. However, the literature is equivocal. Some research has shown MCTs to be inferior to carbohydrates, for example, cycling time trials (8), while other research has shown potential ergogenic effect on performance (8). For instance, Misell et al. showed that 60 g MCT/day for 2 weeks improved endurance running compared to corn oil (102); however, is that the correct comparison? Is the question whether MCT is better than other oils or the traditional fuel for athletes, carbohydrates? This is a significant research gap to date.

Sodium Bicarbonate (Baking Soda)

Sodium bicarbonate loading is used as an ergogenic aid in the belief that it will buffer lactic acid accumulated in muscle and prevent or delay muscle fatigue and dysfunction; however, the mechanisms are complex with significant intraindividual variability (95,103,104). The evidence suggests that bicarbonate, when given in an adequate dose (300 mg/kg 60–90 minutes before exercise or 5 g twice daily for 5 days prior), enhances performance in activities that are brief (i.e., 1–3 minutes) and intense (e.g., 400 m run, 200 m freestyle swim, 3 km cycling) (8,95). In particular, bicarbonate loading may enhance recovery time between repeated bouts of short, high-intensity activity, such as sprinting (8). Some evidence suggests that sodium citrate may have similar effects (95).

Chromium

Chromium functions as a cofactor in the metabolism of glucose and protein, principally by enhancing insulin action. Chromium is reputed to enhance energy metabolism in muscle and thus improve strength and stamina while promoting weight loss; however, the body of evidence to date does not confirm enhanced athletic performance, muscle growth, or fat loss attributable to chromium supplementation (8).

Nitrates

Supplementation with nitrates has become popular, particularly in the form of beetroot juice. Physiologically, nitrates are vasodilators that may lead to increased work capacity, power, and endurance. As a pre-workout supplement (2–3 hours), 300 to 600 mg (0.1 mmol/kg BW) of nitrates are typically well tolerated (8). However, more recent research is turning to daily supplementation (3+ days), which may allow for the benefits to be maintained (95). Improved athletic performance has been observed in some populations but not others, which is consistent with the research on the health benefits of dietary nitrates (8,95). Research is needed to elucidate which population may benefit from nitrates (dietary and supplemental).

Omega-3 and Fish Oil

Fish oil contains the omega-3 fatty acids EPA and DHA, precursors of certain eicosanoids that have been shown to reduce inflammation throughout the body and confer multiple health benefits in doses unlikely to be consumed through diet alone. Further, supplementation may reduce exposure to mercury contamination in some types of seafood, especially larger predators. This is why the American Heart Association has recommended fish oil supplementation and consumption of fatty fish one to two times/week (105). In

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athletes, heart healthy may be even more important, so supplementation is likely prudent. But is supplementation with omega-3 fatty acids ergogenic? Preliminary evidence suggests a potential benefit for endurance exercise (106). Omega-3 likely benefits athletes in terms of recovery with research supporting a role in muscle post-training and in traumatic brain injury (106,107).

Amino Acids Supplements

Individual amino acids, most notably essential amino acids (EAAs), BCAA, glutamine, and arginine are marketed as supplements for muscle growth in weightlifting, bodybuilding, endurance, and other sports.

Essential Amino Acids

In lieu of a pre- or post-training meal, 6 to 12 g EAAs provide maximal protein synthesis (8). However, 6.72 g EAAs in an intact protein source (15 g whey protein isolate) were shown to be more effective than free EAAs in seniors (108).

A subset of EAAs, BCAAs, may provide an alternative energy source once glycogen stores have been depleted. Some research has shown that the primary benefit of EAA supplementation may be due to the BCAAs (109), while other studies support the use of all nine EAAs for maximal protein synthesis (110,111). However, the consensus is that leucine is the most crucial for acute protein translation and, thus, must be optimized, which is likely on the order of 1.7 to 3.5 g/day (8).

Beta-hydroxy-beta-methylbutyrate (HMB), a metabolite of the amino acid leucine, has shown mixed results, likely due to variation in training protocols; it appears that HMB is most effective with maximal training intensity (8). Dosages range from 1.5 to 3 g/day with some support for 38 mg/kg/day (roughly 3 g/day) to increase lean body mass and increase aerobic capacity (8,112,113). Calcium-HMB, which was initially used, is less bioavailable than HMB as a free acid, the newer formulation which is still under investigation (8).

Conditional Amino Acids

Conditional Amino Acids (CAAs) are nonessential except in illness or stress, and the stress of training may trigger the need for exogenous supplies of these amino acids. Glutamine, an important fuel for some cells of the immune system, such as lymphocytes and macrophages, may be immunoprotective after prolonged exercise and in instances of overtraining. However, the research has been mixed. The most likely benefit of glutamine supplementation (0.3 g/kg) is a reduction in self-reported muscle soreness (8).

Arginine supplementation is theorized to be ergogenic because it is a substrate for the synthesis of nitric oxide, a potent endogenous vasodilator that increases blood flow and endurance capacity. However, research has largely found no effect on exercise capacity or endurance with limited support for power improvement (8).

Taurine, which is produced from the CAA cysteine, has been found in higher concentration in trained versus untrained muscle; however, the research on its ergogenic potential has also been mixed (8). Overall, the studies of amino acid supplementation on athletic performance are equivocal, especially in light of a well-nourished athlete.

Nutrigenomics

The joint position statement specified that “nutrition plans need to be personalized to the individual athlete to take into account the specificity and uniqueness of the event, performance goals, practical challenges, food preferences, and responses to various strategies” (5). Much of the evidence for the benefit of supplementation with nutrients, nutraceuticals, or functional foods show the potential for

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substantial interindividual variability, particularly with caffeine, and, to some extent, such variability may account for mixed results in ergogenic aids (114). This variability and the precision nutrition movement are driving the development of nutrigenomics (114,115). Nutrigenomics is the study of the genomic variations that affect nutrition—digestion (bioaccessibility, absorption), transformation/activation, metabolism/utilization, requirements, and excretion—and may be used to make more personalized nutrition recommendations. The benefits of nutrigenomics in sports nutrition are budding with some evidence that genetics-based advice may further motivate the athlete to follow the plan (114). Not only is the field of nutrition moving away from one-size-fits-all recommendations, but there is public demand for personalized nutrition, especially that based on genetic testing. As such testing becomes more available and more affordable, it is likely that any healthcare provider may be brought the results and asked for help in interpreting and implementing the findings. This is where a well-trained clinician can make a significant difference in the patient experience.

CLINICAL HIGHLIGHTS

Interest in the potential for dietary manipulations to enhance athletic performance is widespread and long-standing despite the evidence being relatively sparse. Small tweaks of a health-promoting diet, however, may be conducive to enhancements in strength and/or endurance. Although the recommended protein intake for healthy adults is approximately 0.8 g/kg/day, a level twice that much may support muscle development with resistance training and clearly is safe over the short term. A protein intake up to 2 g/kg/day may support strength as opposed to endurance training, and there is limited evidence that an intake as high as 2.5 g/kg/day may facilitate bodybuilding. The long-term health effects of protein intake at this level are uncertain; a return to more moderate intake once the period of intense training is over is indicated. Although the protein consumed should be of high biologic value (see Chapter 3), there is little evidence to support the use of protein formulas or modified commercial protein products over whole foods other than for matters of convenience, portability, and preference.

Studies of putatively ergogenic nutrients have largely been negative, although there is some evidence of improved endurance with creatine supplementation and caffeine definitively enhances endurance. The evidence that bicarbonate loading enhances tolerance of short bouts of high-intensity exercise is mounting. Moderate to high carbohydrate ingestion for several days before an endurance event seems likely to delay fatigue by sustaining muscle glycogen stores. Fluid replenishment with isotonic fluids to thirst is recommended during high-intensity endurance exercise for 60+ minutes; all others should generally be dissuaded from use of sports drinks and energy bars. These can readily contribute more calories to the diet than are being utilized in such exertions; the scientific support for such products pertains to the serious athlete involved in intense competition with multiple training sessions per day.

Ultimately, a dietary pattern associated with health promotion (see Chapter 45) is, for the most part, associated with optimal functional status as well. There should not be many extreme deviations between the optimal diet of a serious athlete and the optimal diet of any other healthy, active human being. In order to better optimize the health and performance of their patients, healthcare providers must be knowledgeable about dietary trends, marketing gimmicks, and leading research in order to sift the kernels of truth amid the mountains of myth.

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Chapter 33

Endocrine Effects of Diet: Phytoestrogens

Molly Morgan

INTRODUCTION

Natural constituents of foods with hormonal effects are widespread. Phytoestrogens are a diverse group of naturally occurring plant-derived chemicals with varying degrees of estrogen agonism and antagonism (1,2). There is particular interest in use of phytoestrogens, in food or as concentrated supplements, to modify both the symptoms and sequelae associated with menopause. This interest has significantly increased since the data from the Women's Health Initiative (WHI) trial, which indicated that the benefits of pharmacologic hormone replacement therapy (HRT) did not outweigh the risks (3). Subsequently, use of HRT has declined and that of phytoestrogens has increased (3,4). Additionally, the data from the WHI trial have been revisited and since proven to be controversial (5). This controversy is particularly relevant because if HRT is beneficial to certain populations, then finding effective, nutritional alternatives to HR for those populations takes on more urgency. Moreover, it is important to note that for some patient populations, HRT should perhaps be encouraged, with nutritional management applied if/when patients decline HRT.

Phytoestrogen compounds are potentially linked to additional health benefits. For example, epigenetic studies show that the presence of phytoestrogens in wholegrains may be in part responsible for the health benefits associated with their regular consumption (6–8).

OVERVIEW: SOURCES, DIETARY INTERVENTION, AND EQUOL

Phytoestrogens are bioactive molecules that are widely present in many foods, including soybeans, flaxseeds, whole grains, bean curd, bean sprouts, and more. For example, phytoestrogens have even been identified in hops (9), and consequently beer (10), as well as grapes, and consequently wine (11,12). Depypere and colleagues report that hops contain the phytoestrogen 8-prenylnaringenin (8-PN), which is thought to be a more potent phytoestrogen than soy isoflavone (13). Some of the putative health benefits of moderate alcohol consumption may be attributable to phytoestrogen effects (14) (see Chapter 40).

Beyond foods, some herbs have been identified as potentially exerting estrogenic effects on the body—for example dried red clover (15). Many herbs are used to treat aspects of women's health related to hormonal function; the mechanism by which such herbs exert their effects is often through agonism or antagonism of estrogen receptors (16,17). Chinese herbal preparations traditionally used for management of menopause-related symptoms have been found to contain phytoestrogens. In some instances, the potency is commensurate with that of conventional HRT (18,19).

It is plausible that dietary intervention with phytoestrogen-rich foods may substitute for synthetic selective estrogen receptor modulators (SERMs) because of the mix of estrogen agonism and antagonism, mimicking those of SERMs (20–23). To date, isoflavones in soy have been studied most extensively to date, and predominate isoflavones are genistein and daidzein. Isoflavones are known to exert selective estrogen effects, generating both clinical and popular interest in such foods as a natural means to replace

ovarian hormones, alleviate symptoms of menopause, or modify disease risk (24).

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One of the limiting factors in efforts to gauge the potential benefits of phytoestrogens had been their exclusion from standard measures of diet composition (25,26). Once isoflavones were added to the U.S. Department of Agriculture (USDA) Database, consumption could be better measured and evaluated (27).

Chun et al. (28) estimated that dietary isoflavones were only consumed by 35% of adults in a day with an average intake of approximately 3.1 mg/day, resulting in a mean intake of 1.0 mg/day for all U.S. adults; lignans appear to be the most abundant source of phytoestrogens in the American diet (29). It is still unknown what levels are sufficient to produce any of the health effects associated with phytoestrogens (30).

Beyond consumption levels, another factor that may influence health effects is production of equol, a metabolite of the isoflavone daidzein produced by the action of gut microflora (31). It has been estimated that only 30% to 55% of humans have the bacteria capable of producing equol. Current understanding of equol metabolism has not yet fully determined what factors most influence; however, gut physiology, host genetics, and diet appear to contribute to differences in conversion of daidzein to equol. Equol appears to be the most potent of the isoflavones, and evidence of equol production can be measured in urinary excretion; it is estimated that up to 50% of the adult population does not excrete equol after soy consumption (32). Preliminary evidence from clinical studies suggests that compared to these “nonequol producers,” “equol producers” may be a subpopulation that can maximally benefit from soy isoflavones (33,34).

Many clinical studies have been carried out to determine the health benefits of soy protein and the isoflavones contained in soy. In those intervention studies in which plasma S-equol levels were determined, a concentration of greater than 5 to 10 ng/mL has been associated with a positive outcome for vasomotor symptoms, osteoporosis (as measured by an increase in bone mineral density), prostate cancer, and the cardiovascular risk (35). Understanding the pathways through which the equol-producer phenotype modifies response to isoflavones may clarify the role of equol itself. More studies are needed that are designed to address a priori the effect of the equol-producer phenotype on disease risk (36).

Phytoestrogens and Menopause

Symptoms associated with menopause, including hot flashes/flushes, night sweats, sleep disturbances, and vaginal dryness, are related to a decrease in estrogen and can significantly impact quality of life. Asian women experience less vasomotor symptoms in comparison to women living in America or Europe, a difference thought to be related to differing intakes of phytoestrogen-rich foods (37).

The highest intake of phytoestrogens has been reported in Japanese and Chinese populations, with estimations of intakes up to 50 times those of most Americans (38); Wu et al. (39) estimated that isoflavone intakes in Asian Americans fall between levels consumed by typical American and Asian populations.

While trials of phytoestrogens for the amelioration of menopausal symptoms have yielded mixed results, researchers have concluded that phytoestrogens appear to reduce the frequency of hot flashes in menopausal women without serious side effects (40,41).

Recent reviews affirm safety of phytoestrogen use for at least 12 months of continuous use (4). A recent systematic review by Li-Ru Chen et al. concluded that despite limitations in decades of vigorous research on isoflavones, evidence continues to support the use of isoflavones due to their safety profile and benefit to overall health (42). A randomized controlled clinical trial found that women in the intervention group taking 40 mg of isoflavone-containing dried red clover for 12 weeks experienced a reduction in the severity of menopausal symptoms (43). Furthermore, research on the effects of red clover extract shows

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that beneficial changes could extend beyond control of menopausal symptoms and result in lower total cholesterol levels (44). Another recent randomized controlled trial (RCT) comparing the effects of isoflavones to placebo among 51 women demonstrated a clinically meaningful reduction of hot flashes (57%) after 6 months of treatment (60 mg) compared with placebo (18%) (45). Additional studies with rigorous design will continue to add to this body of evidence to develop robust guidelines further (41).

Phytoestrogens and Cancer

Although numerous epidemiological observations have indicated that populations in countries with high dietary intake of soy and other phytoestrogen-rich foods have significantly lower levels of breast and prostate cancer than others (46), evidence from clinical trials has been conflicting. Nevertheless, recent evidence does lean toward support for the role of phytoestrogens in reduction of cancer risk (47–49). Research continues to attempt to address this issue, and several possible explanations have begun to emerge.

The relationship of estrogen relative to breast cancer risk has been widely explored due to estrogen's believed role in breast cancer development and progression. Epidemiological studies have found that the consumption of soy foods has been inversely related to the risk of breast cancer. A population-based prospective study of over 5,000 women concluded that soy food intake is safe and linked to lower mortality and breast cancer recurrence. Further, the study showed a linear and dose–response pattern until soy food intake reached 11 g of soy protein/day, and additional benefits were not observed with intakes beyond that(50). Earlier in vitro studies using breast cancer cell lines have shown that high doses of isoflavones and lignans can inhibit cell growth (51,52), tumor progression, and angiogenesis (53), via both estrogen-dependent and estrogen-independent mechanisms (54–57).

In vitro and animal studies have suggested how isoflavones interact with epigenetic modifications, such as hypermethylation of tumor suppressor genes (58–60). These studies provide evidence on potential epigenetic mechanisms by which the isoflavones genistein, daidzein, and their derivatives might contribute to the prevention of breast cancer. These effects may also be one of the means by which fruits and vegetables in the diet mitigate cancer risk, especially cancer of the digestive tract (61) (see Chapter 12).

A recent systematic review suggests that soy consumption may offer primary preventive protection, with more efficacy in reducing development of breast cancer de novo and less so in prevention of breast cancer recurrence or reduced mortality (62).

Flaxseed intake has been linked with a reduction in breast cancer risk. The 2013 Ontario Women's Diet and Health Study, an observational study and the first known study to connect the consumption of flaxseed with a significant reduction in breast cancer risk (odds ratio [OR], 0.82; 95% confidence interval [CI], 0.69–0.97), as was consumption of flax bread (OR, 0.77; 95% CI, 0.67–0.89) (63). Additionally,Calado et al. summarized that flaxseed has the potential to reduce the growth of tumors in patients with breast cancer and decrease the risk of this type of cancer (64).

The timing, duration, and amount of soy intake may each be relevant to breast cancer prevention. Wu AH. et al. (65) showed in a population-based, case-control trial investigating the association between dietary soy intake and breast cancer risk that AsianAmerican subjects who were the highest soy consumers during adolescence and adult life showed much lower risk (OR, 0.53; 95% CI, 0.36–0.78) compared to subjects who were low soy consumers during those periods.

These results have been corroborated by a population-based cohort study, the Shanghai Women's Health Study, in which a cohort of 73,223 Chinese women has been followed over a mean of 7.4 years. The women who consumed a high amount of soy foods consistently during adolescence and adulthood had

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a substantially reduced risk of breast cancer (RR, 0.57; 95% CI: 0.34, 0.97) (66). These data support a growing speculation that early and substantial exposure to isoflavones in childhood and adolescence, regardless of adult intake, may be what provides the majority of the protective effects against breast cancer (67,68).

The role of equol in relation to cancer has been less widely studied, although two large studies conducted in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohorts reported no association between equol measures and overall breast cancer risk (47). Among estrogen receptor-positive cases in the Norfolk cohort, urinary equol was associated with a slightly higher risk (OR [95% CI] = 1.07 [1.01–1.112]; P = 0.013) in the 95 cases compared with the 329 controls. Bosviel et al. (36) have shown that equol increases the level of expressed oncosuppressors BRCA1 and BRCA2 genes in breast cancer cell lines. Niculescu et al. showed a stronger effect of isoflavone supplementation (900 mg/day for 84 days) on estrogen-responsive genes in peripheral lymphocytes among postmenopausal women who were equol producers (69).

Soy and phytoestrogen intake may also have biologic activity leading to decreased risk of prostate cancer (70,71) and even lung cancer. A meta-analysis of epidemiologic studies found that consumption of soy foods is associated with lower lung cancer risk, yet due to different methods of assessment across studies, more well-designed cohort or intervention studies are still needed (72). Recent studies continue to build on the evidence that soy isoflavones (genistein and daidzein) are associated with lower risk of prostate cancer (73).

Cardiovascular Disease

There is evidence of cardiovascular benefits of soy phytoestrogens, apparently with comparable effects in men and women (74). There are many factors that result in the beneficial impact of isoflavones on cardiovascular health, including reduction in blood lipids and blood pressure, improved endothelial function, and antioxidant activity. An Food and Drug Administration (FDA)-approved health claim stating that including 25 g of soy protein in a low-fat, low-cholesterol diet may reduce the risk of cardiovascular disease has been in place since 1999 (75).

While the health claim has been questioned, a recent cumulative meta-analysis of the soy effect on heart health has been completed by Jenkins, et al.; their study concluded that the data selected by the FDA continue to hold significance linking soy consumption and heart health benefits (76).

Study highlights:

- A randomized crossover trial of 60 healthy postmenopausal by Welty et al. demonstrated reductions in blood pressure and low-density lipoprotein cholesterol levels in women who substituted soy nuts for non-soy dietary protein, with greater effects observed in hypertensive subjects compared to normotensive subjects. Adding soy nuts to the diet for 8 weeks significantly improved glycemic control and lipid profiles in postmenopausal women with the metabolic syndrome (77).
- A randomized crossover trial testing soy isoflavone protein, soy lecithin, and the combination of the two found significant improvements in subjects' lipid profiles after 4 weeks of treatment (78).
- Trials using semi-purified isoflavone supplements found no lipid-lowering effect (79) suggesting that intact, minimally processed soy protein may be required for cardiovascular benefit (80).
- Equol producers, compared with nonequol producers, have significant improvements in total cholesterol/high-density lipoprotein and low-density lipoprotein/high-density lipoprotein ratios (24).
- A randomized controlled trial to assess the effect of isoflavones on endothelial function in postmenopausal women with type 2 diabetes mellitus (T2DM), Curtis et al. (81) have shown that

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equol producers had larger reductions in diastolic BP, mean arterial pressure, and pulse wave velocity (−2.24 ± 1.31 mm Hg, −1.24 ± 1.30 mm Hg, and −0.68 ± 0.40 m/s, respectively; $p < 0.01$) compared with nonequol producers (n = 30).

Bone Health

Studies have shown that isoflavones, via diet or supplementation, may have a protective effect on postmenopausal bone loss (82,83). In one double-blind, randomized controlled trial, women aged 49 to 65 receiving a red clover-derived isoflavone supplement for 1 year demonstrated significantly reduced loss of bone mineral content and density compared to women receiving a placebo (84).

Similar results were achieved with increased dietary soy products (85,86) and the natural phytoestrogen genistein (87). Recent studies of young premenopausal (88) and older postmenopausal (89) women have not found significant effects of soy supplementation on bone mineral density. There are conflicting data about the potential benefits of the synthetic isoflavone analog ipriflavone (90,91), and at this point, the relationship between isoflavones and bone health is still far from fully understood (92,93) (see Chapter 14).

Equol could be a factor at play as well in relation to bone health and soy. Several studies of soy supplementation and bone density suggest that soy products may be more effective in maintaining bone density in equol-producing individuals.

To date, although there is considerable variability in study design and duration, study population, type of soy isoflavone employed in the intervention, and study outcomes, the evidence points to a lack of a protective role of soy isoflavones in the prevention of postmenopausal bone loss (94).

Cognition and Dementia

There have been studies linking the neuroprotective effects of phytoestrogen compounds in animal research and cell culture studies. For example, phytoestrogens have been linked to potentially alleviating the risk of Alzheimer's disease progression. This is in part thought to be linked to the antioxidant properties of soy products as well as the availability of impact cognition through the interaction with estrogen receptors (95).

Additionally, another recent study from the *Journal Alzheimer's Dementia: Translational Research & Clinical Interventions* found that women who produce equol displayed lower levels of white matter lesions within the brain (96). This is crucial because white matter lesions are a significant risk factor for cognitive decline, dementia, and all-cause mortality. In fact, researchers with this study found 50% more white matter lesions in those who couldn't produce equal compared to those who can produce equol. This is another interesting and developing link between phytoestrogens and health that will warrant further studies and evaluation.

Hormonal Effects

Phytoestrogens have been shown to influence sexual differentiation and fertility in animal models (41). Even though some soy-based infant formulas are very rich in phytoestrogens, no adverse effects in humans have been reported (41,97). In comparison, human breast milk by default contains negligible concentrations of isoflavones (32); however, there is evidence that maternal soy consumption significantly increases urinary isoflavone levels in breast-feeding infants (98). There is speculation that early exposure to soy phytoestrogens may reduce the risk of certain chronic diseases later in life (98,99).

A cross-sectional study of postmenopausal women found significant associations between phytoestrogen exposure and circulating sex hormone levels in a large group of postmenopausal women.

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The same investigators also found evidence of phytoestrogen–gene interactions among subjects, lending support to the hypothesis that certain people may gain more or less benefit from phytoestrogens (100).

In vitro studies of cultured adrenal cortical cells suggest that phytoestrogen consumption reduces cortisol production (101), an effect seen with a lactovegetarian diet (102). Despite the common myth that soy has feminizing effects on men, clinical evidence finds that isoflavones do not exert feminizing effects on men at intake levels equal and even considerably higher than typical intakes of Asian males (103).

CLINICAL HIGHLIGHTS

Phytoestrogens act as selective estrogen receptor agonists and antagonists, in much the same way as SERMs. The possibility that phytoestrogen-containing foods or concentrated supplements could be used to ameliorate symptoms and sequelae of menopause is supported by available evidence, which continues to be further evaluated and researched. Phytoestrogens may be an alternative for the management of menopausal symptoms and evidence continues to build.

An eating routine rich in a variety of plant foods, particularly soybeans, flaxseeds, and whole grains, is advisable on other grounds and will provide a rich supply of the best-studied phytoestrogens. The inclusion of such foods, via the effects of phytoestrogens and other beneficial constituents, appears likely to reduce the risk of breast cancer, prostate cancer, cardiovascular disease, and possibly other cancers and osteoporosis, with additional potential health benefits linked to cognition. Yet, the effects with regard to phytoestrogens specifically may depend to a large extent on an individual's distribution of gut bacteria and the ability to generate equol.

Given soy's wide use as a meat substitute, it may be that its protective effects stem not only exclusively from what it provides to the diet but also from what it removes; an eating routine that includes minimally processed soyfoods is more likely to contain less meat and subsequently less associated with cancer risk. As the intake of soy increases with wider acceptance, additional research regarding safe limits of soy food consumption will be needed and perhaps guidelines established to ensure safety. Further, larger, well-designed, long-term trials are needed to define these effectsbetter.

While there may be some cause for concerns about the risk/benefit trade-off of supplementation with soy or other phytoestrogen sources, the benefits of making whole-soy foods a part of the diet, particularly when used as an alternative to meat, are generally both persuasive and reassuring.

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Diet, Sleep–Wake Cycles, and Mood

Atia J. Harris

INTRODUCTION

A potential role for both macronutrients and micronutrients in the regulation of the sleep–wake cycle and mood is of clinical and popular interest. The interaction between diet and mood has the potential to ameliorate or compound affective disorders, eating disorders, and weight gain/obesity. Dietary patterns may influence the quality of nighttime sleep, the propensity for daytime somnolence, vigilance, and concentration.

The role of dietary protein and carbohydrate in the metabolism of serotonin is of particular importance. Pharmacologic manipulation of brain serotonin levels using selective serotonin reuptake inhibitors (SSRIs) has the potential to influence food cravings and dietary patterns as well as affect. Although the literature on nutrition, sleep, and mood is extensive, most studies involve small numbers of subjects. The importance of diet to sleep and mood is increasingly clear; however, more research and data are needed to support specific intervention plans. Sleep deprivation may often be an important contributing factor to weight gain/obesity by several means, including neuroendocrine effects (see Chapter 5).

OVERVIEW

In a variety of ways, dietary patterns and nutrients can influence somnolence, alertness, and the adequacy of sleep. The specific neural mechanisms controlling patterns of sleep and wakefulness are a largely investigated topic (1–5). Alterations in levels of neurotransmitters, particularly serotonin (6), as well as dopamine, acetylcholine, and glutamate, are clearly involved and influenced by diet.

Diet and Neurotransmitters

Tryptophan and Serotonin

The amino acid tryptophan is converted into serotonin, which plays an important role in regulating sleep and mood, with implications for obesity, as discussed later in this chapter. Tryptophan is relatively abundant in meat and fish, and it is thought to be the soporific substance in the time-honored glass of warm milk. *Alpha*-Lactalbumin, a milk whey protein, contains a higher content of tryptophan than does any other protein food source (7). Tryptophan supplements were available and then banned by the Food and Drug Administration (FDA) following an outbreak of the eosinophilia–myalgia syndrome (EMS) induced by contaminated batches of L-tryptophan from Japan. However, restrictions on sales were lifted after 2002 as the FDA stated that it could not necessarily conclude that the occurrences of EMS occurred from the content of L-tryptophan; thus, some high-quality supplements are now available (8). Experimentally induced tryptophan depletion has been shown to disrupt the pattern of the sleep electroencephalogram (9,10) and lead to irritability (11). There is also evidence that tryptophan loading is effective in improving mood and sleep in some adults with mood and sleep disturbances (12). When

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compared with controls, tryptophan-containing foods improved sleep indices, specifically an increase in total sleep time, sleep efficiency, and immobile time was noted. Less difficulty falling asleep, waking at night, and fragmented sleep were reported (13).

The ingestion of carbohydrate triggers an insulin release that facilitates the deposition of circulating amino acids into skeletal muscle. The effect is selective, causing the levels of branched-chain amino acids in circulation to fall by as much as 40%, while negligibly affecting levels of tryptophan (see Chapter 3). However, in the brain, the level of tryptophan is determined in part by its competition with other amino acids; the lower the level of other neutral amino acids presented to the blood–brain barrier, the greater the brain uptake of tryptophan. Since tryptophan hydroxylase, the rate-limiting enzyme of serotonin synthesis, is not saturated at physiological brain tryptophan concentrations, the greater the uptake of tryptophan, the more serotonin is produced (14). Elevations in serotonin enhance mood and promote sleepiness. High-carbohydrate, low-protein meals appear to elevate tryptophan levels (15), with an even greater serotonergic response with high-glycemic-index carbohydrates (16). High-carbohydrate meals have consistently been shown to shorten sleep onset times (17). The combination of such foods with a concentrated source of tryptophan may be particularly soporific. Tryptophan intake has been associated with decreased levels of depression, as well as increased sleep duration (18).

Dopamine

Dopamine, an important transmitter involved in reward and pleasure, is also influenced by diet (19). Studies have shown that dietary fat and sugar reduce dopamine receptor signaling, a high-fat diet alters dopamine reuptake, and the long-term consumption of a low-protein, high-carbohydrate diet decreases dopamine receptor density (20–22). These findings suggest that excessive intake of dietary fat and sugar initially increases levels of dopamine; however, over time, tolerance develops via reduction in signaling, reuptake, and receptor density leading to a reduction in the subjective reward.

The synthesis of catecholamines, including dopamine and norepinephrine, also varies with the availability of the precursor amino acid L-tyrosine. However, the rate of catecholamine synthesis appears to be less influenced by precursor levels than serotonin formation is affected by levels of tryptophan (23).

Acetylcholine

Choline is the precursor to the neurotransmitter acetylcholine, which plays a role in attention and arousal. Choline has been considered a required dietary nutrient since 1998, and experimental data suggest an appropriate intake in adults would be 1 to 2 g of choline chloride daily. This is of more relevance for patients who would benefit from the inclusion of choline in parenteral nutrition. Choline can be found in numerous dietary sources with higher content in foods of animal origin, including liver, eggs, fish, beef, pork, and chicken (24). Acetylcholine is of particular clinical relevance for Alzheimer’s disease and Myasthenia Gravis. In regard to Alzheimer’s disease, studies have identified a possible link between choline and Alzheimer’s disease and sleep disturbances; however, the exact mechanism is unclear and further studies are needed to explore this connection (25). Choline alphoscerate, in conjunction with the acetylcholinesterase inhibitor donepezil, has shown some promise in improving behavioral disturbances in Alzheimer’s diseaseas compared to donepezil alone (26).

Glutamate

The excitatory neurotransmitter glutamate is implicated in the energy balance regulation by the mediobasal hypothalamus. In a study looking at rat models, feeding is associated with rapid release of glutamate, with a greater release of glutamate by foods that stimulate obesity (27).

Diet and Sleep

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There are several micronutrients and macronutrients that contribute to sleep. L-Theanine, a nonprotein amino acid (*gamma*-glutamylethylamide) that occurs naturally in green tea leaves (*Camellia sinensis*), may play a role in sleep quality. In a randomized trial of objectively measured sleep quality in a population of 98 boys diagnosed with attention deficit hyperactivity disorder (ADHD), 400 mg of L-theanine daily was found to be safe and effective in improving the percentage of time in restful sleep, with fewer bouts of nocturnal activity (28). A more recent study in mice showed that a mixture of L-theanine and gamma-aminobutyric acid (GABA) was shown to decrease sleep onset time and increase total sleep duration (29). Vitamins also have a role in sleep. Vitamin B_{12} has been shown to contribute to the secretion of melatonin, a hormone that regulates sleep and wake cycles (30). The last step of the conversion of tryptophan to serotonin is dependent on vitamin B_6, and vitamin B_6 also has some influence on sleep as it was found to increase cortical arousal during rapid eye movement (REM) sleep and to increase the vividness of dreams (31). Vitamin B_3 (niacin) suppresses the activity of tryptophan 2,3-dioxygenase, a key enzyme in the conversion of tryptophan to niacin. Therefore, B_3 supplementation can reduce the “loss” of tryptophan to niacin versus to serotonin and melatonin (32).

The effects of macronutrient distribution on somnolence remain under investigation. Specifics of the most beneficial macronutrient intake are still unclear. However, one study has demonstrated that controlled eating is important. In this study, ad libitum eating over 3 days led to reduction in non-REM Stage 3 (N3) sleep and increased sleep onset time, demonstrating poorer sleep than when eating is controlled (33). The discovery of orexin (hypocretin), a hypothalamic peptide involved in both sleep/wakefulness and energy expenditure, has elucidated the interconnectedness of sleep and satiety (34). In a study of intragastric infusions in nine healthy adult subjects, Wells et al. (35) demonstrated the induction of sleepiness by infusion of lipid as compared with either sucrose or saline. In a crossover trial of 16 adults, somnolence was induced by both a high-fat and a high-carbohydrate test meal (36). In a study of 10 adults, Orr et al. (37) found that sleep latency was reduced by a solid meal, regardless of composition, compared with an isocaloric liquid meal or water. However, some evidence suggests that high-fat meals induce more somnolence, possibly related to the release of cholecystokinin (37). There is also evidence that a low-carbohydrate, high-fat diet decreases the amount of REM sleep, also possibly related to the release of cholecystokinin (38). More recent studies have focused on the effects of protein on sleep. In a study of higher-protein diets, there has been positive correlation between protein intake and sleep duration, quality, and pattern (39). Dietary protein intake supplies the body with the sleep-promoting amino acid tryptophan. Tryptophan is converted to 5-hydroxytryptophan (5-HTP) and then to serotonin, which is metabolized to melatonin; thus, signaling sleep onset (40). Reviews of most recent data have shown that individuals with good sleep (sleep duration >/= 7 hours; sleep onset time </=30 minutes; sleep efficiency >/= 85%) followed diets with higher energy intake from protein sources and lower intake from carbohydrates and fats (41). There may be considerable interindividual variability in susceptibility to postprandial somnolence (42). When a midday meal was compared to a fast in 21 healthy men, time to onset of sleep was comparable, but sleep duration was longer in the fed state (43). There is suggestive evidence that high-fat meals may induce a particular decline in postprandial alertness and concentration as compared with isocaloric meals higher in carbohydrate (44). A high-carbohydrate meal has been shown to counter the stimulatory effects of a bout of exercise (45). As such, a double-blinded, randomized, crossover trial of 10 men showed that a high-glycemic-index meal following an interval training session improved sleep onset time, sleep duration, and sleep efficiency (46). Although obstructive sleep apnea occurs in normal-weight individuals, it is more common in the individuals with

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obesity. While the sleep fragmentation and other sequelae of the syndrome may be ascribed in large measure to excess energy intake (47), evidence suggests that sleep deprivation leads to neuroendocrine dysregulation, resulting in increased hunger and weight gain, increasing the risk for metabolic syndrome (48).

Alcohol and caffeine ingestion can interfere with sleep, particularly in older adults (49,50). Low alcohol consumption may enhance sleep induction and deepen sleep initially, but this effect may reverse over the course of the night (51); higher alcohol intake and withdrawal from regular consumption are known to disrupt sleep patterns. Alcohol in breast milk alters the sleep–wake pattern and generally reduces the total duration of sleep in infants (52–54). See Chapter 41 for more about the potential health effects of caffeine.

In addition to diet's influence on sleep, disordered sleep can lead to changes in diet. Night-eating syndrome consists of insomnia, excessive food intake at night, and anorexia in the morning. It is classified in the *DSM-5* as "other specified feeding or eating disorder" (55). The condition has been shown to be associated with a blunted nocturnal rise in melatonin and leptin levels and elevated levels of plasma cortisol (56), likely impacting the cortisol stress response (57). Features of somnambulism and disordered eating may be concurrent (58), and treatment for both may be indicated. A serotonergic mechanism is hypothesized in which a decrease in serotonin availability disturbs circadian rhythms and decreases satiety, thus increasing evening food intake and eating through the night (59). A randomized control trial found significant symptomatic improvement and weight loss with SSRI treatment (60).

A study examining the relationship between sleep patterns and adiposity in young adult women showed that inconsistent sleep patterns and poor sleep efficiency are related to adiposity, leading the authors to conclude that consistent sleep patterns, including sufficient sleep, may be important in modifying risk of excess body fat in young adult women (61). A similar finding was also seen in a cross-sectional study examining sleep patterns and body composition in very old women (≥80 years), which showed an association between inconsistent sleep–wake patterns and increased fat mass (62). There is also evidence linking sleep deprivation to childhood obesity, with a meta-analysis demonstrating a stronger association between short sleep duration and obesity risk in children than in adults (63). Studies also show stronger and more consistent findings regarding sleep and weight status in younger children (64,65), with some evidence that boys with short sleep duration were at greater risk of being overweight than girls with short sleep duration (66,67). Studies in adolescents also have demonstrated a correlation between insufficient sleep and risk of obesity; however, the evidence suggesting a girl or boy prevalence in this population is not consistent (68,69).

Shift workers have been found to have increased cardiovascular risk factors compared to day workers (70); circadian rhythms in glucose tolerance and energy metabolism, leading to peaks in glucose and triacylglycerol at night, may be involved (71). There is also some evidence suggesting that the morning chronotype (individual circadian rhythm) is associated with a greater intake of calcium and vitamin B_6 versus the evening chronotype, which is associated with a greater energy intake from alcohol, fat, confections, and meat (72). In a study of night-shift workers, Paz and Berry found only modest differences in mood and performance when meal composition was varied. Mood and performance were optimized by meals containing a macronutrient distribution (55% carbohydrate, 18% protein, and 27% fat) closely matching prevailing nutritional guidelines, as compared with meals higher in either protein or carbohydrate (73).

Diet and Mood

There is evidence linking a healthy diet to a lower incidence of mental health issues. In a recent meta-

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analysis analyzing data from 24 independent cohorts, a healthy diet was associated with lower risk of depressive symptoms. This was independent of the type of diet, specifically noting a healthy/prudent diet or a Mediterranean diet (74). Another analysis noted a diet with high intake of fruits, vegetables, whole grain, fish, olive oil, low-fat dairy, and antioxidants and low intake of animal foods was associated with decreased risk of depression (75). In France, a prospective study following a cohort of men and women found that adherence to a Mediterranean diet was associated with a lower risk of depressive symptoms in men; however, the same was not seen in women (76).There is a tendency of patients to use carbohydrate and fat to influence serotonin production and thus mood. In a comparison of 24 stress-prone to 24 control subjects, Markus et al. (77) demonstrated that a high-carbohydrate meal, leading to increased brain serotonin levels, mitigated the effects of induced stress in the predisposed subjects. In a randomized crossover trial comparing carbohydrate-craving subjects with obesity to matched controls, however, Toornvliet et al. (78) found no evidence of mood enhancement with high-carbohydrate meals. Recent analyses have shown no positive effects of carbohydrates on any aspect of mood; however, there were associations of higher levels of fatigue and less alertness seen shortly after ingestion as compared with placebo (79). These findings support opportunities to educate the public on dietary intake and its effects on mood and energy levels.

Another example is seen with seasonal affective disorder (SAD), which tends to result in a craving for carbohydrate. The condition is associated with elevated levels of tyrosine and impaired serotonin metabolism. Melatonin overproduction was initially implicated, but data refute it as the sole contributing factor (80–82). Sunlight exposure and concentrated light therapy constitute the most effective known treatments (83). Evidence for benefit of vitamin D supplementation in SAD is inconsistent (84,85), but it may be helpful in individuals at high risk for deficiency (86).

The intake of carbohydrates and fats to influence serotonin production is associated with weight gain and obesity (87). In a study of nine women with a history of food cravings, Gendall et al. (88) found that subjects who ate high-protein meals experienced a greater tendency to binge on carbohydrates than after consuming a high-carbohydrate or mixed meal. The authors suggest that sensory-specific satiety or a serotonergic mechanism might be involved. The use of SSRIs may be helpful in the management of obesity in select patients, particularly those with symptoms of depression and carbohydrate craving (89). The FDA approved the use of lorcaserin in 2012, a selective serotonin receptor agonist that acts as an appetite suppressant, for weight loss for adults with a body mass index of 27 or greater who have at least one weight-related health condition (90,92). However, due to concerns for increased cancer risks, lorcaserin was removed from the market in the United States in 2020 (93). Chocolate is associated with a stronger pleasure response than most other foods (see Chapter 39). Chocolate craving in some women, particularly associated with menstrual cycle variations (see Chapter 28), is strong enough to have been labeled “addiction.” Although chocolate ingestion in self-labeled “chocolate addicts” is pleasurable, the guilt associated with ingestion obviates any genuine mood enhancement (94,95). While both serotonergic and dopaminergic systems have been implicated in the mechanism of chocolate craving, evidence suggests that this phenomenon is more often a result of emotional eating patterns than a substance-specific “addiction” (96). Similarly, there is an ongoing discussion as to what extent sugar more generally is an addiction (97,98). There is some evidence that it may be addictive for some individuals when consumed in a “binge-like” manner as it has neurochemical effects similar to those of drug intake, albeit in smaller magnitude for sugar (99). Sweetness versus sugar itself may be the inciting factor contributing to increased intake, and thus increased neurochemical and hormonal effects (100).

Popular diet books emphasize the restriction of dietary carbohydrates, and especially sugar, in efforts to improve weight control and overall health. However, Surwit et al. (101) demonstrated that with

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comparable caloric restriction, high- and low-sucrose diets for 6 weeks resulted in comparable degrees of weight loss in women with obesity, with no discernible differences in emotional affect between groups. Depression, hunger, and negative mood decreased in both groups, and vigilance and positive mood increased, suggesting that these benefits may result from weight loss per se. The widely popular ketogenic diet, a low-carbohydrate, high-fat diet known for its effectiveness as a treatment for epilepsy, has demonstrated antidepressant and mood-stabilizing effects; however, this data are inconclusive, given limits clinical trials (102). In a recent randomized, crossover, controlled study, Iacovides et al. showed no effect on mood after 3 weeks of sustained nutritional ketosis on healthy subjects (103). Though findings are inconsistent, studies suggest that dietary approaches to stop hypertension (DASH), vegetable-based, glycemic load-based, ketogenic, and Paleo diets could improve mood as compared to other popular diets (104). However, restriction of all carbohydrates, as has been advocated by fad high-protein diet regimens, has been shown to increase fatigue and negatively impact mood in physically active individuals (105).

Several studies suggest a potential role for dietary fat and serum lipids in mood regulation; in particular, associations have been demonstrated between low consumption or serum levels of long-chain polyunsaturated fatty acids and depression (106), bipolar disorder (107), and risk of suicide (108). Wells et al. (109) found that converting subjects from a 41% fat-energy to a 25% fat-energy diet for a period of 1 month was associated with adverse changes in mood, including more anger/hostility. These effects were independent of any change in plasma cholesterol. Such effects are likely referable to indiscriminate reductions of fat intake that do not facilitate a balanced intake of fatty acid classes (see Chapters 2 and 45).

Pain perception has been shown to be attenuated in the fed as compared with the fasting state, with dietary fat apparently particularly effective at mitigating pain (110,111). The fasted, or energy-restricted state, however, has not produced consistently deleterious effects. A recent randomized clinical trial in calorie-restricted healthy adults as compared with controls showed positive effects on mood, reduced tension, and improved overall health with no negative effects noted (112). Recently, intermittent fasting has become a trendy plan for diet enthusiasts. A large cohort study of 1,422 subjects assigned to a period of intermittent fasting demonstrated an increase in emotional and physical well-being in over 90% of subjects (113). Deficiencies of B-complex vitamins are associated with neuropsychiatric disturbances, including delirium and psychosis. Nominal deficiencies may be involved in mood disturbance; low levels of folate and vitamin B_{12} have been observed in studies of depressed patients (114). Evidence of B vitamin deficiencies in the U.S. population has been increasing; nutrient-poor diets high in refined carbohydrate and processed sugar are particularly likely to induce such B vitamin deficiency states. The avoidance of such patterns, and compensation with a daily multivitamin, may confer benefit to mood in susceptible individuals (115).

Dietary Supplements for Sleep and Mood

Melatonin, a hormone produced by the pineal gland, is available exogenously as a dietary supplement with reported benefits for people with sleep disturbances. The recommended dosage is quite variable, ranging from 0.5 to 10 mg (116). A recent review found shortening of sleep onset time along with increases in sleep efficiency and duration with administration of melatonin in adults (117). Melatonin has also been shown to be beneficial in the pediatric population, though the primary focus on managing pediatric insomnia has continued to be good sleep hygiene (118). Children and adolescents with autism have been found to have significant improvement in sleep disturbances with melatonin in combination with cognitive behavioral therapy as well as with melatonin alone (116). Evidence has also shown

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efficacy with melatonin in treating secondary sleep disorders, those being disorders caused by other factors, such as shift work disorder (118,119). Melatonin also appears to be both safe and modestly effective in alleviating jet lag when crossing multiple time zones (120). Melatonin-receptor agonists, ramelteon and tasimelteon, have been approved for use in specific populations to address sleep disturbances. Ramelteon has been approved for use in insomnia with short-term studies showing improvement in severity of symptoms with no new safety concerns (121–123). Tasimelteon has shown to be a useful treatment for blind individuals with non-24-hour sleep–wake disorder (12).

Valerian is an herb traditionally used to make tea for treating insomnia (124). Apparently effective as a mild tranquilizer (125), valerenic acids and valepotriates are suspected to be the main sedating components. The mechanism of action is unknown; however, speculations on the increase of GABA activity have been investigated (126). The tea has a bitter and rather unpleasant taste. Valerian root extract is available; 150 to 300 mg approximately 30 minutes before bedtime is recommended. However, adverse reactions in the liver have been suggested between valerian and the antipsychotic haloperidol (127).

Magnesium, a GABA agonist, has been shown to improve insomnia in older people (128); some alternative medicine sources recommend 500 mg of magnesium taken 30 minutes before bedtime, or 250 mg of magnesium in conjunction with melatonin and zinc (129). Low intake of magnesium in the diet has also been shown to be associated with depression (130). Some traditional somnolents may exert only a placebo effect. In a double-blind, placebo-controlled study of lemongrass, a common ingredient in sleep-promoting herbal tea, no sedative-hypnotic effects were demonstrated (131).

Chamomile has been studied for management of anxiety and insomnia. Several formulations are available, including tablets, powders, gel caps, and teas. (132). Chamomile contains several compounds that may have therapeutic effects, with apigenin, a flavonoid acting as a GABA modulator, being suspected to create the primary soporific effect (133). A recent systematic review and meta-analysis has shown efficacy and safety of chamomile for sleep and generalized anxiety, though larger studies and trials are needed (134).

Zinc supplementation has also been studied, though numbers are limited. Supplementation in individuals with suboptimal zinc levels showed improvement in global sleep quality scores (135), while also showing improvement in sleep onset latency (136).

The herb St. John’s wort, or hypericum, has been advocated for use in depression. St. John’s wort has been shown in multiple randomized controlled trials to have efficacy equivalent to conventional antidepressants in the treatment of mild to moderate depression (137–139); studies of patients with severe depression have generated conflicting results. The active ingredient, hypericum, appears to inhibit the reuptake of serotonin, dopamine, and norepinephrine (140). The suggested daily intake is approximately 900 mg, divided into either two or three doses (141). Clinical trial evidence remains inconclusive (142). St. John’s wort is also a potent inducer of enzymes that metabolize other medications, and comedication can result in decreased plasma concentrations of drugs including amitriptyline, cyclosporine, digoxin, indinavir, irinotecan, warfarin, phenprocoumon, alprazolam, dextromethorphan, simvastatin, and oral contraceptives. This effect correlates strongly with the amount of hyperforin found in the product with doses <1 mg being less likely to be associated with major drug interactions (143,144). However, a Cochrane review suggests that the hypericum extracts tested in the included trials are superior to placebo in patients with major depression, are similarly effective as standard antidepressants, and have fewer side effects than standard antidepressants (145). A beneficial role of *omega*-3 fatty acids in affective disorders is suggested with some evidence supporting beneficial effects on depression (146–150). A meta-analysis did show strong evidence that bipolar depressive symptoms may be improved by

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adjunctive use of *omega*-3, though the evidence does not support its adjunctive use in attenuating mania (151). The probability of beneficial effects, the general low risk, and the likely benefits to general health (see Chapter 45) make supplementation as a matter of routine reasonable, if not advisable.

Antidepressant effects have also been attributed to vitamin B_6. A review of the pertinent literature demonstrates an association with lower depression and anxiety risk in women; however, the same is not seen in men (156).

Nutrigenomics

Folate metabolism genetic polymorphisms have been studied in regard to age of onset, occurrence, and response to treatment for depression. One study looking at late-life depression found that there were no significant genetic differences that predicted age of onset of depression or occurrence of depression, but there is a genotype (the MTRR A66G) that does predict response to SSRI antidepressants (152). Given mixed results on whether folic acid and B_{12} supplementation potentiate antidepressant medication (153), further studies on the nutrigenomics in regard to folate metabolism and depression will be helpful to determine whether the effects are in fact limited to certain clinical populations.

CLINICAL HIGHLIGHTS

Diet and nutrients influence mood, somnolence, and wakefulness in a variety of ways, many of which are still poorly understood. The role of food intake on levels of serotonin in the brain has emerged as a mechanism of particular importance. What is known of this pathway suggests that a diet rich in complex carbohydrates, consistent with prevailing recommendations, is appropriate to maintain appropriate serotonin levels. Perturbations in serotonin metabolism may account for both affective and eating disorders, and in such situations, pharmacotherapy with SSRIs may be indicated.

Contrary to the view advanced by many popular diet books, high levels of dietary protein have not been shown to enhance energy levels or sense of well-being. Meals high in fat are associated with particularly pronounced postprandial somnolence. Animal research suggests that extreme dietary fat restriction, however, resulting in reduced plasma lipoprotein levels, may favor aggressiveness. Such findings would support the macronutrient distribution advocated throughout the text, with approximately 55% to 60% of calories from predominantly complex carbohydrate, 20% to 25% from fat, and 15% to 20% from protein (see Chapter 45).

Sleep adequate in quantity and quality is supported by the avoidance of excess caffeine or alcohol in the diet. Sleep apnea is often consequent to obesity; therefore, avoidance of excess energy consumption and overweight is important in efforts to ensure normal sleep patterns. A large midday meal induces postprandial somnolence independent of meal composition, whereas smaller snacks throughout the day actually tend to promote alertness. Thus, the food intake pattern conducive to daytime alertness is that supported by other lines of evidence (see Chapters 5, 6, and 38, indicating the value of distributing calories in small meals). At the same time, some conflicting evidence does show that lower tendency for eating during conventional eating hours and greater snack dominance over meals are related to higher intakes of fat and sweets for energy and lower intakes of fruits and vegetables; thus, there are clearly multiple factors at play (154).

Finally, mood may be influenced by intense cravings for food, sharing characteristics of addiction; chocolate appears to be the most important example. Chocolate craving varies with the phase of the menstrual cycle, as discussed in Chapters 28 and 39. In general, control of such cravings is facilitated by consistent, moderate consumption of the craved food in a fed rather than fasted state.

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Various micronutrients may influence affect, but overall, the literature is limited. There is strongest support for *omega*-3 fatty acids, specifically eicosapentaenoic acid and docosahexaenoic acid (155), also (see Chapter 2) at a dose of 1 to 2 g daily as fish oil. However, there is also new support linking vegetarian diets, with reduced intake of arachidonic acid, as well as eicosapentaenoic acid and docosahexaenoic acid, with improved mood (156). Nonetheless, because supplementation is generally advisable on general principles, this recommendation may be made routinely, barring contraindications.

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Chapter 35

Diet and Cognitive Function

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INTRODUCTION

Healthy cognitive function involves the ability to effectively think, learn, and remember, as well as interpret and respond to emotions and physical stimuli. Dementia is a condition of progressive cognitive decline characterized by impaired memory, thinking, judgment, and speaking ability that can eventually destroy functional independence and the capacity to carry out activities of daily living. Rather than being a disease in itself, dementia is a syndrome with many different and sometimes overlapping causes. To date, the most prevalent form of dementia is Alzheimer's disease (AD), followed by vascular dementia, frontotemporal dementia, Parkinson's disease dementia, and Lewy body dementia.

Decades of research on the connection between dietary intake and the prevention of cognitive impairment in older adults have yielded promising but inconclusive results. Epidemiological and animal studies demonstrate that individual nutrients confer a neuroprotective effect on the aging brain, but the scientific evidence so far does not support definitive recommendations of specific foods we should be eating (1). Moreover, other lifestyle and physiological factors have been associated with cognitive function, such as those related to sleep, stress level, and hormonal balance which are in turn influenced to some extent by the nutrient composition and quality of one's diet. From this standpoint, dietary intake exerts both a direct and an indirect impact on cognition.

While rigorous clinical trials are underway, the most current evidence supporting dietary approaches to cognitive health is mostly based on observational studies, in addition to trials using animal models that help explain the biological mechanisms linking nutrients to cell function and neurodegenerative disease (1).

Emerging evidence suggests that certain healthy eating patterns, most prominently the Mediterranean diet, the DASH (Dietary Approaches to Stop Hypertension) diet, and the MIND (Mediterranean–DASH Intervention for Neurodegenerative Delay) diet are associated with positive cognitive outcomes (1). While research has shown that there can be multiple factors leading to dementia, such as education level, socioeconomic status, and genetics (2), scientists are gaining a better understanding of how dietary patterns and specific chemical constituents of foods influence the prevention of cognitive decline and its progression. Some of the nutrients and plant-based compounds that have shown the most potential for maintaining cognitive health include antioxidants, B vitamins, omega-3 fatty acids, carotenoids, and polyphenols, while other nutrients and biochemicals such as iron, omega-6 fatty acids, saturated fats, and high levels of homocysteine in the blood have been associated with negative cognitive outcomes. The following provides an overview describing to what extent diet may influence this area of health and aging.

OVERVIEW

Diet

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The human brain is highly susceptible to various internal and external insults, including viral and bacterial infections, inflammatory cells, pro-inflammatory cytokines, and reactive oxygen species (ROS). The blood–brain barrier (BBB) consists of a layer of endothelial cells that is mostly impermeable and protects the brain by tightly regulating the movement of molecules between the brain and blood. However, despite the presence of this protective neurovascular entity, inflammation, oxidative stress, hypertension, stroke, human immunodeficiency virus (HIV), lipids, smoking, alcohol intake, mental stress, and lowered cerebral blood flow may heighten its permeability, leading to a weakening of the barrier and eventually to neurodegeneration. While the underlying molecular mechanisms are not fully understood, studies have shown that oxidative stress is positively associated with impaired cognitive function due to the production of harmful by-products that compromise cell function and damage deoxyribonucleic acid (DNA) (3). The brain is particularly vulnerable to damage by free radicals because of its relatively low antioxidant content and high oxygen consumption rate (4).

Studies report a strong association between dementia risk, including AD, and blood levels of antioxidants. Research on mice suggests that vitamins A, E, and C may protect the BBB (3), and bioactive compounds, particularly flavonoids and carotenoids, are also protective (5). One prospective study found that the combined daily use of 400 IU vitamin E with 500 mg vitamin C was associated with the reduction of both prevalence and incidence of AD (6). Another population-based prospective cohort study also found a modest decrease in risk of dementia with vitamin E supplementation (7), while a 15-year cohort study indicated that vitamin E supplementation in patients with AD extended survival (8). However, subsequent randomized clinical trials have not found convincing evidence that vitamin E supplementation improves cognitive outcomes in older adults (9–12).

There are many preclinical trials involving foods high in antioxidants, such as fruits, nuts, and vegetables, which have identified the potential benefits of phytochemicals in the prevention or delay of brain aging. The presence of bioactive compounds in foods such as green leafy and cruciferous vegetables, legumes, beets, mushrooms, walnuts, grapes, and blueberries may impact gene expression, cellular metabolism, and cellular signaling, thereby counteracting the effects of oxidative stress and inflammation. Epidemiological studies of fruit and vegetable intake have found a positive correlation with their consumption and cognitive status (13).

Though vitamins E and C have garnered much attention from scientific investigators, prospective studies have shown mixed results. Vitamin E serves many biological functions, one of which is as a scavenger of free radicals—leading to an interest in the use of vitamin E supplements to treat mild cognitive impairment (MCI) and AD. A recent Cochrane Review found little evidence for the efficacy of supplementary vitamin E (alpha-tocopherol) in the treatment of AD or functional decline (14).

Vitamin C (ascorbic acid) is believed to have a role in mitigating specific factors linked to AD, because of its ability to scavenge for ROS and suppress β amyloids (Aβs, proteins that aggregate in the brain to form plaque and believed to be one of the major factors in the pathogenesis of AD). Researchers have observed that the ascorbic acid levels in plasma are decreased in both AD and MCI patients, and an association between cognitive impairment and low antioxidant status in general. It remains unclear as to whether oxidative stress associated with the disease is responsible for the reduction of antioxidants, or whether the low antioxidants contribute to the progression of the disease (15).

Clinical studies on ascorbic acid have shown inconsistent results in part because of insufficient standardization between single nutrient consumption and use of multivitamins. Ascorbic acid supplementation has shown a beneficial effect when a nutritional deficit is corrected or deficiency is

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prevented, but it remains unknown what levels are needed to beneficially modify brain aging. Randomized clinical trials have not been able to demonstrate any association between ascorbic acid activity and a delay in AD neurodegeneration (15).

Vitamin D_3 has also been looked at for potential antioxidant and neuroprotective activity. Researchers found that when they induced dementia in rats with intracerebroventricular injections of streptozotocin (a compound that produces effects mimicking molecular and pathological characteristics of AD), the group that was pretreated with vitamin D demonstrated significantly improved spatial learning and memory function. The same was not true for those that were given vitamin D after the injection, suggesting that vitamin D has a possible prophylactic impact but a not therapeutic one for disease that is already present (16).

Grimm et al. have reported that there is a strong link between fat-soluble vitamins and AD, given that enhanced serum or plasma levels of vitamins A, D, E, and K have been associated with increased cognitive function. Deficiency results in increased cerebral Aβ levels and weakened cognitive performance in animal models, while supplementation with these micronutrients appears to diminish the amount of Aβ plaque. However, further large trials are needed to analyze the impact of the different micronutrients on the molecular mechanisms that underlie the pathogenesis of the disease (17).

Moreover, difficulties in assessing the relationship between antioxidants and cognitive impairment include the possibility that cognitive impairment alters dietary intake (18), as well as the inherent difficulty in obtaining accurate dietary intake data from cognitively impaired individuals. In addition, many of the cross-sectional studies demonstrating positive associations between nutrient intake and cognitive function use food-frequency questionnaires, which only measure intake of whole foods, to estimate intake of specific micronutrients.

There is a growing body of evidence that suggests hypertension, particularly if it emerges during midlife, is a leading cause of age-related cognitive impairment. At the same time, a steep decline in blood pressure from middle life to late life is also associated with a higher risk of dementia. Hypertension is implicated in cerebral atrophy, white matter microstructural damage, and cerebral small vessel disease with evidence suggesting that its damaging neurological effects may be cumulative. Few longitudinal studies have assessed blood pressure or have retrospectively determined how hypertension throughout life relates to cognitive function. These types of studies are important for a better understanding of the relationship between blood pressure and neural function; therefore, specific recommendations for clinical antihypertensive therapies to be used as an intervention in cognitive decline remain elusive (19,20).

Cardiovascular risk factors and cognitive dysfunction share atherosclerosis-related complications. A meta-analysis of statin use found no short-term effects on cognition, but the short duration of these studies may have been a significant limitation. A much longer, cross-sectional observational study involving 4,095 participants who answered surveys on cardiovascular risk factors in 1997 to 1998, 2001 to 2003, and 2003 to 2006 (the third survey included questions on cognitive function) also found no association between statin use and problems with cognition (21).

Studies have also found a strong association between AD and diabetes (see Chapter 6), where risk of AD is approximately doubled in people with diabetes (22,23). This relationship is even stronger in people who have the APOE epsilon-4 gene (24). It is thought that insulin signaling plays a key role in the health of neurons, including the development of neurotransmitters, memory formation, and, importantly, regulation of the phosphorylation of tau proteins (believed to be a causative factor in the pathogenesis of AD) (25,26). Disruption of insulin signaling in the brain seen in patients with AD mimics peripheral disruption of insulin signaling found in diabetes (25), and some have proposed referring to AD as “type 3 diabetes” (27). Some older adults with type 2 diabetes but who do not have dementia have impairments in

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brain function and cognition as evidenced by neuropathology and neuroimaging studies that show cerebral atrophy and subclinical infarction in these patients. Many individuals with MCI eventually develop dementia, and the simultaneous presence of diabetes may increase the risk. Moreover, higher levels of glycated hemoglobin, an indicator of chronic hyperglycemia, are associated with poorer cognition in diabetic patients. These effects can be attributed to microvascular changes, oxidative stress, and the accumulation of advanced glycation end products.

Interestingly, while there is a very strong correlation between levels of postprandial hyperglycemia and the risk of dementia, there is also a link between severe hypoglycemia and dementia risk as well (28). Surprisingly, better glycemic control does not appear to result in better cognitive outcomes. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) follow-up study found that better glycemic control did indeed result in less brain atrophy; however, it had no impact on changes in cognitive function (28).

Evaluating whether antidiabetic medications attenuate risk for dementia in patients with type 2 diabetes is complicated by the fact that there are multiple approaches to treatment. In addition to recommendations involving diet and physical activity, treatment of type 2 diabetes may involve several drug classes. Observational studies have shown mixed findings, but a large body of literature suggests that antidiabetic therapies may potentially help with dementia, particularly because type 2 diabetes and AD appear to share abnormalities in insulin signaling, mitochondrial dysfunction, abnormal energy homeostasis, and neuroinflammation. Promising effects of antidiabetic medications have been observed in relatively small trials, but much larger studies are needed in this area (29).

The evidence linking cigarette smoking to cognitive decline in either men or women have been mixed (30,31). However, more recent studies indicate that former and/or active smoking is related to a significantly increased risk for AD and has been associated with the disease's neuropathology in preclinical models and humans. Smoking-related cerebral oxidative stress is viewed as a possible mechanism underlying increased AD risk (32).

There are reports of a potential beneficial effect of moderate alcohol intake, especially wine, on cognitive function (33). One study that followed 121 patients with MCI for 3.5 years found that those with moderate daily wine intake (approximately 15 g of alcohol) had a significantly lower rate of progression to dementia than those who did not drink alcohol (Hazard ratio [HR], 0.15; 95% cognitive impairment [CI], 0.03–0.77) (34,35), with no additional protection apparent with more than one drink per day. Another study followed women for over 34 years, tracking alcohol intake and dementia incidence, and found that wine was associated with a decreased risk of dementia, whereas other alcoholic beverages were associated with unchanged or even increased risk. These differences may be attributed in part to components in red wine other than ethanol (36). Indeed, high alcohol consumption's link to an increase in dementia risk has been evidenced by postmortem reduction in brain volume and signs of brain damage observed through MRI scans. Past research on low-to-moderate alcohol consumption on dementia risk has yielded mixed findings, most likely confounded by the impact alcohol can have on other organs as well as other variables such as gender, body weight, acetaldehyde dehydrogenase type, and susceptibility. Different dosage definitions, the age of the participants, risk stratifications, lengths of assessment intervals, and lengths of studies can lead to different outcomes, and therefore no recommendations can be made without further study (37).

Numerous studies have explored specific dietary components and patterns on age-associated cognitive decline, with evidence pointing to the idea that it is the combination of foods and nutrients that has a positive synergistic effect (38). However, investigations of dietary patterns in order to find one that significantly prevents dementia have shown inconsistent results, but epidemiological and animal studies have laid the foundation on which to explore the neuroprotective effects of individual nutrients, such as

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vitamin E, the B vitamins, and the n-3 fatty acid DHA (docosahexaenoic acid). There are also data, though more limited, on the neuroprotective benefits of monounsaturated fat, carotenoids, polyphenols, and vitamin D. Diets high in saturated and trans fats have been shown to increase cognitive decline, and the excessive intake of iron, as well as synthetic folate or folic acid by individuals with low vitamin B_{12} status, is also implicated in having harmful effects on cognitive status (1).

A few studies have investigated the long-term impact of overall dietary patterns. One study involved assigning a Western diet or a "healthy" dietary pattern to 45- to 60-year-olds. After a 13-year follow-up, researchers found that following a healthy diet in midlife that provides micronutrients, fiber, and antioxidants while regulating intake may promote healthy aging (remaining free of chronic disease and having good physical and cognitive functioning) (39).

In a randomized clinical trial, 447 healthy volunteers at high risk for cardiovascular disease were enrolled and randomly assigned for about 6 years to one of three diets: a Mediterranean diet (characterized by high consumption of fruits, vegetables, legumes, and fish and moderate consumption of alcohol) supplemented with extra virgin olive oil (1 L per week), a Mediterranean diet with mixed nuts, or a controlled diet (reduced dietary fat). The Mediterranean diets that were supplemented with olive oil or nuts were associated with improved composite measures of cognitive function (40).

Similar to the Mediterranean diet, the DASH diet also specifies a high consumption of plant-based foods and additionally limits the intake of saturated fats, total fat, cholesterol, as well as sodium, and has been shown to be a promising dietary pattern for cognitive health, even though it was developed to address cardiovascular risk factors. The MIND dietary pattern is a combination of the Mediterranean diet and the DASH diet and is based on dietary components that are neuroprotective. It also calls for the consumption of berries and green leafy vegetables (41).

A systematic review indicates that higher adherence to the Mediterranean, DASH, or MIND diets is associated with less cognitive decline and a lower risk of AD (the evidence for an association with dementia was inconsistent), as demonstrated by 10 out of 14 cross-sectional studies, 1 case-control study, 21 out of 33 longitudinal studies, and 4 out of 6 intervention studies. The MIND diet may be more protective against cognitive decline and AD than the Mediterranean and DASH diets alone, according to observational studies, but more evidence is needed to make a firm conclusion (41).

There is evidence that high intake of linoleic acid (polyunsaturated, n-6) may accelerate cognitive decline, whereas fish consumption and consequent n-3 polyunsaturated fat intake may be protective (42–44). One randomized controlled trial (RCT), which assigned patients with AD to a daily intake of 1.7 g DHA and 0.6 g of eicosapentaenoic acid (EPA) or a placebo for 6 months, found a significant reduction in cognitive decline rate among a subgroup of patients with milder dementia (Mini-Mental State Exam >27 out of 30 possible points) but no significant benefit in patients with more advanced dementia (45). A prospective study of elderly participants in the Chicago Health and Aging Project found that individuals who consumed fish weekly had a 10% to 13% slower rate of cognitive decline over 6 years of follow-up compared to those who consumed fish less than once per week. Notably, this observed effect became less significant when adjusting for intake of other types of fat, indicating a possibility that it was not the fish itself but rather the reduced saturated-fat diet of regular fish eaters that made the difference (46). However, follow-up analysis on 899 men and women in the Framingham Heart Study did find a significant inverse relationship between plasma DHA levels and development of dementia, with a relative risk of 0.53 of developing all-cause dementia among subjects in the highest quartile of baseline plasma DHA levels (95% CI, 0.29–0.97) (47); the authors suggest that DHA, found in concentrated amounts in brain tissue, may play a specific role in cognitive function and the development of dementia (48).

Other studies have not found any significant benefit in n-3 supplementation on the cognitive function in

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healthy elderly adults (49). The authors comment that supplementation of n-3 fatty acids is generally well tolerated and perhaps longer trials are needed to discern benefit. An 18-month trial of DHA supplementation in 295 patients with mild-moderate AD found no benefit when compared to placebo (50). In a more recent systematic review and meta-analysis of RCTs, researchers investigated the effects of higher versus lower n-3, n-6, or total polyunsaturated fats and outcomes related to new neurocognitive illness, newly impaired cognition, and/or continuous measures of cognition. Looking at adults participating in studies with a duration ≥24 weeks (38 RCTs, 49,757 participants), the authors found no difference in effects by dose, duration, intervention type, or replacement. In addition, the effects of increasing α-linolenic acid, n-6, or total PUFA were unclear. Long-chain n-3 supplements do not protect older adults from cognitive decline (51). Researchers evaluated the association between intakes of unsaturated fatty acids at midlife and cognitive performance 13 years later. A global cognitive score was calculated as the sum of T-scores of the six tests. In multivariable models, total monounsaturated fatty acid (MUFAs) total polyunsaturated fatty acid (PUFAs) and n-6 PUFAs were positively associated with overall cognitive functioning, while n-3 PUFA intakes showed positive associations only among participants who received a supplement (39).

Associations have been reported between caloric restriction in the context of intentional weight loss and deficits in cognitive function. Several studies have found that individuals on a severely calorie-restricted weight-loss plan demonstrate deficits in memory, attention, processing speed, and concentration (52,53). However, the data of RCTs found no clear evidence of this (54,55), and there is increasing speculation that deficits in recall and task planning among dieters may be associated with preoccupation with dieting and body image rather than calorie restriction (53,56).

Conversely, several cohort studies have revealed a significant positive association between total calorie intake and cognitive decline (57,58). Caloric restriction has been shown in animal models to increase life span and decrease inflammatory processes. Current research is well on its way to elucidating the mechanism for these effects (see Chapter 31). This phenomenon is thought to occur in part via decreased oxidative damage. Researchers have therefore sought to examine whether total caloric intake might be involved in the development of dementia, in particular AD. One cohort study that followed 980 elderly, nondemented individuals found that those falling into the highest quartile of total caloric intake had an increased risk of developing AD over the 4 years of follow-up compared to individuals in the lowest quartile (HR, 1.5; 95% CI, 1.0–2.2); moreover, this association was significantly more pronounced among the subgroup of individuals with the apolipoprotein E4 allele (HR, 2.3; 95% CI, 1.1–4.7), a known predictor for AD (59). It has recently been determined that SIRT1, a key regulatory protein in producing the effects observed in caloric restriction, may have direct actions on Aβ accumulation (60).

In examining the association between calorie intake and cognitive function in community-dwelling older adults, researchers took a look at population data from the Korean Frailty and Aging Cohort Study, and selected 543 subjects, aged 70 to 84 years, who answered nutritional surveys about their daily calorie intake, using the 24-hour dietary recall. Neuropsychological tests evaluated their cognitive characteristics. Subjects with cognitive impairment mainly showed memory loss. After adjusting for confounding factors, respondents who consumed less than the recommended amount were observed to be more susceptible to cognitive impairment compared to those who had met recommendations (adjusted odds ratio [OR], 7.70; 95% CI, 1.01–58.45). The lower the calorie intake than the recommended level, the higher the odds ratio of cognitive impairment, leading the authors to suggest that an adequate calorie intake may protect against cognitive decline (61).

Researchers have also taken a look at the possible relationship between obesity (and its associated

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anthropometric measurements) and cognitive impairment. Increasing age coupled with the negative metabolic consequences of obesity, such as type 2 diabetes, is a factor likely to contribute to neurodegenerative pathologies and incidence of dementia. In addition, stress is identified as a potential risk factor for promoting abdominal obesity and thereby contributing to cognitive dysfunction. However, obesity may also confer potential protective effects against cognitive decline in older adults (62).

There is fairly consistent evidence that iron-deficiency anemia, the most common anemia in the United States, is associated with cognitive impairment (see Chapter 13). In a study of 14 obese women, Kretsch et al. (63) demonstrated that severe caloric restriction for 15 weeks resulted in signs of iron deficiency despite supplementation. A placebo-controlled study on reproductive-age women found that subjects with adequate iron levels at baseline performed better and faster on cognitive tasks than those with baseline iron deficiency, and that treatment of iron-deficient subjects restored cognitive performance significantly. Furthermore, the investigators found that increased serum ferritin saturation was related to a five- to seven-fold improvement in cognitive performance, and increased hemoglobin was related to enhanced speed of task completion (64).

High body iron status has also been shown to be associated with adverse health outcomes, including cognitive function. A study of Chinese adults tested the effect of iron intake and Body Mass Index (BMI) on cognition. Researchers used data from the China Health and Nutrition Survey (n = 4,852; age ≥55 y) from 1991 to 2006. Of the participants, 3,302 had completed cognitive screening tests in ≥2 surveys. Cognitive function was assessed in 1997, 2000, 2004, and 2006, and dietary iron intake was obtained from a 3-day food record. Results showed that high iron intake was associated with poor cognition, and was stronger among those with a high BMI compared to those with a low BMI. Among the participants with a BMI (kg/m^2) >24, across quartiles of iron intake the ORs (95% CIs) for poor cognitive function were 1.00, 1.27 (0.91, 1.78), 1.41 (0.97, 2.04), and 2.04 (1.38, 3.01) (65).

Elevated levels of homocysteine, considered a marker for folate and vitamin B_{12} deficiency, is a well-established risk factor for vascular disease (see Chapter 7); evidence from prospective trials points to hyperhomocysteinemia as a strong, independent risk factor for the development of dementia and AD as well (66,67). Furthermore, elevated plasma homocysteine levels have been correlated with cerebral white matter changes in patients with AD, leading to speculation of a direct pathogenic mechanism of homocysteine (68). Nevertheless, data from recent RCTs examining the potential cognitive benefits of folic acid or vitamin B_{12} supplementation have not shown a benefit in improving cognitive function or slowing decline in patients with AD or patients with normal cognition (69–72), but some trials involving high-risk subjects, which have taken into account baseline B vitamin status, showed a slowing of cognitive decline and of atrophy in critical brain regions (73).

Epidemiological studies have suggested a link between hormone changes at menopause and the development of dementia (74), indicating the potential benefit of hormone replacement therapy (HRT) (75); however, data from the Women's Health Initiative Memory Study refuted this hypothesis (76), and estrogen replacement is not currently recommended for prevention of dementia in postmenopausal women (77,78). Another review concluded that different hormone replacement therapies overall had no major impact on cognition outcomes (79), but in a nationwide case-control study conducted in Finland, researchers found a small increase in absolute risk for AD. Postmenopausal women (n = 84 739) in Finland who, between 1999 and 2013, received a diagnosis of AD from a neurologist or geriatrician, and who were identified from a national drug register, were matched by age to control women without a diagnosis (n = 84 739). After analyzing data on hormone therapy use, results indicated it was associated with a 9% to 17% increased risk of AD. The risk of the disease did not differ significantly between users

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of estradiol only (OR, 1.09, 95% confidence interval 1.05–1.14) and those of estrogen–progestogen (OR, 1.17; 95% CI, 1.13–1.21). The increased risk in users of estrogen–progestogen therapy were not related to different progestogens (norethisterone acetate, medroxyprogesterone acetate, or other progestogens); but in women who initiated HRT when they were younger than 60, the increases in risk were associated with hormone therapy exposure of over 10 years. The use of vaginal estradiol showed no risk (80).

The effects of dietary carbohydrate on tryptophan levels have been linked to both stress tolerance and short-term cognition (81), and early evidence suggests that cognitive performance can be enhanced with dietary carbohydrate ingestion (82,83). Responding to stress is associated with activity in the serotonergic systems in the brain. Low levels of serotonin are implicated in disorders of mood (see Chapter 34) and are associated with certain aspects of cognition as well. Dietary tryptophan serves as a precursor to serotonin; thus, serum tryptophan can influence the quantity of serotonin in the brain. Insulin facilitates the entry of large neutral amino acids, with the exception of tryptophan, into skeletal muscle. In response to carbohydrate ingestion and an insulin spike, the ratio of tryptophan to other large amino acids rises, theoretically raising the relative availability of tryptophan for use by the brain; ingestion of protein will tend to have the opposite effect (84). In one recent study, the intake of tryptophan-methionine peptides suppressed the production of inflammatory cytokines, activation of microglia, and infiltration of activated microglia around Aβ depositions in mice. The peptide intake reduced Aβ deposition in the cortex and hippocampus and then improved the object recognition memory. Taken together with previous studies, the current findings indicate that ingestion of tryptophan-related peptides or foods rich in tryptophan-related peptides represents a potential preventive approach for cognitive decline and dementia related to inflammation (85).

NUTRIENTS, NUTRICEUTICALS, AND FUNCTIONAL FOODS

Dehydroepiandrosterone

Dehydroepiandrosterone (DHEA) and its sulfate, DHEAS, have become extremely popular supplements among patients based on the theoretical possibility that they have neuroprotective effects. Although there is no evidence of adverse effects, there is also no convincing evidence to date that supplementation with DHEA or DHEAS can significantly attenuate cognitive decline in the elderly (86), or bolster cognitive performance and well-being in healthy older adults (87). Further long-term, high-quality trials are warranted before reliable clinical recommendations can be made.

Ginkgo biloba

Ginkgo biloba is extracted from the leaves of the ginkgo tree, which can live as long as 4,000 years (88). Leaf extract, which has been used as a tonic in China for more than 1,000 years, contains antioxidant flavonoids and terpenoids. One of the constituents of standard preparations, ginkgolide B, exerts an inhibitory effect on platelets (89) by antagonizing platelet-activating factor. This characteristic is responsible for the principal toxicity of the extract, an increased bleeding propensity, particularly in patients taking aspirin (89). Nevertheless, available evidence suggests that co-administration of ginkgo and aspirin does not constitute a safety risk (90).

Standardized *Ginkgo biloba* leaf extract has been shown to inhibit Aβ oligomers, a main compound implicated in the pathogenicity of AD, in both in vitro (91) and in vivo (92) studies. The benefits of *Ginkgo biloba* in dementia have been demonstrated with varying consistency in RCTs (93–95). Effects on brain function are supported by evidence from electroencephalography of a stimulatory effect of the

extract (93).

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Several recent trials have found no difference between ginkgo treatment and placebo, and although these results are not evident of null effect for all populations, the most recent Cochrane review concluded that *Ginkgo biloba* has uncertain effects on cognition and inconsistent effects on dementia (96). A large, multicenter RCT placebo-controlled study of *Ginkgo biloba* in adults over 75 years found no significant effect in reducing incidence of dementia or cognitive decline in individuals with normal or impaired cognition (97,98).

Ginseng

Ginseng is an adaptogenic herb that comes from the roots of plants in the Panax genus. Traditionally, it has been used as a stimulant, an aphrodisiac, or a "cure-all" supplement. In a review of five RCTs, ginseng was found to impart mild improvement in cognitive function and quality of life with no serious adverse effects (99). The most common side effects of ginseng include insomnia, headaches, nausea, diarrhea, and nose bleeds (100). The authors conclude that there is little convincing evidence of cognitive enhancement in either healthy patients or patients with dementia, and that better designed and larger clinical trials are needed (89).

Choline

Choline is an essential nutrient found in foods like meats, eggs, and cruciferous vegetables (101). Choline serves as a precursor for acetylcholine, an important neurotransmitter, which facilitates muscle control and memory, and it is also found in the phospholipid phosphatidylcholine (PC), a molecule found in cell membranes. The National Academy of Medicine recommends intake of 550 mg of choline for males and 425 mg of choline for females per day. Recommendations for pregnant and lactating females are increased to 450 and 550 mg, respectively (102). One egg contains 113 mg of choline, a pound of broccoli contains 182 mg, and a quart of 1% milk has 173 mg (103). One study from the National Health and Nutrition Examination Survey found that among postmenopausal women, a mere 2% consumed the recommended amount of choline (104).

Choline supplementation comes in the form of lecithin, a soy or egg derivative, as well as in phospholipid form, PC. A commonly endorsed supplement, PC is thought to promote synthesis and transmission of neurotransmitters (105). A review of PC found that 600 to 1,000 mg daily supplementation in patients with cognitive impairment or dementia was associated with a positive effect on memory in the short- and medium-term (106). A recent prospective trial in Finland yielded positive results on cognitive function with higher dietary intake of choline in middle-aged and older men who were followed for more than 21 years (107).

CLINICAL HIGHLIGHTS

Identifying effective dietary interventions to prevent and treat the most pervasive forms of dementia carries enormous relevance for public health. To date, there is not enough evidence based on large, prospective clinical studies that support specific dietary recommendations. However, observational data along with smaller clinical trials involving both human participants and animal models have provided strong clues as to where further research should be directed.

It does appear that diet and lifestyle interventions that support cardiovascular health may indeed protect cognitive function as well via the same physiological pathways affected by oxidative stress and systemic inflammation. The observed benefits of dietary patterns such as the Mediterranean, DASH, and MIND

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diets appear to lend credence to the theory that as certain combinations of food may reduce the risk of heart disease, stroke, and type 2 diabetes, in so doing they may protect against dementia as well. For now, the most promising dietary approach is a focus on fruits (including berries), vegetables (including leafy greens), nuts, whole grains, fish and other seafood, legumes, and olives oil, and limited red meat, saturated fats, and sweets. There are no current recommendations for alcohol use or intake of any dietary supplement specifically for the prevention and treatment of cognitive decline. Clinical trials are ongoing and may one day provide a clearer and more certain path to addressing the complexities surrounding brain health and aging.

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Chapter 36

Diet and Vision

Xuan Cao and and Anna Artymowicz

INTRODUCTION

Amino acids, vitamins, and minerals derived from dietary consumption are crucial for the normal functioning of cellular processes, especially important in the development and maintenance of the visual system. This presents an important question—how, if at all, can nutrition increase the chances of maintaining good vision throughout life?

This chapter presents the current understanding of the interaction between nutrition and vision, focusing on common diseases and processes that affect vision. The text is divided by nutritional categories—vitamins/minerals, pigments (namely lutein/zeaxanthin), and other supplements. The function of each nutrient in the visual system will be outlined along with a review of the literature regarding the clinical importance of these nutrients.

OVERVIEW

Despite scientific advancements and development of new therapies, processes causing vision loss continue to significantly contribute to decreased quality of life around the world. In 2017, a meta-analysis pooled global data about vision impairment from a staggering 3,983,541 participants around the world. Their data revealed the leading causes of blindness and impairment in distance vision globally: uncorrected refractive error, cataract, age-related macular degeneration (AMD), glaucoma, and diabetic retinopathy in decreasing order (A1). Although many other disease processes and genetic disorders can cause vision loss, this chapter will focus on the aforementioned processes.

Cataract

Second only to uncorrected refractive error (which can be corrected with prescription glasses), cataracts are the leading cause of blindness globally. A cataract is a clouding of the natural intraocular crystalline lens that focuses light that enters the eye. There are several types of cataract, including age-related, traumatic, and metabolic. Age-related cataract is the most common type. This chapter will focus mostly on the age-related cataract and how nutrition can affect its development.

Age-related cataracts develop slowly, often leading to a gradual decline in vision that cannot be corrected with glasses. The risk of cataract increases with each decade of life beginning around age 40. Data from the national institutes of health (NIH) reveals that in the United States, 70% of Caucasians, 61% of Hispanic Americans, and 53% African Americans will have cataracts by the age of 80 (A2).

The prevalence of cataracts is expected to increase with the aging baby-boomer population. From 2000 to 2010, for instance, the NIH reported that the number of cataract cases in the United States rose by 20%, up from 20.5 to 24.4 million.

Cataract surgery is the only definitive treatment for cataracts. It is among the most effective and commonly performed medical procedures, with over 3 million Americans electing to undergo cataract

surgery each year, and an overall success rate of 97% or higher when performed in appropriate settings.

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As detailed in the following "Cataract" subsection, the role of nutrition in the primary prevention of cataracts has not been firmly established, while reviews of nutritional supplements as anti-cataract therapies have produced mixed results (C12,C13).

Age-Related Macular Degeneration

AMD is a vision-threatening disorder of the retina affecting central vision. AMD has a racial predilection for those of European descent. In 2010, 2.5% of White American adults over 50 years old had AMD. By comparison, AMD affects 0.9 % each of African Americans, Hispanic Americans, and other races of the same age group (A3). The prevalence of AMD also increases sharply with age, affecting more than 14% of White Americans age 80 and older (A3).

Management of AMD depends on its severity. The less severe, nonexudative (dry) form of AMD is most often managed with observation, risk factor modification, and nutritional supplementation. The more severe, exudative (wet) form of AMD is managed with intravitreal injections blocking anti-vascular endothelial growth factor (anti-VEGF) or, less commonly, laser treatments.

Though genetic predisposition plays a major role in explaining which individuals become clinically affected, genetic, environmental, and nutritional processes all interact to affect the degenerative processes observed in AMD. In fact, exogenous supplementation of certain nutrients has become standard in the treatment of AMD.

Glaucoma

In the United States, primary open-angle glaucoma (POAG) is the most common form of glaucoma and is the leading cause of irreversible blindness in African Americans. Because the vision loss begins in the periphery, patients often do not notice symptoms until they have sustained advanced visual field loss. While many risk factors have been correlated with the development of POAG, including elevated intraocular pressure (IOP), advanced age, family history, African ancestry, myopia, and possibly presence of systemic diseases such as diabetes and hypertension, its precise etiology remains unclear and is currently an active focus of research (A17).

The mainstay of glaucoma treatment is the reduction of IOP. However, a report from Canada showed that one in every nine patients with glaucoma used complementary and alternative medicine in the treatment of their condition (A4.5). A considerable amount of research suggests that an individual's diet may have an effect on IOP, the incidence of glaucoma, and the progression of the disease (A4).

Diabetic Retinopathy

Diabetic retinopathy refers to retinal changes that occur in patients with diabetes mellitus. These changes affect the small blood vessels of the retina and can lead to vision loss.

The biggest factor in primary prevention of diabetic retinopathy is maintaining good control of glucose and blood pressure. As such, nutrition plays a crucial role in disease prevention. Each 1% reduction in the mean HbA1c (a measure of glucose levels in the blood) is associated with reductions in risk of up to 37% for microvascular complications such as diabetic retinopathy (A5). The topic of nutrition and diabetes mellitus is addressed in more detail in Chapter 6.

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Age-Related Cataracts

Antioxidants form part of normal cellular processes that neutralize free radicals, among their many functions. Examples of antioxidants include vitamins C and E, selenium, and carotenoids, such as β-carotene, lycopene, lutein, and zeaxanthin. Overall, there is some evidence that an antioxidant-rich diet is associated with delayed onset and incidence of cataracts, but results from trials using nutritional supplements to prevent cataract formation have had mixed results (A6).

Several correlational studies have found a significantly decreased incidence or severity of age-related cataracts in people with higher dietary intake of antioxidants (1,A8,A12) or with dietary supplementation with antioxidants (A9). The Australian Blue Mountain Study found multivitamin and vitamin A use was inversely associated with cataract formation, while vitamins E and C did not impact cataract formation (2). Multivitamin use was also noted to decrease the risk of cataracts by 27% in the Physician's Health Study (3). However, this study's reliability was limited by relying partially on self-reporting cataracts rather than on medical exams. Moreover, other studies have found that the use of high-dose (but not low-dose) single vitamin C or E supplements is associated with an *increased* risk of age-related cataracts (4,A13).

In order to explore more causal relationships, in 2004, a randomized control trial followed more than 1,000 people over four years and found no difference between cataract formation between those taking vitamin E and those taking placebo pills (5). The Age-Related Eye Disease Study followed over 4,500 people for more than 6 years to find no significant difference in age-related cataract formation in those taking a high-dose formulation of vitamin C, vitamin E, and β-carotene (A10) and those not taking the supplements. A large-scale randomized trial following over 5,400 women at high risk of cardiovascular disease for over seven years found that daily supplementation with a combination of folic acid, vitamin B_6, and vitamin B_{12} had no significant effect on age-related cataract formation (A11). The Roche European American Cataract Trial followed 445 patients over three to four years. Their study demonstrated a small, but significant, effect on cataract density in subjects taking a combination of β-carotene and vitamins C and E for 3 years (6), where supplementation produced a small deceleration in the progression of age-related cataract.

In summary, a healthy diet rich in antioxidants has been found in several studies to be associated with delayed formation of age-related cataracts. However randomized control studies fail to show a clear causative effect of exogenous supplementation of antioxidants on cataract formation. Moreover, high-dose supplementation of vitamins E (≥268 mg) and C (≥500 mg) has been found to be associated with accelerated cataract formation (C11).

On review of the existing literature in 1998, Brown et al. (7) suggest "reasonable" doses for daily supplementation that may offer benefit to eye health with little risk of toxicity. Suggested supplements include 1 mg of vitamin A, 500 to 1,000 mg of vitamin C, up to 300 mg of vitamin E, and 20 mg of zinc; other recommendations mirror the recommended dietary allowances.

Glaucoma

A review article by Ramdas et al. in 2018 reviewed 36 papers on the topic of vitamins and their effect on open-angle glaucoma (OAG) and pooled data from 940 OAG cases and 123,697 controls for their meta-analysis. It was found that dietary intake of vitamin A and C was inversely associated with the diagnosis of open-angle glaucoma (A7). Future randomized clinical trials would be required to verify the role of these vitamins in glaucoma. Although nutritional supplementation may be used as an auxiliary treatment in

persons with advanced glaucoma, a clear effect on the disease has not been shown to date.

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Age-Related Macular Degeneration

Many observational studies have explored the association between diet, nutrient intake, and AMD. For instance, the Rotterdam Study (A14) published in 2005 found that high dietary intake of *β*-carotene, vitamins C and E, and zinc was associated with a 35% reduction in incident AMD risk in older persons.

When it comes to randomized controlled clinical trials on the subject, the Age-Related Eye Disease Studies (AREDS/AREDS2) are the largest and most well known (8). Completed in 2006 and 2011, respectively, the AREDS and AREDS2 studies followed over 4,000 participants each to find that taking AREDS or AREDS2 supplements reduces the risk of progression from intermediate to advanced AMD by about 25% in those who have intermediate AMD in one eye and advanced AMD in the other eye (C1). The AREDS/AREDS2 supplements did not prevent AMD onset.

Both the AREDS/AREDS2 formulations contain 500 mg vitamin C, 400 IU vitamin E, 80 mg zinc, and 2 mg copper. Additionally, the AREDS formula includes *β*-carotene, while the AREDS2 formula replaces the *β*-carotene with 10 mg lutein and 2 mg zeaxanthin. Based on the AREDS/AREDS2 studies, patients with mild and intermediate AMD are often recommended to take AREDS or AREDS2 formulation on a daily basis (C2.5). However, smokers are advised to avoid the AREDS formulation, as the *β*-carotene included in the supplement was linked to an increased risk of lung cancer in smokers (C3), and instead opt for the AREDS2 formulation.

The Blue Mountain Eye Study, a large cohort study of vision and common eye diseases published in 2008 (A15), supported the AREDS finding of a beneficial effect of zinc in AMD progression. When 2,454 patients were re-examined 5 and 10 years after initial study enrollment, it was found that patients in the top decile of total zinc intake (≥15.8 mg/day) were significantly less likely to develop any AMD when compared with the remaining population.

The Blue Mountain Eye study also found that higher *β*-carotene intake was associated with an increased risk of neovascular AMD, even after adjusting for smoking status. The ARDS study found this association only in smokers, leading to the recommendation for smokers with AMD to take a formulation of the AREDS vitamins without *β*-carotene. In fact, the AREDS2 formulation of vitamins excludes *β*-carotene for this reason.

Carotenoids: Lutein, Zeaxanthin, and *β*-Carotene

This section outlines relevant studies regarding the carotenoids lutein, zeaxanthin, and *β*-carotene, all of which have a role in maintaining eye health.

Carotenoids are a diverse family of pigments, some with and some without provitamin A activity (see Appendix E). Both *β*-carotene and *α*-carotene are moderate antioxidants with provitamin A activity. Although essential for eye function as a component of rhodopsin, which is the visual pigment of rod cells in the retina, vitamin A does not appear to play a role in the development or prevention of macular degeneration.

Lutein, zeaxanthin, and *β*-carotene all share a similar chemical structure and belong to the xanthophyll class of compounds (C2).

Cataracts

It is postulated that in the eye, carotenoids neutralize the free radicals that contribute to cataract formation. Higher lutein and zeaxanthin intake has indeed been associated with slower/reduced cataract formation in several studies (9–14). For instance, higher lutein and zeaxanthin intake was associated with 22% risk

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reduction for cataract surgery in the Nurse's Health Study (10,15). Among a Finnish cohort of older men and women, high plasma lutein and zeaxanthin levels were associated with a decreased risk of developing nuclear cataracts (16). Another cross-sectional cohort study assessing antioxidant intake from vegetables in Congolese subjects with type 2 diabetes found a significant decrease in the rate of cataract development in those subjects stating they had high daily intakes of vegetables high in antioxidants (17). Further research on the possible beneficial effects of lutein on preventing eye disease is still warranted.

Age-Related Macular Degeneration

As discussed above (see the AMD section under "Vitamins and Minerals"), the AREDS2 trial includes lutein and zeaxanthin supplementation in its formula used clinically for preventing AMD progression. Higher lutein and zeaxanthin intake has been associated with slowed progression/better visual acuity in AMD in numerous studies (18–23,C9,C14). For example, a cross-sectional study of more than 3,500 patients in an Indian hospital found a significant risk reduction of AMD among those patients with high intakes of dietary lutein, zeaxanthin, and carotene (24). One randomized, double-masked, placebo-controlled trial found an improvement of retinal function in early age-related macular degeneration after lutein and zeaxanthin supplementation (21).

Lutein and zeaxanthin are carotenoids found abundantly in dark green vegetables. They are preferentially taken up by the macula and are key components of macular pigment (18,25). The unique presence of these nutrients in the center of the macula, their antioxidant properties, and blue light–filtering properties are all hypothesized to play a role in general eye health as well as preventing progression of AMD (26,27).

Nutrigenomics and Age-Related Macular Degeneration

Two genes (lipase C [LIPC] and lipoprotein lipase [LPL]) that metabolize high-density lipoprotein (HDL) molecules have been associated with AMD due to the HDL molecules' transport mechanism for the carotenoids lutein and zeaxanthin. Merle et al. (28) made this association in their population-based prospective study of 963 older people in Bordeaux, France. In their study, the TT genotype of the LIPC rs493258 variant was found to be associated with a decreased risk for developing AMD. The LPL genotype variant was associated with early AMD. A study by Seddon et al. (29) at Tufts Medical Center conferred an association of the TT genotype of the LIPC variant with a decreased risk of AMD, regardless of environmental and demographic factors. In a separate study, Lee et al. found that two promoter variants of LIPC were associated with advanced AMD in two independent Caucasian populations, which further confirms the role of LIPC as genetic risk factor for AMD (C5).

Other possible contributing polymorphisms for AMD include the rs754203 C allele in the CYP46A1 gene, which has been associated with a higher risk for developing exudative AMD according to research done by Fourgeux et al. (30), and the SNP rs2872060 in the IGF1 receptor gene. This SNP was found to be associated with the development of advanced AMD (31). Another large population-based study in Korea found associations between AMD and low serum (HDL) level, HBsAg serum positivity, history of ever smoking, and elevated systolic blood pressure (32).

Lutein/Zeaxanthin Summary

Supplements containing lutein and other carotenoids are now being heavily marketed in health food

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stores; however, there is some concern that lutein and zeaxanthin in supplement form may not provide the same benefit as that found naturally in foods such as leafy green vegetables, pistachio nuts, salmon, and other highly bioavailable sources like eggs (C9,C14,33).

In general, lutein and zeaxanthin are potent antioxidants, with many studies that support their favorable effects on eye health. While additional studies are necessary to elucidate the various other ways that these nutrients interact with the body, a diet rich in lutein and zeaxanthin can help maintain eye health and prevent disease.

Other Supplements/Nutritional Components

Ginkgo Biloba

Another popular nutriceutical/supplement of interest is the herb *Ginkgo biloba*, which belongs to the polyphenol class of compounds. It is thought to be a potent antioxidant and blood thinner (by means of decreasing blood viscosity and increasing erythrocyte deformation) (34). One small, non-generalizable study (N = 20) found a statistically significant improvement in visual acuity after 6 months of randomized treatment compared with placebo versus 80 mg twice-daily *Ginkgo biloba* supplementation (35). The herb has also been reported to increase ophthalmic artery blood flow, thus potentially decreasing, at least in theory, IOP in patients with glaucoma (36,C6). A retrospective study also showed that patients with normal-tension glaucoma who received 80 mg of *Gingko biloba* had decreased progression of their visual field damage compared to placebo (C4). While these results are encouraging, more research is needed to elucidate *Gingko*'s potential benefit in glaucoma as well as in other diseases. It is important, however, that supplementation with *Ginkgo biloba* is not without risk; there are many published papers relating adverse effects of *Ginkgo biloba* and interactions with conventional drugs (A16).

Bilberry

Bilberry fruit is also considered potentially beneficial in eye disease. Current literature has shown a protective role of bilberry extract in vitro and in animal studies. Further human trials will be necessary to elucidate its clinical benefits in humans (C7,C8).

Postmenopausal Estrogen and Age-Related Macular Degeneration

Postmenopausal estrogen replacement has been found to be associated with delayed progression and development of AMD, as has a higher intake of ω-3 fatty acid (18,37,38,C10). Edwards et al. found that both hormone replacement therapy (HRT) and oral contraceptives have protective associations in women with AMD, especially in the neovascular form (C10).

Fatty Acids and Age-Related Macular Degeneration

There is interest in the possible role of dietary supplementation with long-chain polyunsaturated fatty acids, especially of the n-3 class, in the development and protection of the macula (39–43). A large prospective cohort study by Cho et al. (44) found that frequent consumption of fish containing ω-3 fatty acids was associated with reduced risk of developing macular degeneration and high plasma total ω-3 fatty acid levels were also associated with a reduced risk for developing late AMD in the Alienor study in Bordeaux, France (45,46). As such, the evidence in support of dietary n-3 fatty acids is growing but is still inconclusive (40,47,48). Surprisingly, despite the low ω-3 fatty acid intake in the American diet, the prevalence of AMD among people in the United States aged 40 and older decreased by approximately 3% between the 1994–1998 and the 2005–2008 NHANES studies.

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Studies suggest that intake of high glycemic-index (GI) carbohydrates can increase the risk of AMD and cataract development (49–54), whereas intake of cereal fibers, breads, and grains decreased the risk of developing soft drusen (55). One study of over 2,300 twelve-year-old students in Sydney, Australia, showed a significant decrease in the retinal vessel width among kids who drank one or more sodas (a very high-GI drink) a day in comparison to those who did not drink soda (56), indicating direct damage to retinal blood vessels from beverages of high GI. In their prospective study, Chiu et al. estimated that 7.8% of new advanced AMD cases would be prevented in 5 years if people consumed a low-GI diet (52,57). Current research does not delineate whether or not sugar or starch alone versus total carbohydrate load contributes to the development of AMD or cataracts.

CLINICAL HIGHLIGHTS

While further studies are ongoing to evaluate the role of additional nutrients and their specific benefits in the eye, substantial evidence is available to suggest that dietary factors may play a protective role. Consumption of a diet rich in green leafy vegetables should be recommended as primary prevention of age-related eye disease. Smoking cessation is clearly indicated for this and other clinical goals. Multivitamin/multimineral supplementation may also be beneficial, with the strongest support being AREDS2 vitamin supplementation (a combination of 400 mg vitamin C, 400 IU vitamin E, 10 mg Lutein, 2 mg zeaxanthin, 2 mg copper, and 80 mg zinc) for the prevention of AMD progression.

As discussed elsewhere (see Chapter 11 and Appendix E), zinc deficiency may also be widespread in the United States; use of a daily mineral supplement is supported by the potential role of zinc in protection of both the macula and the lens. Inclusion in the diet of ω-3 fatty acids from fish or plant sources is advisable on general principles and may prove to be of benefit to vision (see Chapter 45). Intake of this class of fat may be particularly important to the eyes, as it appears to be for cognitive development, during infancy (see Chapters 27 and 29). The dietary pattern tentatively associated with protection of vision, rich in fruits and vegetables, is advisable on general principles and may be recommended with conviction.

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Chapter 37

Diet and Dentition

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INTRODUCTION

Nutrition and oral health are inextricably linked and represent a complex interrelationship that sets the stage for good or poor dentition throughout the lifespan. The availability of specific nutrients is critical for the development, maintenance, and repair of healthy teeth and gums. Inadequate nutrition can affect oral health, increasing the likelihood of developing dental caries and periodontal disease. In turn, bad oral health can negatively affect food choices and dietary intake, resulting in compromised nutritional status and quality of life. Poor dentition, particularly in older adults, is associated with mastication problems and related malnutrition. This chapter examines the pathogenesis of dental caries, as well as the diet-related factors that influence its etiology and prevention.

OVERVIEW

Etiology and Pathogenesis of Dental Caries

Teeth are composed of an outer mineralized layer of enamel and an inner layer of dentin, which supports the structure of the tooth and surrounds the pulp—a neurovascular bundle in the tooth's center. Erosion of the outer mineralized layers of the teeth leads to the formation of cavities, also known as caries. Dental caries is an infectious disease of the oral cavity and teeth and remains a significant public health problem in the United States, despite declines over recent decades attributable primarily to fluoridation of the water supply and recommended practices in oral hygiene. It is the most common and chronic infectious disease in the world, affecting 2.3 billion people, and is associated with pain and tooth loss due to tooth decay and/or periodontal disease (1).

Tooth decay occurs when the products of sugar fermentation by bacteria contained in dental plaque (biofilm) adhere to the tooth surface, promoting the development and progression of lesions or cavities through the production of acids that demineralize the enamel. These lesions are the clinical manifestation of disease. The term *caries lesion* includes the loss of tooth structure in the form of "white spot" enamel demineralizations as well as large cavitations that reach the dentin (2). Aside from mouth bacteria and fermentable sugars, other factors that influence the development of caries are the volume and composition of saliva, genetically induced susceptibility, deficient exposure to fluoride, and inadequate intake of other dietary micronutrients.

Dental plaque is composed of oral bacterial flora, polysaccharides, and salivary proteins. Much of the bacterial makeup within plaque is highly acidogenic following exposure to sugars. *Streptococcus mutans* (*S. mutans*) is the prime bacterial initiator of plaque and a potent producer of acid (3) and has therefore been long thought of as the largest causative factor of dental caries. Streptococci in particular are highly well adapted to the oral cavity due to their receptor interactions with host cells, salivary glycoproteins, and other components. The bacteria bind to other microbial cells, lectins, as well as certain food

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components, and therefore has powerful binding abilities far greater than those of other microorganisms that populate the oral cavity (4). However, more recent research has called into question the outsized role of *S. mutans* in the pathogenesis of tooth decay with evidence showing that individuals with high levels of this bacterial species do not necessarily develop caries, while lesions have been detected in those with low levels (5).

Rather than being considered an infectious disease caused by a specific microorganism, tooth decay is now understood to be a biofilm-mediated disease attributable to a large ecological shift in the plaque microbial flora. This shift creates an imbalance in the physiological equilibrium between tooth mineral and biofilm components, which tilts the balance towards demineralization and lesion formation. The critical factors that trigger a sharp rise in the acid-producing and aciduric elements of the oral microbiome are environmental factors such as frequent exposure to dietary sugar or salivary dysfunction (5).

About 700 to 800 bacterial species have been identified in the human oral microbiome, rendering the mouth the most microbiologically diverse environment in the human body. Both traditional and newly identified bacterial species have an important role in the initiation and progression of tooth decay, involving the ecology-based premise that the disease is the result of a skewed microbial community caused by environmental changes (5).

Diversity of oral bacterial species is highly variable among individuals, while age, diet, oral hygiene level, living conditions, and cultural habits influence variation. However, once bacteria have become established on the tooth surface after permanent teeth eruption, an individual's normal microbiome is typically stable unless the immune system is challenged or a microbial dysbiosis emerges (4).

While the presence of sucrose and other fermentable carbohydrates initiates the demineralization of tooth enamel by acid, the demineralized tooth can be repaired by remineralization when acid production diminishes or acids are neutralized by intrinsic or extrinsic buffering agents in dental plaque. Balancing the equilibrium between demineralization and remineralization is central to the prevention or reversal of dental caries (6). It is important to note that restorative dental treatment does not change the microbiome dysbiosis or the cariogenic environment in the rest of the mouth, and so there is often continuing tooth decay development in high-caries-risk populations after such treatments (6).

Dietary Sugars

Epidemiological studies show that dietary sugars are implicated in the etiology of dental caries. Frequent carbohydrate ingestion plays a significant role in modifying the oral microbiome (6) and is metabolized (fermented) to organic acids, including lactic, butyric, acetic, formic, and propionic. A decline in plaque pH ensues, with dissolution of tooth surface enamel at a pH between 5.3 and 5.7. Any acid can lead to tooth demineralization and the formation of caries. *S. mutans* produce polysaccharides in the presence of sucrose that facilitates adhesion of bacteria to dental surfaces. Other commonly ingested sugars behave like sucrose and precipitate a comparable fall in the pH of plaque.

Because of several properties, dried fruits, cereals, cookies, crackers, chips, and breads all contribute to the formation of caries. Although they contain concentrated sugars, fresh fruits tend to be of low cariogenic potential because of their high water content and the presence of citric acid, which promotes the secretion of saliva. Foods containing citrate stimulate saliva production and may be beneficial if only moderate citrate is ingested.

Saliva plays an important role in the prevention of caries—xerostomic patients develop caries at particularly high rates. Saliva mobilizes food particles, directly buffers acid in plaque, depresses bacterial counts, and promotes remineralization by transporting calcium, phosphorus, and fluoride. The

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acid content of fruit may inhibit bacterial fermentation, but when high, as in lemons and oranges, it may directly erode enamel.

Meats, hard cheeses, nuts, and most vegetables appear to be uninvolved in the formation of caries. Cheese has been shown to enhance remineralization of enamel, and certain hard cheeses prevent dietary sugar from lowering plaque pH. These effects may be due to activation of protective saliva and release of calcium and phosphorus from cheese during mastication (7). The implication is that certain foods may specifically protect tooth enamel from the effects of sugars in other foods.

The adherence of starchy foods to the teeth contributes to cariogenesis. Processed foods high in starch tend to adhere to teeth for protracted periods and therefore may contribute disproportionately to cavity formation (8). Refined and processed grains contain modified starch susceptible to the action of salivary amylase. The release of maltose results, and its fermentation lowers plaque pH and contributes to demineralization. Of note, dietary starch present in vegetables is noncariogenic. It appears that complex starches eaten in the context of a low-sugar diet have low cariogenicity, while the processed starches typically found in modern diets, combined with high sugar consumption, are particularly inductive of caries (9,10).

The frequency of meals or snacks containing starch or sugar correlates directly with the formation of caries. Foods that adhere to teeth and which are eaten between meals increase the risk in particular. Food sequence is influential as well. When sugar-containing foods are consumed at the end of a meal or snack, they produce the most protracted fall in plaque pH. Other foods eaten after sources of starch or sugar can immediately attenuate their effects.

Although sugar in solution adheres less to teeth surfaces than does sugar from solids, sweetened drinks are associated with increased risk of caries (11,12). The risk appears to be most significant with sodas and sugar-based powdered beverages, while 100% fruit juices may be slightly less cariogenic (12,13). Soda consumption may compromise dental health independently of the cariogenic effects of sugar; phosphoric acid may exert an erosive influence on enamel (11,14).

Maternal Diet and Oral Flora

There is some evidence to show that development of caries in children younger than 5 years of age is significantly impacted by their mothers' gestational intake of fats and sugars (15). One study of 315 Japanese mother–child pairs found a significantly decreased risk of childhood dental caries among mothers who consumed more cheese but not milk or other dairy products during pregnancy (16). Recent studies suggest that there is an association between prenatal vitamin D (25-hydroxyvitamin D) concentrations in mothers and the onset of early childhood caries (ECC), with low levels detected in prenatal and cord blood having a positive impact on risk (17). Maternal oral health during pregnancy (18,19) and postpartum oral flora may also play a role. It is believed that the main source of transmission of *S. mutans* to young children is through the saliva of their mother or other caregiver, which typically happens within 2 years of tooth eruption (20).

Artificial Sweeteners in Popular Beverages

The potential benefits of artificial sweeteners are under investigation (see Chapter 42). Although less cariogenic because of their lack of sugar (21), sugar substitutes, such as xylitol used in chewing gums and aspartame used in diet sodas, may generate false security because people may automatically believe that sugar-free products are safe on teeth (22).

Diet sodas that are acidic, and generally contain aspartame, may be as damaging to teeth as non-diet varieties; the acid content contributes directly to demineralization (22,23). A similar process appears to

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occur with energy drinks and to a much lesser degree with sports drinks. One study, in which teeth were submerged in a variety of popular sports and energy drinks, showed a disproportionate degree of enamel dissolution. Energy drinks had significantly higher titratable acidity levels (lower pHs) and significantly increased resultant enamel dissolution (two times higher) than did sports drinks. High titratable acidity in drinks serves as a significant predictor of enamel dissolution. Therefore, enamel weight loss varies inversely with the pH of the drink (24).

Energy drinks are widely consumed worldwide, but little is known about their impact on oral health. In one study, five energy drink brands (Lucozade, Red Bull, Monster, Rockstar, and Relentless), representing 75% of the energy drink market in the United Kingdom, were selected and tested for pH and sugar content. All five energy drinks investigated had pH values below the critical value (5.5) associated with dental erosion; the lowest pH was 2.72 (Lucozade) and the highest was 3.37 (Monster). The drinks also contained excessive amounts of free sugars, ranging from 25.5 g (Red Bull) to 69.2 g (Rockstar). Differences in sugar content were mainly explained by portion size. Additionally, the energy drinks were found to contain various acids that are also linked to oral health. The researchers concluded that the consumption of energy drinks may contribute to dental erosion (25).

Sugar Alcohols

Sugar alcohols, such as mannitol and sorbitol, are fermented more slowly than monosaccharides and disaccharides, and they are less cariogenic, although bacterial acclimation appears to occur if habitual intake is high. Lactose does not appear to be cariogenic, and milk consumption is associated with a slightly reduced risk of caries (26).

Some sugar substitutes have been studied extensively such as xylitol, a five-carbon sugar alcohol that has been shown to have antibacterial effects specific for *S. mutans* by compromising its metabolism and colonization. Controlled studies demonstrated that several exposures daily to high-content xylitol-containing chewing gums or other confections containing it significantly inhibited caries prevalence and incidence. The largest reduction of lesions occurred on the smooth surfaces of the teeth, while the fissures and pits were least affected (2).

While xylitol-sweetened gum has been shown in studies to inhibit the growth of *S. mutans* in both children (27) and adults (28), the Xylitol for Adult Caries Trial (X-ACT), a 33-month double-blinded, placebo-controlled interventional trial that tested the effectiveness of daily xylitol lozenge use (up to 5 g/day) versus placebo lozenge use to prevent caries in adults at elevated risk of experiencing caries, showed no significant differences between the prevalence of caries in the intervention and placebo groups (29). Therefore, xylitol is not currently recommended for use in the prevention of caries. A more promising sugar substitute investigated for preventing dental caries is erythritol.

In a 3-year-long intervention trial assessing dental plaques in 7- and 8-year-old children chewing candies containing erythritol versus xylitol- or sorbitol-containing candies, the intervention group was noted to have reduced plaque growth, lowered levels of plaque acetic acid and propionic acid, and reduced oral counts of mutans (30). A 2016 literature review found evidence demonstrating better efficacy of erythritol compared to sorbitol and xylitol to improve and maintain oral health (31).

Fluoride Toothpaste

Studies have long shown that consistently brushing with a fluoride toothpaste at least twice per day is beneficial for caries prevention (32,33). In an updated Cochrane review that included 96 studies published between 1955 and 2014, researchers compared the effects of toothpastes of different fluoride concentrations (parts per million [ppm]) in preventing dental caries in children, adolescents, and adults.

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They looked at randomized controlled trials that compared toothbrushing with fluoride toothpaste with toothbrushing with a non-fluoride toothpaste or toothpaste of a different fluoride concentration, with a follow-up period of at least 1 year. The primary outcome was caries increment measured by the change from baseline in the decayed, missing, and filled surfaces in all permanent or primary teeth. The investigators found that in primary teeth of young children, brushing teeth with a toothpaste containing 1,500 ppm fluoride reduced the amount of new decay when compared with non-fluoride toothpaste; the amount of new decay was similar with 1,055 ppm compared with 550 ppm fluoride toothpaste; and there was a slight reduction in the amount of new decay with 1,450 ppm toothpaste compared with 440 ppm fluoride toothpaste (34).

With respect to permanent teeth of children and adolescents, the researchers found that there was less new decay when toothbrushing with toothpaste containing 1,000 to 1,250 ppm or 1,450 to 1,500 ppm fluoride compared with non-fluoride toothpaste, and that toothbrushing with 1,450 to 1,500 ppm fluoride toothpaste reduced the amount of new decay more than the 1,000 to 1,250 ppm toothpaste. There was a similar amount of new decay when children and adolescents used a toothpaste of 1,700 to 2,200 ppm or 2,400 to 2,800 ppm fluoride compared to 1,450 to 1,500 ppm toothpaste. The evidence for the effects of other strengths of toothpaste was less certain (34).

Early Nutrient Deficiencies

During tooth development, protein–calorie malnutrition can retard tooth eruption and reduce tooth size. Deficiencies that are especially relevant to tooth development, repair, and maintenance involve folate and other B complex vitamins, vitamins A, C, and D, calcium, fluoride, and protein (35). Vitamin A deficiency during development results in malformed teeth. Deficiencies of vitamin D, calcium, or phosphorus impair tooth mineralization. The availability of fluoride in sufficient, but not excessive, quantity strengthens tooth enamel; excess mottles the teeth. However, for some children, those considered to be at high risk of tooth decay, the benefits to health of preventing tooth decay outweighs the risk of fluorosis (36). Iodine deficiency delays tooth eruption and alters growth patterns. Protein and calorie malnutrition and vitamins A and D, calcium, fluoride, and iodine deficiencies are all implicated in the development of caries. Vitamin C deficiency has been implicated in impaired tooth development and possibly in the development of caries.

Several studies on nutrition and dental caries have been conducted in Peru, where investigators have observed that one mild-to-moderate episode of malnutrition during the first year of life is associated with increased caries in both primary and permanent teeth. Another study found that stunting was a significant risk indicator for tooth decay in permanent teeth over a three-and-a-half-year period, independent of other well-known risk factors for caries development. Another study found no correlation between nutrition status and dental caries, while others have reported a possible connection between malnutrition, enamel defects, and dental erosion (37).

Obesity

Childhood and adolescent obesity is another possible contributor to the formation of dental caries, as it has been associated with earlier eruption of teeth in children and increased gingival inflammation, respectively (38). Earlier rupture of teeth may put children at higher risk of caries due to the extended length of time exposed in the oral cavity (39). Indications of increased gingival inflammation in obese adolescents included lower salivary secretion rate and higher secretory Immunoglobulin A (sIgA) levels. This is an important public health concern as rates of obesity among children, adolescents, and adults have reached epidemic levels (see Chapter 5). In a case–control study, a sample of 71 obese adolescents

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(age range 11–18) and 54 age-sex-matched normal weight adolescents were selected to compare oral health indicators: dental caries, periodontal status, and erosive tooth wear (ETW). The groups were defined using the body mass index and growth curves for Flemish adolescents. Obese participants reported a significantly higher intake of sugar-rich and caloric food items than the normal weight group. The consumption of acidic drinks was similar. Obese adolescents presented significantly higher incidence of caries, gingivitis, and plaque, although after adjusting for age and sex, obesity became significantly associated only with the presence of dental plaque. The prevalence of ETW did not differ significantly between groups (40).

Baby-Bottle Tooth Decay

Infants and toddlers between the ages of one and two are at risk of baby-bottle tooth decay (41), which results when they are allowed to fall asleep drinking milk or formula from a bottle. The pooling of sugar-containing fluid around the teeth produces a characteristic, and sometimes severe, pattern of tooth decay. The condition is avoided by limiting nighttime and naptime fluid intake to water after the teeth have erupted. Human breast milk is apparently not cariogenic (42,43), whereas bovine milk and infant formulas (both milk-and soy-based) have been shown to induce enamel erosion and higher levels of lactobacilli in study participants and are, therefore, considered cariogenic (44,45). A recent meta-analysis found that breastfeeding was more effective at preventing dental caries in early childhood than bottle feeding (46).

Older Adults

Physical and psychosocial factors place the older adults at particularly high risk for poor nutrition. Their diets are frequently monotonous with a low energy and nutrient content and deficiencies in calcium, zinc, magnesium, iron; vitamins D, E, B6 and B_{12}; thiamin, folic acid, retinol, and carotenes. Poor oral health status is one of the most frequent causes of malnutrition due to its effect on mastication and swallowing, which can lead to severe deficiencies in energy and nutrient intake. Data on the oral health of the older adults show an elevated prevalence of caries and moderate periodontal disease, frequent edentulism, and numerous cases of dry mouth and oral cancer, resulting in highly negative effects on quality of life (47).

Poor nutritional status among older adults is also a risk factor for the development of frailty. In examining the potential association between oral health and frailty in hospitalized older adults, researchers conducted a cross-sectional study of 168 geriatric inpatients older than 65. Oral health, nutrition, and frailty were assessed using previously validated tools, namely, the Geriatric Oral Health Assessment Index (GOHAI), Mini Nutrition Assessment (MNA), and Reported Edmonton Frailty Scale (REFS). Other data collected included demographics, comorbidities, level of education, and history of smoking and alcohol consumption. After adjusting for nutrition and comorbidities, self-reported oral health was found to have an independent negative association with frailty ($p = 0.019$) (48).

Receding gingiva also place older adults at risk for caries due to exposed surfaces of tooth roots. These surfaces lack enamel and are susceptible to caries at an accelerated rate. Implicated foods include sweetened beverages and starches. Care of the gingiva is fundamental to the prevention of this condition.

Gingivitis, inflammation of the gums, and periodontitis—a more serious infectious process involving the attachment apparatus of the tooth—are thought to be influenced by nutritional status, but evidence for specific associations is still limited (49). Because both processes are infectious and inflammatory, nutritional adequacy with regard to immune function (see Chapter 11) likely plays a role in the health of the gingiva and periodontal tissues, indirectly if not directly. The evidence that periodontal disease correlates with systemic inflammation and contributes to conditions such as coronary atherosclerosis, metabolic syndrome, and hypertension is now persuasive (50,52).

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Additionally, diabetes mellitus, a widespread condition throughout the world, is associated with progression of periodontal disease, including a greater number of exposed root surfaces at risk for root caries, putting diabetics at even greater risk of systemic infection and microvascular complications (53–55). Proper oral hygiene in this unique population is likely beneficial as some researchers are finding a correlation between the number of caries identified and hyperglycemia in study populations (56).

Tooth decay and loss affect nutritional status (57–59). About 19% of adults aged 65 and over were edentulous in 2011 to 2012. Edentulism was twice as prevalent among adults aged 75 and over compared with those aged 65 to 74, although little difference was seen in the prevalence of edentulism between men and women (60).

Many medications reduce saliva production (61), and for this reason, as many as 50% of the older adults have iatrogenically induced reductions in saliva production. Reduction of saliva can accelerate tooth decay and interfere with the functioning of dentures if already placed. The stimulation of saliva through the use of chewing gums containing xylitol may be helpful (62).

Gene Variants Relevant to Dentition

There is evidence indicating certain individuals are genetically resistant to developing tooth decay despite being on a highly cariogenic diet. It appears that genetic variations influence differences in taste perception and dietary habits that in turn affect risk for developing tooth decay (63). Common polymorphisms in the sweet taste receptor (TAS1R2) and glucose transporter (GLUT2) genes are associated with dental caries according to an 80-subject cohort study of healthy Caucasian individuals aged 21 to 32 years. Subjects were genotyped for the previously mentioned polymorphisms, stratified accordingly into four groups, and then assessed for dental caries. Carriers of the Ile allele for GLUT2 showed increased amounts of DMFT, while those with the Val allele for TAS1R2 demonstrated lower caries scores (64). Another case-control study analyzed the same two polymorphisms in children with dental caries and healthy controls in the Czech population involving 637 unrelated Caucasian children, aged 11 to 13 years. One hundred and fifty-five caries-free children and 482 children with a history of dental decay were recruited. Compared with subjects with the common Thr allele, carriers of the Ile allele of GLUT2 had significantly more frequency of dental caries ($p < 0.05$; OR = 1.639; 95% CI, 1.089–2.466). Similarly, children with the Val allele for the TAS1R2 Ile191Val polymorphism were more frequently affected by caries than children who carried the Ile allele ($p < 0.05$; OR = 1.413; 95% CI, 1.014–1.969) (65). This research indicates that there are important genetic factors that need to be taken into account when assessing and caring for patients with dental caries (64), but there are also environmental and cultural factors that influence taste perception that may confound the results (63). Clearly, further research is needed in this area.

NUTRIENTS, NUTRICEUTICALS, AND FUNCTIONAL FOODS

Calcium and Vitamin D

Adequate intake of vitamin D and calcium may be necessary for the maintenance of healthy teeth. Dental caries and vitamin D inadequacy are known to affect children worldwide. Vitamin D has a vital role in tooth formation. There is growing evidence linking suboptimal serum vitamin D level with dental caries in children (66). In examining the relationship between vitamin D status and dental caries in 1,017 Canadian school-aged children, investigators found that the presence of tooth decay was associated with low levels (<75 nmol/L) and (<50 nmol/L) 25(OH) vitamin D, lower household education, absence of

twice-daily brushing, and yearly visit to the dentist (67).

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In another study involving adults, researchers evaluated the diets of 106 women in their mid-twenties for protein, calcium, and vitamin D intake. Subjects with the highest scores for the development of caries had significantly lower calcium and vitamin D levels, and a significantly higher protein intake and daily soft drink consumption (68).

Fluoride

The evidence pointing to a reduction in the rate of dental caries throughout the world attributable to water and dentifrice fluoridation is irrefutable. Water fluoridation is the most widely adopted public health intervention, reaching more than 370 million people in 27 countries. Many studies have shown the effectiveness and safety of fluoridating water supplies, with the exception of dental fluorosis as a possible side effect. A Cochrane meta-analysis included 107 studies with an estimated average of 35% prevented fraction of caries lesions in the primary dentition (decayed, missing, and filled teeth [DMFT]), 26% prevention of lesions in permanent teeth (DMFT), and 15% prevention of any new lesions (primary disease prevention). However, 72 of the studies were conducted prior to the widespread use of fluoride toothpaste, yet, prevention through the use of such toothpastes is independent of fluoridated water exposure; therefore, a combined benefit is to be expected (2).

Fluoride is incorporated into the hydroxyapatite of teeth, rendering tooth mineral less susceptible to demineralization. Fluoride also inhibits the replication and enzymes of *S. mutans*. A substantial decrease in the risk of caries for both children and adults is associated with fluoride at a dose of one part per million in the drinking water. This dose, studied extensively, is not associated with any known adverse health effects, although critics of systemic fluoridation claim it is the cause of increased rates of osteosarcoma, osteopenia, and other disorders of bone metabolism. These claims are not supported by current epidemiologic evidence (69,70).

A careful balance is needed between preventing tooth decay with fluoride and the development of fluorosis to maximize the benefit of this compound. Fluoride treatments of public water sources, table salt, fluoridated toothpaste, sealants, and even milk are recommended for both children and adults as they have been found to be safe and effective means of decreasing risk of dental caries (71–76). The incorporation of fluoride into skeletal bone may also confer benefit (see Chapter 14).

Bottled water, used increasingly in the United States, may or may not have adequate fluoride concentration (77). When water is not fluoridated, fluoride supplementation for children (in tablet, drop, or lozenge forms) is indicated; the dose recommended is 0.05 mg/kg/day (78). Fluoride supplementation is recommended for infants breast-fed beyond 6 months, beginning at that age, as the fluoride content of breast milk is low. Prenatal supplementation is of uncertain benefit (79). Because young children will swallow a portion of toothpaste used, small amounts should be dispensed to prevent excess fluoride ingestion. A systematic review by Santos, Oliviera, and Nadanovsky showed that low-fluoride toothpastes significantly increased the risk of dental caries in preschoolers but did not decrease the risk of developing sequelae of fluorosis in upper anterior permanent teeth. The authors do not recommend the use of low-fluoride toothpastes for these reasons (80).

Cranberry

Cranberry (*Vaccinium macrocarpon*), a fruit long touted as a treatment for urinary tract infections, is currently being investigated for its potential preventive characteristics in regard to dental caries. In a recent study, *S. mutans–Candida albicans* biofilm was grown on saliva-coated hydroxyapatite discs that were then treated with 500 to 1,000 μg/mL cranberry extracts. After 24 hours, biofilms were then

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assessed for acidogenicity, metabolic activity, exopolysaccharide (EPS) or microbial biovolumes, structural organization, and colony-forming unit (CFU) counts. The results showed extracts produced significant reductions in acidogenicity and metabolic activity ($p < 0.0001$) compared to the control-treated biofilms. A significant decrease in biovolumes of the EPS ($p = 0.003$) and microbial biofilm components ($p = 0.007$) was also seen. Qualitative assessment of confocal biofilm images revealed that the cranberry extract disrupted biofilm structural architecture. Finally, significantly fewer *S. mutans* ($p = 0.006$) and *C. albicans* ($p = 0.036$) CFUs were recovered from the cranberry-treated biofilms than from the control-treated biofilms (81).

In previous studies, the polyphenols of these small fruits, including proanthocyanidins and anthocyandins, demonstrated inhibition of *Streptococcus* bacterial adhesion to hydroxyapatite pellets pretreated with saliva (82). Other studies also suggested that cranberry extracts prevent the formation of biofilms by cariogenic streptococci, implying that cranberry extracts slow the development of dental plaque (83,84). Among other effects, cranberry extract is also thought to inhibit acid production by cariogenic bacteria as well as their proteolytic activities, therefore leading to less potential for the development of caries and periodontal disease (85).

Probiotics

A relatively new field of biotherapeutics includes the possibility of using probiotic therapy for oral health. Probiotics (or microorganisms with beneficial health benefits) have been shown to decrease the pH of the oral cavity so that plaque bacteria (generally thought to be *streptococcus mutans* species) cannot form the dental plaque that causes periodontal disease (86).

In their review of meta-analyses on effects of probiotics on teeth in children, Twetman and Stecksén-Blicks found six studies showing a hampering effect on *mutans streptococci* and/or yeast in the mouth with ingestion of lactobacilli- or bifidobacteria-derived probiotics (87). Different strains, however, may have differing cariogenic potential as outlined by a study comparing the effects of two differing *Lactobacillus reuteri* strains on the biofilm (88). Despite these different effects, probiotics produce antioxidants that prevent plaque formation by neutralizing free electrons needed for mineral formation (89). While a selection of probiotics has demonstrated beneficial effects, clinical studies have typically used surrogate endpoints such as *S. mutans* counts, salivary flow, plaque or gingival scores, and pocket depth to evaluate efficacy. These studies provided a promising outlook; however, there need to be further randomized double-blinded placebo studies with specific target sites in the oral cavity (90).

Iron

Multiple studies have found a significant association between low serum iron levels and ECC among children (91,92). Children with more ECCs were also found to have low serum ferritin levels in one case–controlled study and in a separate population study. These children were subsequently at greater risk of being anemic (93,94), which has advanced public health implications, including permanent effects on growth and development. Further research should be done to evaluate the clinical relevance of low serum iron levels in the development of ECC. Iron-deficiency anemia remains an important pediatric public health problem. Iron deficiency has also been associated with impaired salivary gland function causing reduced salivary secretion and buffering capacity leading to increased caries. In a recent study, researchers explored an association between dental caries and serum levels of iron and ferritin in children aged 3 to 12 years. The study group included 120 children, hospitalized for uncomplicated medical problems. Blood reports were evaluated to determine serum iron and ferritin levels and history of dental caries was assessed. Thirty-eight children showed low serum iron levels, of which 31 children

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had dental caries, and 9 out of 15 children in the high serum iron level group showed dental caries. High ferritin levels were seen in three children, among which two children were caries-free (95).

Xylitol

As previously mentioned, xylitol has been evaluated as an intervention for dental caries. Recent results of randomized trials testing the efficacy of xylitol in caries prevention have been conflicting (96). The X-ACT, a 33-month double-blinded, placebo-controlled interventional trial that tested the effectiveness of daily xylitol lozenge use (up to 5 g/day) versus placebo lozenge use to prevent caries in adults at elevated risk of experiencing caries, showed no significant differences between the prevalence of caries in the intervention and placebo groups (29). A systematic review of five randomized controlled trials showed that xylitol had a small effect on reducing dental caries (standardized mean difference = −0.24; 95% CI = −0.48 to 0.01; p = 0.06) with a very low quality of evidence and considerable heterogeneity. Studies with higher xylitol doses (>4 g/day) demonstrated a medium caries reduction (standardized mean difference = −0.54; 95% CI = −1.14 to 0.05; p = 0.07), with these studies also having considerable heterogeneity and very low quality of evidence (97). Currently, the efficacy of xylitol as a preventative for dental caries remains uncertain.

High-Fructose Corn Syrup

Because of its wide use as a food additive, increasing attention has been paid to the health effects associated with a high intake of high-fructose corn syrup (HFCS). As discussed, sucrose is known to be the most cariogenic carbohydrate because it significantly increases the efficiency of *S. mutans* adhesion and accumulation within plaque. However, HFCS is almost identical to sucrose and is found in many commonly eaten foods and beverages, and so the question arises as to whether its use may be preferred over sucrose in the prevention of tooth decay. HFCS is a derivative of corn starch and is a mixture of 55% fructose and 45% glucose, while sucrose is 50% fructose and 50% glucose. There is little conclusive information available regarding the cariogenic impact of HFCS. An in vitro study showed that the drop in pH in biofilm inoculated with *S. mutans* in the presence of HFCS was significantly larger and faster than that in the sucrose media. However, the percentage of adherence of *S. mutans* in HFCS media was significantly lower compared to what was observed in the sucrose culture (98). Another in vitro study that involved demineralization testing showed that the microhardness of teeth decreased by a greater extent in response to HFCS compared to sucrose (99). Given the uncertainty, more research is needed, especially utilizing in vivo conditions.

CLINICAL HIGHLIGHTS

Diet influences dental health throughout life, and dentition and oral health impact dietary intake and nutritional status, particularly in older adults. Dental caries is a complex, multifactorial disease in which diet and nutrition play a role in its etiology and progression. The dietary factors that are most known to contribute to tooth decay are sugar and other fermentable carbohydrates, and the frequency of exposure to them. The incidence of dental caries can be reduced by limiting sugar intake, avoiding sugary or starchy snacks, as well as sugar-sweetened beverages. In addition, using chewing gum sweetened with xylitol or other nonfermentable sweeteners, and frequent brushing with fluoride toothpaste to remove trapped food particles, are also beneficial. Dietary adequacy, in general, is important to optimize immune function and promote healthy tooth development in children and good oral health in adults.

Fluoride intake over years greatly influences susceptibility to caries. The fluoride content of drinking

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water should be addressed in primary care; physicians should advise supplementation when the water fluoride is low in local water systems. Children should be weaned to diets that are moderate in sugar content and, in particular, should not be allowed to take a sweetened beverage to bed. Careful attention to the dentition of aging adults is essential to the preservation of native teeth, which in turn influences the adequacy and quality of the overall diet.

Probiotic therapy to maintain optimal microflora as well as clinical considerations of genetic susceptibility to tooth decay may constitute novel interventions in future dental care.

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Chapter 38

Hunger, Appetite, Taste, and Satiety

Meagan L. Grega

INTRODUCTION

Control over the process of energy and nutrient intake is vital to the survival of an individual and a species. Minimally, food intake is influenced by *hunger*, the sensation induced by a deficit in readily metabolizable energy sources. However, it is also influenced by *appetite*, a desire for food influenced by cravings for specific tastes and/or nutrients, and the palatability, familiarity, and availability of specific foods. Also important is *satiety*, the sensation that the impulses that have led to food consumption have been satisfied (see Table 38.1).

In humans, food intake is the product of physiologic, psychological, and sociologic factors that defy simple classification. The conditions of endemic and epidemic obesity that are increasingly common in industrialized countries, while ascribable to an imbalance in the regulation of energy intake, are less readily ascribed to a particular component of the complex governing systems. There is evidence that redundant processes in humans govern energy intake, a state that may have conferred survival benefit throughout human prehistory, when the adequacy of dietary energy was often in question.

TABLE 38.1

Fundamental Factors Governing Energy Intake and Balance

Factor	Definition/Influence
Hunger	The various sensations associated with a deficit in the body's supply of "fuel"; a physical compulsion to eat
Appetite	A desire for a particular food or craving for a particular taste; may not involve hunger at all
Satiety	The effect that eating now has on eating later; how long the state of feeling full and satisfied lasts

The properties of specific foods and the physiologic responses evoked by their consumption appear to have implications for the regulation of energy intake, although simple explanations are elusive and perhaps ill-advised. Sufficient insights and evidence have accumulated to permit clinical recommendations that may be expected to contribute to salutary energy balance.

OVERVIEW

Physiologic defenses against undernutrition are far more robust than those against overnutrition (1). The case may even be made that *Homo sapiens* has no native defense against caloric excess, never having needed one throughout most of our history. Even so, were physiology alone responsible for nutrient energy consumption, food intake would begin with hunger and end with satiety. The characteristic physical sensations of hunger and fullness, however, are one part of a complex interplay of physiologic and

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nonphysiologic factors governing the quantity, frequency, and variety of food intake (2–4).

Social, environmental, psychological, economic, and biological factors all influence our intake of food (5–8). Most creatures have a fairly simple and straightforward relationship with food: eat to live. Whether or not humans live to eat is debatable, but our relationship with food is certainly a lot more complicated than eating to live (9). Humans eat for almost every reason imaginable: to reward ourselves, punish ourselves, console ourselves (10); celebrate and commemorate; sustain and satisfy ourselves; and often, perhaps, just because we can.

Dietary choices are very much influenced by cultural norms and the prevailing choice architecture of the surrounding environment (11,12). Such norms are influenced by the familiarity of food, the accessibility of food, and the convenience, cost, and context of food. There is no real rhyme or reason to eating certain foods for breakfast and other foods for dinner; for example, it is all a matter of what a given culture considers normative.

How much people eat is influenced by the volume of food, the number of ingredients, the timing, the form (liquid vs solid), and even the packaging (shape and size) and ambient lighting (13). Food intake can be influenced by something as trivial as how much food is set in front of a person at any given time (14–16). The evidence is strong that portion size influences food consumption (17,18). In our era of supersized portions, this influence on our patients is pervasive and adverse. The concept of *mindless eating* refers to the empirical finding that, each day, people make 20 times more decisions about food than they are aware of, and thus, can be subconsciously influenced by numerous environmental cues—"family and friends, packages and plates, names and numbers, labels and lights, colors and candles, shapes and smells, distractions and distances, and cupboards and containers." Seemingly inconsequential decisions about how we interact with, store, and serve food all influence how much and how often we eat (19).

People eat to address a wide array of emotional needs, some of them as profound as depression, some as superficial as wanting a brief feeling of comfort or reward (20). Social factors also strongly influence dietary patterns (21), as do environmental settings (22). Palatability—how tasty and pleasant food is—and social norms and expectations interact to influence the amount of food consumed on any given occasion (23).

Intake of highly processed food seems to be particularly challenging to self-regulate. Recent research demonstrates that inpatient study subjects eating an ad libitumultra-processed diet consumed approximately 500 additional calories per day compared to the same participants when offered an unprocessed diet matched for presented calories, energy density, sugar, sodium, fiber, and macronutrient content (24). Ultra processed foods are ubiquitous throughout our society. Analysis of NHANES survey data reveals that ultra processed foods comprise 57.9% of the respondents' total energy intake and account for 89.7% of the calories derived from added sugars (25) and that overall dietary quality decreases as ultra processed food consumption increases (26). We are surrounded by hyper palatable food that is designed to evade our physiologic satiety signals (27).

Cost incentives around the world tend to drive people toward more energy-dense food (28,29). Highly processed foods tend to be low in volume but high in calories and therefore energy dense. Such foods are widely available, highly palatable, and generally inexpensive, creating frequent opportunities for overconsumption, leading so often toward obesity. Unfortunately, ultra processed food intake is highest among our youngest citizens, as well as those in marginalized settings who experience less education and lower income (30), which does not bode well for the future trajectory of chronic disease.

The composition of foods can be manipulated considerably by manufacturers without consumers even being aware (31,32). This is done routinely in ways that may influence appetite and food consumption (33,34), such as the addition of salt to sweet foods or sugar to salty foods. Both the energy density of food

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and portion size influence the calories taken in at any given meal; modifications of either can help produce satiety with fewer calories or stimulate appetite and caloric intake (35). Taste also exerts a powerful influence on appetite (36–38), an influence independent of the need for any particular nutrient (39). The composition of snack foods in particular can and is being manipulated in various ways to increase how much we eat (40).

The Gut–Brain Axis in the Regulation of Food Intake

Complex signals influencing hunger, appetite, and satiety produced in the brain interact with those signals produced in the gastrointestinal tract, all of which vary based on current energy status, external cues, genetic factors, and the specific composition of foods (41,42). A basic understanding of gut–brain axis biology provides a useful framework for understanding the interplay between hunger and satiety. Ultimately, food ingestion and fasting trigger a release of hormones produced by the gastrointestinal tract, adipose tissue, and the brain to promote energy balance (43).

The hypothalamus is the main regulatory center of human appetite. The ventromedial hypothalamus appears to be important in the generation of satiety, whereas hunger is in part regulated by the lateral hypothalamus. When the body is in need of fuel, the hypothalamus produces and releases neuropeptide Y, which in turn raises levels of insulin and glucocorticoids. Neuropeptide Y is coexpressed with agouti-related protein, which works synergistically to increase appetite and decrease metabolism and energy expenditure. These master hormones work from the top down to stimulate hunger, the physical sensation of needing food for energy. Hunger then manifests as appetite, the motivation to eat food. In turn, the stomach produces the hormone ghrelin, which interacts with neuropeptide Y secreting neurons in the brain to stimulate appetite. Other chemicals that stimulate appetite include galanin, melanin-concentrating hormone, norepinephrine, glucocorticoids, and orexins or hypocretins (I and II) (44). Additionally, hypothalamocortical and hypothalamolimbic projections contribute to the awareness of hunger, and somatic processes controlled by the hypothalamus—vagal tone, stimulation of the thyroid, and the hypothalamic–pituitary–adrenal axis—impact energy balance.

Following a meal, the increase in insulin level triggers a release of the hormone leptin from adipocytes, which contributes to satiety through multiple mechanisms, including inhibition of NPY/AGR neurons within the arcuate nucleus; thereby decreasing the release of neuropeptide Y and enabling adipocytes to signal repletion to the brain (45). The communication between body fat, the gastrointestinal tract, and the brain plays a major role in appetite and weight regulation over time (46). Adipose tissue releases leptin, which triggers satiety, and adiponectin and resistin, which contribute to appetite. Fat is a very active hormone-producing organ, in constant communication with the hypothalamus, and potentially fighting hard to maintain its current state (i.e., “set point”) (47)—validating the well-known lament about the difficulties involved in permanently losing excess body fat. Substantial weight loss leads to reduction in the circulating levels of leptin, peptide YY, cholecystokinin, insulin, and amylin, along with increasing levels of ghrelin, gastric inhibitory polypeptide, pancreatic polypeptide, and subjective rating of appetite. These hormonal changes strongly encourage weight regain and have been shown to persist even one full year after the initial weight loss, dramatically increasing the risk of relapse (48).

Chronically elevated leptin concentrations due to excess adiposity lead to leptin resistance, primarily through an increase in the ratio of free to bound leptins that influences the signaling activity of leptin in the central nervous system. Dietary fat content may also affect the response of hypothalamic neurons to leptin levels. Animal models demonstrate a decreased response to leptin after 3 to 5 days of high-fat feeding, even before adiposity levels increase significantly (45).

Satiety is also immediately driven by signals from stretch receptors in the stomach and by the delivery

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of nutrient energy to the small intestine (49). Activation of the “ileal brake” through absorption of nutrients in the distal small bowel has been shown to increase glucagon-like peptide-1 (GLP-1), peptide YY, and subjective measurements of satiety while decreasing ghrelin levels and energy intake at the subsequent meal (50). The effects of ingestion on satiety are mediated by the vagus nerve and by gut hormones. A litany of gut hormones has been shown to influence satiety, including cholecystokinin, GLP-1, oxyntomodulin, pancreatic polypeptide, somatostatin, calcitonin, gastrin-releasing peptide, obestatin, neuromedin C, and peptide YY3-36 (PYY) (51,52). The best-studied satiety hormone to date is cholecystokinin, which shortens the duration of feeding. The entry of gastric chyme into the duodenum is a stimulus for the release of cholecystokinin. Cholecystokinin slows gastric emptying, increasing the signals to gastric stretch receptors and contributing to a sense of satiety. Cholecystokinin may also provide direct signaling of satiety to the brain. Macronutrient absorption in the small bowel stimulates the vagus nerve, which also signals satiety to the brain. The pace at which food is consumed and whether the food is consumed in solid or liquid form also influences the rate of absorption, and hence, the effect on satiety (53,54).

The signals of satiety delivered before or during nutrient absorption are reinforced by postabsorptive signals. Nutrient entry into the portal vein results in signals of satiety from the liver to the brain via the vagus nerve. The mechanisms of signal exchange between the liver and central nervous system are not yet fully known. Circulating levels of glucose, insulin, and amino acids may all feed back to the brain to confer the sensation of satiety (see Figure 38.1).

In essence, the control of appetite and energy balance is tightly regulated by a complex neuronal network in the brainstem and hypothalamus that receives inputs from the periphery via nutrients, hormones, and afferent nerve fibers (55). Hormones produced in the gut feed back to the hypothalamus to modify the hypothalamic response. Processes from other cerebral loci are involved as well. Information from the limbic system and the cerebral cortex is relayed directly to the hypothalamus to modify appetite. Appetite regulation is an immensely complex process involving the gastrointestinal tract, many hormones, and both the central and autonomic nervous systems. Redundancy in central regulation of energy intake may confer a survival advantage but obviously complicates efforts to isolate genetic or metabolic defects responsible for perturbations of energy balance, such as those leading to obesity or severe anorexia. Interestingly, functional magnetic resonance imaging (MRI) data suggest that individuals with obesity demonstrate increased activation of reward and attention neural pathways in response to highly palatable food cues, such as a chocolate milkshake, but may also experience decreased activation of the reward response after consuming the food (56). Similar patterns have been detected in adolescents whose body mass index (BMI) or percentage of fat mass increased over several years, providing some insights into the neural mechanisms that may contribute to difficulty maintaining a neutral energy balance in an environment of hyper-palatable, high-calorie food (57,58).

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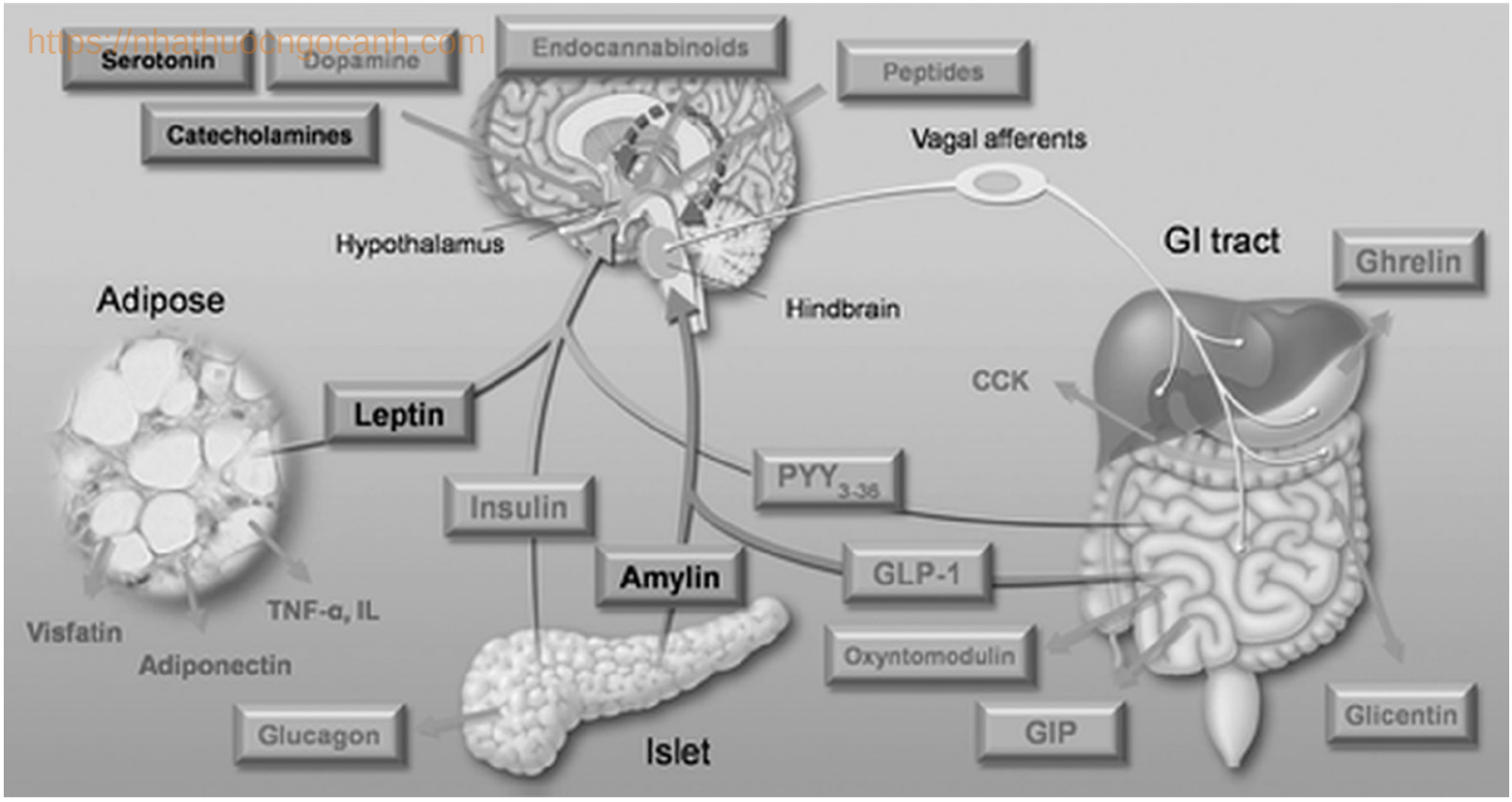

FIGURE 38.1 Peripheral and central signals: Regulation of food intake, body weight, and metabolism. (Adapted from Badman MK, Flier JS. *Science*. 2005;307(5717):1909–1914. With permission from AAAS.) CCK, cholecystokinin; GIP, gastric inhibitory polypeptide; GLP-1, glucagon-like peptide-1; IL, interleukin; PYY3-36, peptide YY3-36; TNF-α, tumor necrosis factor-alpha.

A variety of homeostatic, external sensory, hedonic, and genetic factors influence the gut–brain interactions to tip the scale back and forth between hunger and satiety. Body energy requirements are clearly one factor driving ghrelin release and subsequent hunger and appetite. The availability of nutrient energy is reflected in diet-induced thermogenesis, the generation of heat for a period of approximately 6 hours following ingestion due to the metabolic work of digestion and activation of the sympathetic nervous system. A rise in body temperature due to diet-induced, or postprandial, thermogenesis signals the adequacy of nutrient energy supplies, whereas a decline in temperature between meals is an indication of declining energy supplies and a stimulus for appetite.

An interaction among core body temperature, heat generation by brown adipose tissue, and serum glucose levels has been theorized to influence hunger and consequent energy intake. When core temperature falls, heat generation by brown fat increases, with resultant extraction of glucose from serum. Relative hypoglycemia is likely a stimulus for ingestion. With ingestion, core temperature rises, along with increased oxygen consumption demonstrated in both brown and white adipose tissues, and in skeletal muscle. Whole-body energy expenditure increases after a meal, likely due to the metabolic demands of nutrient absorption and storage (59). Postprandial thermogenesis may influence the initiation and termination of meals, as well as their size and frequency. The evidence for the role of this mechanism in the control of food intake is preliminary.

Taste, texture, temperature, and visual cues all contribute to the effects that food has on appetite and satiety. Food enters the mouth, where at least three chemicals are involved in perception of taste and

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responses to it: substance P, cholecystokinin, and opioids (42). The flavor of foods is perceived as the combination of taste, smell, and chemical stimuli, each activating different systems. Taste is mediated by taste buds, clustered in fungiform papillae over the anterior tongue and foliate papillae on the posterior tongue. The gustatory system is innervated by branches of the seventh and tenth cranial nerves. While there are myriad flavors, there are seven widely accepted flavor categories: sweet, sour, salty, bitter, savory, astringent, and umami.

A large volume of research and anecdotal clinical evidence indicates that taste is a malleable sensation as taste buds respond and adapt to available foods. Taste perception is influenced by food intake. By choosing foods that are more nutritious and allowing time to acclimate to this new taste, we can actually come to prefer the healthier foods over those loaded with sugar, salt, and fat. The beginning of taste preferences commences within the womb with fetal taste bud activation during the 30th week of gestation via substances within the amniotic fluid that are influenced by the maternal diet, with continued taste adaptation occurring through exposure to a variety of flavors during consumption of breast milk as an infant (60). Research into sucrose detection thresholds has demonstrated an age-related stepwise decrease in detection threshold from childhood through adolescence and then to adulthood. Children require a 40% more concentrated sucrose solution than adults do to detect a sweet taste, with adolescents falling in between the child and adult thresholds for sweetness detection (61). Interestingly, children and adolescents with obesity demonstrate less sensitive taste buds when compared to their leaner counterparts (62). Regardless of whether or not this is a cause or a consequence of the obesity epidemic, the opportunity exists to reverse engineer this taste insensitivity. Similarly, patients with type 2 diabetes mellitus demonstrate significant blunting of their sensitivity to sweet taste compared to normoglycemic controls (63). Consumption of a low-fat diet (<20% of calories from fat) for 8 weeks results in a significant increase in participants' sensitivity to the taste of fat compared to baseline, along with upregulation of free fatty acid receptor 4 (FFAR4) gene expression in the fungiform papillae (64). This concept of *taste bud rehab* requires time and the patience necessary to learn to prefer more nutritious foods through habituation and then rely on these foods to help facilitate satiety. Substituting options with less sugar, salt, and fat may be unappealing at first, but within a few weeks the novel taste and texture become the new normal and the health benefits follow suit.

Olfaction is mediated by neurons in the nasal cavities that are components of the first cranial nerve and lead directly to the olfactory bulb in the brain. Acuity of sense of smell is affected by feeding status, with olfactory perception increasing during fasting and decreasing after a meal. Interestingly, genetically engineered mice lacking leptin (*ob/ob*) or leptin receptors (*db/db*) are able to smell and find food approximately 10 times faster than wild-type mice. The hyper-acute sense of smell in these mice can be suppressed via leptin injection. Ghrelin has been shown to boost olfactory acuity in both rats and humans. The chemical properties and physiologic responses that permit the discernment of diverse smells remain speculative. However, there is ample evidence that various odors can either positively or negatively affect appetite and food-seeking behavior (65).

There is also a somatosensory component to taste, responsible for the perception of chemical irritants such as capsaicin. This system is subtended primarily by the trigeminal nerve. There may be some overlap between the perception of chemical irritants and the perception of temperature in the oral cavity (e.g., spicy is perceived as "hot," and menthol is perceived as "cold"). Whereas the function of the chemosensory tissues influences food intake, nutritional status also influences the activity of these tissues, which are metabolically active and have a high rate of cellular turnover.

The visual system is also intimately involved in recognizing and categorizing food cues in the environment in anticipation of consumption. Brain regions involved in object recognition, attention,

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reward processing, and executive decision-making respond differentially to visual cues of food compared with nonfood objects (66–68). Functional neuroimaging techniques reveal an attenuation of activity in the brain's reward area in response to visual food stimuli when humans are fed. This suggests that the physiological state of hunger influences the reward valuation of food (69). This same attenuation can be recreated in the fasted state by the administration of anorectic gut hormones. Furthermore, differences in the brain activity between lean individuals and those with obesity are now providing additional insight into the complex etiology of overeating (70). Food cue reactivity, as well as the conscious experience of craving, is a conditioned response that directly affects food consumption and weight gain in both children and adults. Visual cue reactivity demonstrated for preferred food has many parallels with the craving response to drug cues in the context of drug addiction. Visual food cues delivered via pictures and video have a similar effect as exposure to real food in human subjects. This finding has important implications for both personal and public health interventions in regards to minimizing exposure to advertising messages in an obesogenic food environment (71).

This discussion introduces the distinction between the metabolically regulated, more automatic appetite, controlled by homeostatic mechanisms, and the dimension of food intake that is cognitive-behavioral in nature. As discussed, the gut, along with numerous peripheral signals, influences feeding behavior by generating hunger and satiety signals that are conveyed to the brain. Characterization of the biochemical signals involved in hunger, meal initiation, and satiety has been the subject of extensive research for many years. More recent research reflects the notion that an increasing proportion of human food consumption is driven by pleasure—the hedonic side of food intake. Increased attention is being directed toward the influence of reward sensitivity, the brain's dopaminergic reward pathways, mechanisms of executive function and inhibitory control, and the neurobiology of liking and wanting. In an obesogenic environment, it is abundantly clear that the hedonic response to food stimuli can overwhelm the careful homeostatic balance of the gut–brain axis (72).

Food intake does not follow the neat energy balance paradigm described by the yin and yang of appetite and satiety. Consumption may be in excess of that required to meet energy needs when the food is particularly palatable or the social context is conducive to overindulgence. Food intake may fail to meet the demands of hunger, even when ingestible energy is abundantly available, if the food is unfamiliar or unpalatable. Cravings, for example, represent an extreme expression of appetite, not necessarily driven by physiologic hunger but usually occurring in a particular social or physiologic context, such as during pregnancy, at a party, or at a particular stage of the menstrual cycle. The predominant example of food craving is chocolate (see Chapter 39). Many theories have been advanced to account for various food cravings under various circumstances, but none is entirely conclusive. Cognitive processing of chemosensory properties of food interfacing with the brain's mesolimbic reward pathways determines the hedonic properties, or the capacity of food to induce pleasure. Neuroimaging data show that many of the most pleasurable foods activate the same dopaminergic neural circuits that underlie addictive behaviors (73). The cornerstone ingredients of our obesogenic environment—sugar, salt, and fat—may be undermining the prefrontal executive control that allows us to make rational, healthy choices (74).

The role of genetic and epigenetic factors in regulating energy balance, and consequently body weight, remains a subject of intense interest (75). The ob gene, originally identified in mice in 1994, has been cloned from humans. The gene encodes for leptin, a protein produced by adipocytes that acts as a satiety signal (76). Whereas obese mice homozygous for ob gene mutations are deficient in leptin (77), in humans with obesity, leptin levels correlate positively with percentage of body fat (78). Originally dubbed as "the obesity gene," the ob gene is now one of dozens of genes implicated in weight regulation in humans (see Chapter 5).

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Neuropeptide Y stimulates appetite by elevating levels of insulin and glucocorticoids. In turn, insulin and cortisol stimulate release of leptin, completing an inhibitory feedback pathway between adipose tissue and the hypothalamus. Insensitivity to leptin appears to be the defect resulting from ob gene mutation in humans and is a potential contributor to disordered energy regulation and obesity (79) (see Chapter 5). Epigenetic factors such as deoxyribonucleic acid (DNA) methylation, histone modification, micro-RNAs, endocrine-disrupting chemicals ("obesogens") and factors associated with the intrauterine environment have all been implicated as influencing metabolism and risk of obesity (80). While many of the factors influencing dietary intake patterns appear to be heritable, it is clear that the motivation toward energy intake is multifactorial.

Physical activity can induce an energy deficit comparable to fasting. However, the effects of physical activity on appetite appear to be distinct. Limited evidence suggests that fasting increases hunger, whereas exercise may not (81–83). In fact, evidence indicates that active people have sharper hunger-satiety mechanisms, and hence, improved control of appetite (84). Contrary to popular belief that physical activity increases appetite and caloric intake, men and women can tolerate exercise-induced energy deficits without compensating by overeating (85–87). Conversely, it has been shown that reducing physical activity does not induce a compensatory decrease in energy consumption, thereby promoting a positive energy balance (88). However, studies on the immediate metabolic impact of physical activity are limited by short duration and poor dietary assessments.

Sleep duration, quality, and timing can impact food consumption and metabolism in both children and adults. Sleep deprivation causes elevated levels of cortisol and ghrelin, decreased concentrations of leptin and growth hormone, and can result in impaired glucose tolerance (89,90). These hormonal changes may contribute to increased food intake, preference for calorie-dense food, and changes in basal metabolic rate. A cross-sectional study of children aged 6 to 18 years old revealed that children with short sleep duration demonstrated an increased likelihood of consuming salty snacks, sugar-sweetened beverages, and fast food, along with a decreased likelihood of choosing fresh or dried fruit, fruit juice, milk, or yogurt (91). A small, randomized control trial of adults identified as habitually short sleepers demonstrated a decrease in consumption of free sugars, percentage of fat calories, and grams of carbohydrates after a sleep extension intervention (92). The impact of inadequate sleep is especially significant for night-shift workers, increasing their risk for obesity and impaired glucose tolerance (93).

Aging is associated with apparently minor reductions in taste and smell sensitivity in healthy individuals, but memory deficits, comorbidity, and medication use are issues that compound dietary patterns in older people. Older adults may be subject to nutritional deficiencies due to declines in taste, olfaction, or the regulation of appetite, complicated by social factors that may limit dietary diversity (94).

Dietary preferences are also strongly influenced by cultural factors (95). The physiology of appetite regulation interacts with an array of social and behavioral influences on dietary selection in producing a particular dietary pattern (2). There is reason to believe that early food exposures may play an important role in establishing lifelong preferences, possibly during specific developmental periods (96), although much remains uncertain to date.

Despite this dynamic array of influences, the evidence for central control of appetite and food intake is clear and compelling (97). The complex array of neurochemical signals that influence appetite and satiety appear to converge at the hypothalamus (42,43,98–106). Considering how fundamental food choice is to survival, it is unsurprising that brain regions are demonstrably committed to this function. Even social and environmental factors that influence eating do so, ultimately, by affecting neurophysiology (107) (see Figure 38.2). However, it is now clear that in addition to the homeostatic mechanisms of energy balance, the hedonic influence of reward and pleasure is at play. These central mechanisms governing appetite

evolved in a world of relative caloric scarcity and their functioning are reflective of that (108). That physiology does not clearly facilitate portion control in the modern world should thus come as no surprise. We are genetically hardwired to seek, eat, and covet food as essential means of survival and reproduction. Indeed, food and sex subserve the intrinsic reward system of the brain and are the very reason that the phenomenon of addiction exists!

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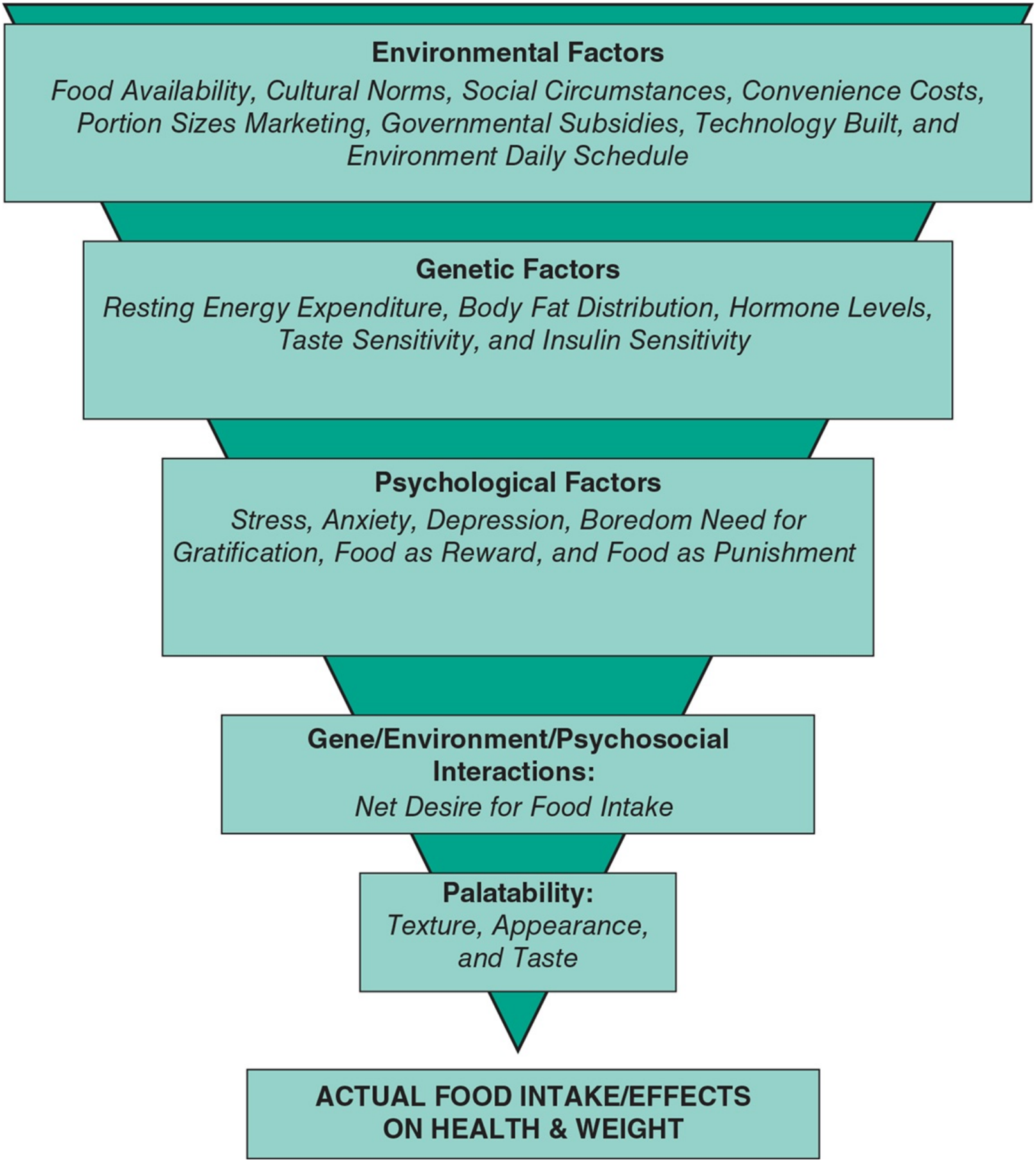

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FIGURE 38.2 The confluence of factors influencing hunger, appetite, and satiety. (Data from Hetherington MM. The physiological–psychological dichotomy in the study of food intake. *Proc Nutr Soc*. 2002;61:497–507.) Ultimately, all such influences must converge to exert an effect on the appetite center in the hypothalamus.

Ideally, many of the modern-world factors (109) that contribute to widespread overeating and weight gain could, and should, be managed by making significant changes in the contemporary environment so that eating well and being active become the path of least resistance (11,12,110–113). Until or unless such environmental changes accumulate, the patient is obligated to overcome the obesogenic challenges of the modern world or succumb to them. The clinician's understanding of the interaction between environmental and physiologic factors influencing appetite and food intake is the starting point for constructive exchanges and productive counseling (see Chapter 47). To gain permanent mastery over appetite, our patients must manage their personal food environment in a way that fosters healthful choices but still allows for flexibility in food choices (13,114). The dietary intake of children can be influenced simply by changing what is conveniently available in the home (115). A book for lay readers offers comprehensive guidance in establishing a "safe" nutritional environment in the home responsive to these considerations (116).

Diet

Foods directly from nature—such as vegetables and fruits—tend to be relatively high in volume and low in calories. Processed foods, in contrast, cram an abundance of calories into minimal space. Numerous studies, predominantly by Dr. Barbara Rolls and her colleagues at Penn State, have demonstrated the importance of food volume to appetite and satiety (117,118). Decreasing food volume contributes to overeating. Simply increasing the volume of foods facilitates satiety when total calories are held constant (119,120). This important concept is the basis for Dr. Rolls's excellent book, *The Volumetrics Weight-Control Plan: Feel Full on Fewer Calories* (121).

One way to increase food volume is to increase fluid content, by eating soups and stews. However, controversy persists regarding the effects of shifting calories from solids to liquids (122,123). In some situations, more liquid calories can actually increase total consumption. A small study involving older adults who consumed 25% of their daily energy needs as either a solid or liquid meal replacement found that postprandial reports of hunger and stated desire to eat were decreased following the solid meal replacement in comparison to the liquid form. Interestingly, insulin and ghrelin levels were also lower after ingestion of the solid meal replacement, with the ghrelin concentration remaining below baseline four hours after meal consumption. In contrast, the liquid meal replacement resulted in a faster glucose spike, and the ghrelin level returned to the participant's fasting baseline by four hours post-ingestion (124).

Energy density is related to volume because it refers to the number of calories per given serving size. Food is energy dense if it packs a lot of calories into a relatively small serving. Highly energy-dense foods likely lead to increased overconsumption (125–129).

Foods high in fat content are the most energy dense, but processed foods with a high sugar content come in a close second. Many processed foods are dense in both fat and sugar and thus are a concentrated load of calories. Because fiber takes up space in food but provides no calories, it has been suggested that simply increasing fiber intake could help control appetite and weight (130). The highly processed food supply has just the opposite influence, stripping fiber from grain products, such as breads, cereals,

crackers, and chips.

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Diets high in energy-dense foods almost certainly contribute to obesity (131), although not every study affirms this (132). Most authorities agree that a shift from high-energy-density foods to low-energy-density foods can be helpful to both weight loss and weight maintenance (133,134) while generally enhancing the healthfulness of the diet.

Reducing the fat content of the diet can help reduce energy density, but only if this means eating more naturally low-fat foods, such as vegetables and fruits, and if highly processed foods are avoided. When calories from fat are removed and replaced with “low fat,” yet equally energy-dense processed sugars (e.g., SnackWell cookies), the all-too-often advertised benefit of weight loss and appetite control appears to be lost (135).

The fiber, protein, and water content of foods all contribute to their ability to produce a sense of fullness with fewer calories, whereas fat content has the opposite effect, increasing the calories needed to achieve satiety (136). High-carbohydrate foods are generally more filling and satiating than high-fat foods (105,137). However, carbohydrate foods can be made energy dense by removing fiber and water and adding sugar and refined starch; and when this happens, they can contribute to excess calorie intake almost as readily as fatty foods (138,139). These are exactly the food supply trends over recent years in the United States and ostensibly the reason carbohydrate is implicated in epidemic obesity (see Chapter 5). While sugar and fat substitutes can be used to take calories out of foods, it’s not at all clear that they can be relied upon to help with weight control (see Chapter 42). The tendency to compensate for these “missing” calories by eating more at other times appears to prevail (140). First, the trend was to cut out fat with “low-fat” diets that actually increased weight gain with processed carbohydrates. Now the trend is to restrict carbohydrates in order to lose weight. Ultimately, it appears that a middle ground with a balanced diet consisting of filling foods with high fiber, water, and protein content may be the winner—a trend toward the middle (141).

All calories are not created equally. Calories from different macronutrients, the properties of individual foods, and the interaction between food groups differentially impact the perceived senses of appetite and satiety.

The lipostatic theory links stores of body fat to regulation of food intake. The release of leptin by adipocytes may be the mediating messenger. Leptin binds to receptors on cells in the hypothalamus that are responsible for the production and release of neuropeptide Y; reduced secretion of neuropeptide Y suppresses appetite (142). Reduced levels of neuropeptide Y stimulate release of norepinephrine, which in turn influences insulin levels and action. The actions of leptin are complex and incompletely understood; some effects may be mediated by interleukin 1, prostaglandins, or both (143,144). Leptin levels vary directly both with fat mass and satiety. The relationship between leptin and satiety apparently is maintained, although perhaps weakened, even in individuals with obesity (145).

A preference for dietary fat among individuals with obesity has been suggested, but the role of taste differences or altered hedonic responses to food in the etiology of obesity remains controversial. Ingested fat induces satiety, but there is evidence that it does so less effectively than does carbohydrate. The energy density of fat, the facility with which it is stored, and its limited satiating effects may all partly explain the epidemiological link between diets high in fat and obesity. A preference for dietary fat can be induced by morphine and suppressed with opiate antagonists, indicating that fat ingestion is reinforced through endogenous opiate production (146).

Physiologic habituation to high fat intake, in the form of enhanced oxidation, has been demonstrated in animals, suggesting that dietary fat may be more rewarding when habitual intake is high (147). In addition to physiologic adaptation, the familiarity of a high-fat diet has been shown to produce preference (148). -

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Post-ingestion effects of dietary fat have also been shown to influence preference (149). In humans, both sugar and dairy fat have been shown to induce dose-dependent pleasure ratings, with the fat not producing an upper threshold (150). The association of sugar and fat in the diet may contribute to excess energy intake, with sugar serving as a vehicle for the caloric density of fat (151).

Calorie for calorie, protein is the most satiating of the nutrient classes (152), followed by complex carbohydrate, then simple carbohydrate, and, finally, fat (137,153–156). Thus, it takes more calories from fat than from either carbohydrate or protein to feel comparably full. Because fat is the least satiating of the nutrient classes, high-fat foods can contribute to overconsumption of calories (157–165).

Given the potent satiety-inducing effect of protein, increasing protein intake—as is recommended in some popular diets—may be of use in weight control (166–168). The aminostatic theory posits that protein status dominates in control of appetite. There is interest in tryptophan as a precursor to serotonin synthesis and in tyrosine and histidine as precursors to catecholamines and histamine, respectively, as these compounds suppress appetite. To date, no direct evidence of specific amino acid effects on satiety has been established. When a diverse source of nutrients is available, protein intake generally constitutes approximately 15% of total calories, suggesting that a protein-specific appetite may be operative. The need for amino acid ingestion would be the putative teleologic basis for a protein appetite.

There is a clear difference between the satiating power of simple and complex carbohydrates (169), and there are very compelling reasons for this. For one thing, complex carbohydrate sources such as vegetables, fruits, and whole grains tend to be rich in fiber, water, or both and thus are high-volume foods. Fiber content may be particularly important because fiber increases food volume without the addition of calories and also can slow the absorption of nutrients into the bloodstream, thereby lowering blood glucose and stabilizing blood insulin levels (170). For lasting weight control, it makes far more sense to choose carbohydrate foods wisely than to abandon them altogether (171).

Some studies have shown that foods with a high glycemic index tend to be less filling than foods with a low glycemic index when calories are matched (172,173), although other studies have failed to confirm this (125,138). (For further discussion of the glycemic index and the glycemic load, see Chapters 5 and 6).

Carbohydrate is less readily stored than fat, less calorically dense, and generally more satiating; nonetheless, ingestion of carbohydrate may contribute substantially to obesity. Sugar, in particular, may stimulate appetite and be subject to a higher satiety threshold than other nutrients (174). Individuals with depression, and particularly those with seasonal affective disorder, may develop carbohydrate cravings. This tendency has been postulated to be a response to low levels of brain serotonin. Low serotonin may be causally related to both depression and excessive hunger (see Chapter 34). Carbohydrate ingestion increases brain uptake of tryptophan, a serotonin precursor.

It has also been suggested that different types of simple carbohydrates have a differential impact on satiety, hunger, and health. In a recent study, glucose reduced cerebral blood flow to brain regions that regulate appetite and reward while fructose did not. Likewise, glucose increased the subjects' feelings of fullness and satiety while fructose did not (175). The degree of polymerization (i.e., mono- and disaccharides, oligosaccharides, and polysaccharides), the type of chemical bonds between the monomers, and the food matrix in which the carbohydrate is contained (i.e., liquid vs solid, cooked vs raw) influence the digestion, absorption, and metabolism of the carbohydrate in question. Additionally, the perception of relative sweetness of various sugars impacts the number of calories required to achieve the desired taste. High doses of pure fructose have been singled out in some studies as being particularly harmful, especially in terms of its effect on the liver. However, humans rarely consume fructose in isolation. Instead, fructose is usually found paired with glucose in the disaccharide sucrose. Mice fed

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fructose and glucose together in a 1:1 ratio, which is the usual scenario in human consumption, demonstrated that a large fraction of the fructose absorbed in the small intestine is converted to glucose in the enterocytes, with minimal fructose spill over to the hepatic circulation (176). In any case, it is clear that simple sugars do not curb appetite and hence contribute to caloric surplus and obesity.

There are many reasons complex carbohydrates would have a favorable influence on appetite and weight control, and simple, highly processed carbohydrates would tend to have the opposite effects. In general, slowly absorbed carbohydrates that result in small, sustained elevations of glucose and insulin are more satiating than rapidly absorbed carbohydrates. This fact suggests that carbohydrate sources rich in fiber, and especially soluble fiber, are more satiating in general than low-fiber sources. Overall, the evidence that whole grains tend to result in a lasting feeling of fullness is quite convincing (177,178). A systematic review of whole, fresh fruit consumption found no evidence of increasing adiposity in study subjects, despite the simple sugar content found in fruit, and noted a trend for decreased overall energy intake associated with fruit consumption, especially when consumed prior to a meal or when utilized as a displacement for more energy-dense foods such as desserts (179). There is evidence that lowering the glycemic load of the diet can help in achieving weight control without hunger (180). A diet with a low glycemic load is limited in highly processed foods and rich in vegetables, fruits, whole grains, and lean protein sources.

Consumption of pulses has been shown to be particularly satiating. A small, randomized cross-over study of healthy adults demonstrated decreased hunger sensations at breakfast following an evening meal of brown beans, in addition to decreased concentrations of ghrelin, blood glucose, insulin, and inflammatory markers, and increased levels of the satiety hormone PYY (181). Adults with overweight and obesity randomized to adding at least five cups of pulses per week to their habitual diet for 8 weeks demonstrated reductions in waist circumference, systolic blood pressure, hemoglobin a1c (HbA1c), high-density lipoprotein (HDL), and C-peptide that were similar or superior to subjects who were randomized to an energy-restricted diet with a goal of decreasing energy intake by 500 kcal/day (182) Again, despite trends toward the extremes, the evidence indicates that a diet that is based on healthful, wholesome foods within each nutrient class facilitates both health and lasting weight control (183). Anecdotal evidence, both from widespread use of the NuVal scoring system and from work with individual patients, indicates that the more nutritious the food, the higher the level of satiety. A higher satiety index is intrinsic to better nutrition. It is, therefore, possible to slim down without starving oneself by trading up for more nutritious food choices and leveraging satiety to fill up on fewer calories.

Simply adjusting the levels of various macronutrients in the diet is unlikely to exert a significant influence on total calories consumed over time (156,184–187). When foods are mixed together, as they always are in any reasonable diet, the satiating influence of each macronutrient class is mitigated by that of each of the other classes (188). There is evidence that the pattern, or distribution, of foods within meals and throughout the day can also influence satiety (189–193).

Overall, the literature on appetite indicates that restricting or emphasizing a single nutrient class is unlikely to have a major influence on appetite or weight, although modest benefits are plausible. Because a balance among the macronutrients—and, more importantly, foods—is required for optimal health, there are bounds imposed upon this strategy by other overriding considerations (see Chapter 45).

Among the forces that influence appetite is *sensory-specific satiety*, the declining pleasure we experience when eating the same food or flavor over time. Our ancestors struggled to achieve the dietary diversity needed to meet nutrient requirements, as discussed in Chapter 44. Some nutritionally challenged populations still do (194). The result is that the human appetite center is specifically adapted to encourage a variety of foods. In nutritionally challenged populations, dietary diversity is desirable. Populations in

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industrialized countries, however, are victims of our successful efforts to make an abundant and diverse food supply continuously available.

The evidence for the influence of sensory-specific satiety on dietary intake is strong (195–198). The variety of food presented at a meal has a measurable impact on the amount consumed (199). Studies demonstrate that repeated exposure to the same, or even similar food, results in achieving satiety on fewer calories (190,200). Raynor et al. (201–204) have conducted several trials suggesting that voluntary limits on food variety are associated with weight control and that imposed restrictions on food variety may be a useful strategy for facilitating weight loss and maintenance. The group advises further study of this strategy. Another study involved a 12-week trial of a meal plan predicated on a purposeful distribution of flavors (i.e., designed to exploit sensory-specific satiety) and providing consistent, high standards of overall nutrition, in 20 overweight adults. The mean weight loss at 12 weeks was 16 lb, and improvements in blood pressure, lipids, serum glucose, and endothelial function were all significant (205).

Independent of other factors, variety in the diet can apparently contribute to excess intake and weight gain (206–210). Energy density and volume potentially alter the point at which sensory-specific satiety is reached (119), suggesting that appetite or satiety influences interact. Flavor may exert a particularly strong influence (211,212).

NUTRIENTS, NUTRICEUTICALS, AND FUNCTIONAL FOODS

Levels of vitamins and minerals derived from our natural diet can have a profound impact on effect on our sense of taste and perception of hunger and satiety.

Vitamin A

Vitamin A deficiency is associated with impairment of taste and smell that may lead to or exacerbate malnutrition. The condition is reversible with vitamin A supplementation (213).

B Vitamins

Atrophy of taste buds occurs with various B vitamin deficiencies, as does glossitis. The condition is quickly reversed with B vitamin supplementation.

Chromium

As addressed in Chapters 5 and 6, chromium supplementation may ameliorate insulin resistance. A small double-blind, randomized study involving overweight patients with binge eating disorder demonstrated reduction in fasting glucose in subjects receiving chromium picolinate supplementation in comparison to placebo controls, with a trend toward weight loss in the chromium supplementation group (214). There is evidence that chromium may suppress hunger in some patients (215).

Copper

Copper deficiency is associated with reduced sensitivity to the taste of salt and a relative salt craving. Copper repletion reverses the condition.

Zinc

Zinc deficiency may impair taste, but definitive evidence in humans is lacking.

Salt

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Preferences for salt have been proved malleable in response to habitual exposure. Exposure to high- or low-salt diets over a period of 6 to 8 weeks has been shown to alter preferences.

Nutraceuticals

A nutraceutical is a product isolated or purified from foods that are generally sold in medicinal forms and not usually associated with foods. Many nutraceuticals have a demonstrated or claimed physiologic benefit to aid in appetite suppression and weight loss. Some of the most popular nutraceuticals are reviewed here.

Hoodia gordonii

Extracts from the plant *Hoodia gordonii* have received considerable media attention as a potential weight loss aid. Chewed by indigenous people of the Kalahari Desert, the plant is purported to suppress appetite. Studies of the plant and its extracts are as yet insufficient to permit any evidence-based conclusion, however (216,217). A recent review suggests that consumption of *H. gordonii* may indeed produce weight loss; however, the lack of robust study data and the potential side effects of hypertension, loss of skeletal muscle mass, and gastrointestinal discomfort preclude it from being recommended for use at this time (218).

Caffeine

Caffeine may slightly boost weight loss or prevent weight gain, but there is no sound evidence indicating that this effect is generalizable or of long term. One theory underlying the possible weight loss and caffeine connection is appetite suppression. Caffeine may temporarily blunt the desire to eat (219). Research also indicates that caffeine, capsaicin, and various teas have the potential to produce significant impact on metabolic targets such as satiety, thermogenesis, and fat oxidation (220).

Sugar Substitutes

Marketed for their ability to promote healthy weight maintenance and weight loss, accumulating evidence now suggests that these substances may not help and may actually undermine weight loss goals (221,222). Research in animal models suggests that sugar substitutes actually increase appetite for sweet foods and promote overeating, perhaps by uncoupling sweetness and energy and blunting the body's ability to gauge caloric intake (223). The dissociation between sweet taste and caloric consequences diminishes the ability of sweet tastes to evoke physiologic responses that regulate energy balance. This model is complemented by a study showing that real sugar is more potent than low-calorie sweetener in stimulating brain areas related to satisfaction and satiety (224). Emerging evidence regarding the effect of sugar substitutes on the microbiome has also raised concerns. Consumption of nonnutritive and low-calorie sweeteners causes quantifiable, and often rapid, changes in the microbiome in rodent and human studies, which may help explain deleterious effects on glucose tolerance and weight gain observed in subjects exposed to sugar substitutes (225,226). To date, there is currently no official recommendation about using artificial sweeteners as a tool for weight control.

Mangosteen (Garcinia mangostan)

Mangosteen is a tropical evergreen tree that produces the mangosteen fruit—sweet and tangy, juicy, and somewhat fibrous with an inedible, deep reddish-purple colored rind. Mangosteen is touted for its

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antioxidants, especially xanthones, and it is promoted to support microbiological balance, help the immune system, improve joint flexibility, and provide mental support. Various parts of the plant have been used in traditional medicine for its anti-inflammatory properties in the treatment of skin infections, wounds, dysentery, and urinary tract infections. Products containing its fruits are now sold widely as "liquid botanical supplements." Evidence for the health benefits of these products is still lacking, and some pharmacokinetic studies reveal poor absorption of active compounds (227,228), although evidence from in vitro and animal studies demonstrates that xanthones inhibit proliferation of a wide range of human tumor cell types by modulating various targets and signaling transduction pathways (229). The American Cancer Society maintains that "there is no reliable evidence that mangosteen juice, puree, or bark is effective as a treatment for cancer in humans" (230). With regard to its ability to promote satiety, the high fiber content may indeed work to this effect, although this is based solely on anecdotal evidence and opinion at this time.

Green Coffee Bean Extract

Green coffee beans are coffee beans that have not yet been roasted and therefore have a higher level of chlorogenic acid—a polyphenol antioxidant—compared to regular, roasted coffee beans. Chlorogenic acid is thought to have health benefits for heart disease, diabetes, and weight loss by reducing the absorption of fat and glucose in the gut and lowering insulin levels to improve metabolic function. Although this product has received much attention in the popular media, few published studies have examined the extract's effects on weight loss and none over the long term. Results from a study funded by a company that manufactures green coffee bean extract found that subjects who took the extract lost about 18 lb on average (231). However, a 2011 review found that green coffee bean extract only lowers body weight by an average of 5.5 lb compared to placebo, and these studies may be compromised by poor quality and design. Moreover, the ingestion of too much chlorogenic acid may actually raise the risk of heart disease by elevating homocysteine levels (232). Given the relatively modest weight loss and lack of long-term data and side effect profile, the verdict is still not out and consumers should approach with caution.

Functional Foods

Functional foods are those foods that are intended to be consumed as part of the normal diet and that contain biologically active components, which offer the potential of enhanced health or reduced risk of disease (233). In other words, these foods contain specific minerals, vitamins, fatty acids, dietary fiber, and/or biologically active substances, such as phytochemicals or other antioxidants and probiotics that have physiological benefits, and/or reduce the risk of chronic disease beyond basic nutritional functions. In the supermarket, functional foods are ubiquitous, including calcium-fortified orange juice, bread fortified with iodine and folate, margarine that lowers cholesterol, and yogurt with probiotics.

Satiety is a weapon in the war on weight, and sales of satiety-promoting functional foods are skyrocketing. The global retail sales value of fortified or functional products amounted to approximately $300 billion in 2017 and is expected to increase to over $440 billion by 2022 (234). Many of these products, such as yogurts and cereals, come with added protein and fiber blends. Flavored water drinks are now sold as replacements for sugared drinks or juices to those trying to lose weight. "Calorie-burning" drinks have become wildly popular as well.

Studies suggesting a possible neuroprotective effect of docosahexaenoic acid (DHA) omega-3 fatty acids, caffeine, and vitamin D (235,236) have encouraged the development of nutritional products promoting brain health in the aging population. Moreover, of course, there is the research investigating the

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connection between the microbiome and chronic diseases (237), which has the potential to spawn numerous products, such as prebiotics and probiotics, designed to manipulate the bacteria that influence our physiologic processes and improve health status. Supplementation with inulin-type fructans prebiotic in diet-induced obese (DIO) mice resulted in reduced fat mass gain, decreased energy intake, partial improvement in sweet taste perception, and modulation of gut dysbiosis in comparison with controls (238). Whether or not these products will have a measurable impact to reduce the human chronic disease burden has yet to be determined, but the future is ripe for further research.

Other

The identification of hormones involved in the regulation of appetite, hunger, and satiety is fostering investigation into synthetic compounds that mimic or block these effects. Some examples are discussed in Chapter 5. Pramlintide, a synthetic analog of the pancreatic hormone amylin, has been approved by the Food and Drug Administration for diabetes management. A 6-week clinical trial showed evidence of suppressed appetite and food intake and facilitated weight loss (239). GLP-1 receptor agonists have shown promise in improving satiety, reducing hunger, and decreasing ad libitum energy intake, as well as delaying gastric emptying, in addition to their beneficial effects in the treatment of hyperglycemia (240). This literature is evolving rapidly and requires continuous monitoring.

PATIENT RESOURCES OF PARTICULAR RELEVANCE

The following books address specific strategies for appetite control while adhering to high standards of overall nutrition for health promotion:

- *The Way to Eat* (116): Provides an overview of strategies for appetite control.
- *The Flavor Point Diet* (205): Explains sensory-specific satiety and offers a 6-week, family-friendly meal plan.
- *The Volumetrics Weight-Control Plan* (121): Provides appetite control guidance and a meal plan based on food volume.
- *Mindless Eating: Why We Eat More Than We Think* (19): Provides insights about diverse influences on food intake.*
- *How Not to Diet: The Groundbreaking Science of Healthy, Permanent Weight Loss* (241): Provides evidence-based guidance on weight-loss strategies.
- *The Pleasure Trap: Mastering the Hidden Force that Undermines Health & Happiness* (242): Explains the "Motivational Triad"—the pursuit of pleasure, the avoidance of pain and the conservation of energy—that influences the lifestyle choices we make daily, and how to consciously influence those choices.

*Some of Professor Wansink's subsequent research has been retracted due to allegations of academic misconduct. In this chapter, we have decided to reference portions of his work highlighting salient points that have been reinforced in other literature.
https://statements.cornell.edu/2018/20180920-statement-provost-michael-kotlikoff.cfm

CLINICAL HIGHLIGHTS

The capacity of clinicians to influence health outcomes in their patients by means of dietary manipulation is ultimately dependent on the patients' capacity to change dietary patterns. This capacity, in turn, is

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dependent on the factors that govern dietary patterns and dietary preferences in the first place. Appetite, hunger, and satiety are mediated by a complex array of biopsychosocial factors.

Although neither patient nor clinician can directly control much of the physiology of appetite, compensations may be built into dietary practices to defend against specific vulnerabilities. When the principal threat to health is excess dietary intake, diet may be manipulated to optimize its satiating properties and minimize the stimulation of appetite. Among the many pertinent strategies (see Chapters 5 and 47) are increasing intake of fiber and complex carbohydrates, avoiding excessive variety within a given day or meal, optimizing protein intake, and restricting dietary fat intake. The effects of volume on satiety support the common practice of drinking water before a meal to help curb appetite, as well as eating foods with a low-energy density, such as salad or whole fruit, as a first course. Conversely, when appetite is poor and dietary intake is inadequate, restricting fiber, increasing variety, and increasing fat intake may provide some compensation (see Chapter 26).

Efforts should be made to encourage parents to establish judicious eating habits in their children early, as dietary habits may be increasingly resistant to change over time. Creativity in the use of ingredients can be used to reduce the fat, sugar, salt, and calorie content of foods while preserving familiar aspects of the diet important in the provision of pleasure (see Section VIII).

A short list of strategies that are supportive of appetite and weight control, and of overall nutritional health, may be confidently conveyed to patients. These include increasing mean food volume by eating naturally high-volume foods such as vegetables and fruits, as well as soups and stews; consuming lean protein foods, predominantly those of plant origin, toward the high end of the recommended intake range to harness the satiating power of both protein and fiber; consuming an abundance of fiber in whole grains, beans, lentils, vegetables, and fruits; and avoiding an excessive variety of foods and flavors at any given meal or snack.

Patients who have been provided with information about the physiology of appetite may be able to make better use of nutrition labels to guard against manipulative food industry marketing schemes. A shared understanding between patient and clinician of the complex and largely involuntary nature of appetite and satiety is supportive of counseling that is practical, productive, and compassionate (see Chapter 47).

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Chapter 39

Health Effects of Chocolate

Adrienne Silver

INTRODUCTION

The epitome of nutritional indulgence (see Chapter 38) that chocolate has over recent years attracted increasing attention because of its health effects. The predominant saturated fatty acid in cocoa butter, stearic acid (18:0), has been found to be nonatherogenic (1–3). Dark chocolate with cocoa content of approximately 60% or more is, in general, a highly concentrated—if not the most highly concentrated—source of bioflavonoid antioxidants as compared to other commonly available foods. Dark chocolate is a relatively concentrated source of fiber as well. Studies have demonstrated benefits of dark chocolate consumption on blood pressure, insulin sensitivity, lipids, and endothelial function; there is observational evidence of a beneficial effect on susceptibility to heart disease. While much about both the allure and the health effects of chocolate remain to be elucidated, the available evidence makes a fairly strong case for the inclusion of dark chocolate in a healthful diet and a decisive case for the substitution of dark chocolate for milk chocolate. Chocolate serves as a particularly good demonstration of the principle that eating well is best achieved by making well-informed choices within any given food category rather than abandoning categories of foods. That even an indulgence can be health-promoting belies the oft-heard lament that “if it’s good, it can’t be good for you.” Dark chocolate, by most accounts, is both.

OVERVIEW

While modern confections containing a great many ingredients are often referred to as “chocolates,” chocolate, per se, is a product of the seeds of the cacao tree, indigenous to Central and South America. Initially used by Mesoamerican peoples to brew a bitter drink, chocolate has been in the human diet for over 2,000 years. The origins of chocolate as a sweet delicacy can be traced to the 16th century and conquest of Central America and Mexico by the Spanish. Cacao was among the spoils of war and thus introduced to European epicures. The addition of sugar to cacao likely first occurred in Spain. Sweet preparations of chocolate were popular among Spanish aristocracy, who had privileged access until sometime after the turn of the 17th century. Chocolate then became a delicacy sought by all the royal courts of Europe; the rest, as the saying goes, is history.

The uniquely alluring, if not addictive, attributes of chocolate are well recognized but only partially understood. Chocolate has a nutritional composition that explains part of its appeal; it is a concentrated source of both fat and, in most commercial preparations, sugar, which are associated with hedonic responses. The texture of chocolate may enhance its appeal, with melting in the mouth serving to distribute and enhance flavor. Of particular interest is variation in chocolate craving associated with the menstrual cycle.

Chocolate craving could be partly explained by biologically active constituents of chocolate, including methylxanthines, biogenic amines, and cannabinoid-like fatty acids, along with a potential influence of chocolate consumption on levels of both serotonin and dopamine (4). Rozin et al. (5) found evidence of

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stronger chocolate craving in females than in males, with menstrual cycle variation. Some have hypothesized that chocolate craving associated with the menstrual cycle is a learned behavior that functions as a strategy for coping with perimenstrual symptoms (6). Hormes and Timko offer an alternative explanation (7). In their study, women reporting chocolate cravings related to the menstrual cycle exhibited different eating behaviors and attitudes compared with women reporting noncyclic chocolate cravings. Menstrual cravers had significantly higher body mass indices and reported greater feelings of guilt, greater levels of dietary restraint, and lower flexible control over intake compared with noncyclic cravers. The authors speculate that menstrual cravings for chocolate may be the result of dietary restriction in attempt to manage cyclic weight fluctuations. On the other hand, recent studies suggest that menstrual cravings may be largely mediated by culture. The work of Rozin et al. suggests that it is the sensory properties of chocolate, rather than neurochemical effects of its xanthine constituents, that account for the cravings it elicits. A 2006 review by Parker and colleagues also concluded that chocolate's sensory properties and palatability are the most likely explanation for its psychoactive properties (8). Because chocolate craving is apparently both potent and rather common, whatever the mechanism, the identification of healthful formulations of chocolate is of genuine clinical significance.

Composition of Chocolate

The nutritional properties of products called "chocolate" naturally vary with their composition. Cacao itself is a fairly concentrated source of caffeine and another related stimulant, theobromine. The attribution of energy-boosting properties to chocolate is likely justified, although it provides less of a jolt than the extract of the coffee bean. While the caffeine content of chocolate is considerably lower than that of coffee (see Appendix E), chocolate is still a relatively concentrated source of the compound. The level of caffeine intake associated with chocolate in the diet is unlikely to pose a health threat to individuals with normal caffeine tolerance, including pregnant women. Highly sensitive individuals and those with cardiac rhythm abnormalities may be adversely affected by caffeine from chocolate (9).

The oil in cacao, referred to as cocoa butter (the name "cocoa" is apparently an early adulteration of "cacao"), is a mixture of predominantly monounsaturated and saturated fatty acids. In the monounsaturated fraction, oleic acid predominates, as it does in olive oil. Roughly 20% of the fat in dark chocolate is monounsaturated.

The saturated fat content in cocoa butter is the most noteworthy. In solid dark chocolate, nearly 80% of the fat is saturated. The predominant fatty acid in cocoa butter is stearic acid (see Chapter 2 and Tables 39.1 and 39.2), an 18-carbon molecule. Whereas shorter-chain saturated fatty acids such as myristic acid (14:0) and palmitic acid (16:0) are associated with increases in low-density lipoprotein (LDL) cholesterol and atherogenesis, stearic acid is not (1). Thus, the fat in dark chocolate is at worst neutral with regard to health effects, if it is not actually salubrious. The nonatherogenic nature of stearic acid was specifically acknowledged by the 2010 Dietary Guidelines Advisory Committee (10), though it was not mentioned in either the 2010 or 2015–2020 edition of the *Dietary Guidelines for Americans*. The reasons for this omission are not obvious, but because the development of the Dietary Guidelines is often influenced by politics and must take into account feasibility and utility of messages for the general population, the continued inclusion of stearic acid under the umbrella of harmful solid fats is likely not due to a lack of scientific evidence. Milk chocolate is slightly more concentrated in palmitic and myristic acid than dark chocolate by virtue of higher milk fat content (the addition of some milk fat to dark chocolate is permitted under the current standards of identity in order to soften the bite of the chocolate) (11), but these differences are modest. The marked divergence in health effects of milk and dark chocolate is most convincingly attributed to the difference in antioxidant content.

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TABLE 39.1

Salient Features of the Nutritional Composition of Common Formulations of Milk Chocolate and Dark Chocolate

Nutrient	Milk Chocolate, 44 g (1.55 Oz) Bar	Dark Chocolate, 44 g (1.55 Oz) Bar, Special Dark
Energy	235.0 kcal	233.0 kcal
Fat	13.0 g	13.0 g
Saturated fat	6.3 g	10.8 g
Myristic acid (14:0)	0.3 g	—
Palmitic acid (16:0)	2.6 g	—
Stearic acid (18:0)	2.7 g	—
Monounsaturated fat	5.8 g	2.0 g
Polyunsaturated fat	0.4 g	0.2 g
Fiber	1.5 g	2.7 g
Calcium	83.0 mg	12.0 mg
Magnesium	28.0 mg	13.0 mg
Arginine	0.1 g	Not provided
Bioflavonoids	Not provided	Not provided

Data from US Department of Agriculture Agricultural Research Service. Nutrient data laboratory. http://www.nal.usda.gov/fnic/ foodcomp/search; accessed November 7, 2007.

TABLE 39.2

Fatty Acids in Cocoa Butter, Dark Chocolate, Milk Chocolate, and Milk Fat[a]

	Product			
	Cocoa Butter[b]	Dark Chocolate[b]	Milk Chocolate[c]	Milk Fat[b]
Saturated Fatty Acids				
4.0				3.5
6.0				2.1
8.0				1.2
10.0				2.8
12.0				3.1
C4.0–C12.0	0.0	0.0	1.3	12.7
14.0	0.1	0.1	1.6	11.0
15.0	0.0	0.0	0.0	0.0
16.0	26.9	25.7	25.4	28.9
17.0	0.0	0.2	0.0	0.0

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18.0	35.2	34.9	32.3	13.4
20.0	0.0	0.9	1.0	0.0
22.0	0.0	0.1	0.0	0.0
24.0	0.0	0.1	0.0	0.0
Monounsaturated Fatty Acids				
14.1	0.0	0.0	0.0	0.0
16.1	0.2	0.2	0.4	2.4
18.1	34.5	34.6	31.6	27.6
20.1	0.0	0.0	0.0	0.0
Polyunsaturated Fatty Acids				
18.2	3.0	3.2	3.0	2.4
18.3	0.1	0.2	0.4	1.5
Other	0.0	0.0	3.2	0.0
Total	**100.0**	**100.0**	**100.0**	**100.0**

[a]*Dark and milk chocolate samples represented are industry averages. Fatty acids are expressed as a percentage of total; all columns add up to 100%*.

[b]*Values derived from* US Department of Agriculture, Agricultural Research Service. *Nutrient data laboratory*. http://www.ars.usda.gov/ba/bhnrc/ndl.

[c]Values derived from Hurst WJ, Tarka SM, Dobson G, et al. Determination of conjugated linoleic acid (CLA) concentrations in milk chocolate. *J Agric Food Chem*. 2001;49:1264–1265.

Whereas the fat content of dark chocolate is at worst neutral in its health effects, other constituents of cocoa render it decidedly favorable in its overall health impact. Salient among these are the bioflavonoid content and antioxidant capacity of dark chocolate. Based on the oxygen radical absorbance capacity (ORAC) as a measure of overall antioxidant potential, dark chocolate is a more concentrated source of antioxidants than most fruits, and it offers more than twice the antioxidant potency of milk chocolate (12).

Along with wine and tea, dark chocolate is a concentrated source of polyphenols that are widely distributed but generally less concentrated in fruits, vegetables, and cereal grains. Animal and cell culture studies suggest protective effects of polyphenolic antioxidants against cardiovascular diseases (CVD), cancers, neurodegenerative diseases, diabetes, and osteoporosis, although definitive human studies in vivo are as yet lacking for the most part (13).

Dark chocolate with 60% cocoa or higher is the most concentrated food source of antioxidants readily available, with a higher antioxidant capacity than green tea (14). The flavonoids in chocolate contribute to its bitterness (15). It is worth noting that cocoa powder that has been treated with alkali, or “Dutched,” contains significantly reduced concentrations of flavanols (16,17). Miller and colleagues compared the flavanol content of commercially available natural (nonalkalized) and Dutched cocoa powders, and found that flavanol content was reduced by 60% to 78% depending on the level of alkalization (17). In addition to flavonoids, dark chocolate is a concentrated source of magnesium, fiber, and the amino acid arginine (see Table 39.1). As discussed elsewhere (see Chapter 7 and Appendix E), arginine may contribute directly to vasodilatory capacity and enhanced endothelial function.

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Epidemiologic Studies

Studies of dark chocolate have quite consistently suggested health benefits (18–20), attributed largely to the flavanol content (21). In their meta-analysis of 10 observational studies, Zhang et al. reported a 25% reduced risk of CVD outcomes associated with the highest versus lowest level of chocolate intake (22). A prospective study and meta-analysis of 6,851 Swedish adults confirmed that chocolate consumption is associated with a lower risk of myocardial infarction (MI) and ischemic heart disease (23). Research on hypertensive subjects demonstrates that a diet high in polyphenols (high consumption of fruits and vegetables, berries, and dark chocolate) resulted in a significant improvement in established markers of CV risk (24).

Epidemiological studies have found inverse associations between more frequent chocolate or cocoa consumption and myocardial infarction (25), stroke (25,26), CHD (coronary heart disease) (27), cardiac mortality (28,29), all-cause mortality (28), and diabetes (30). These findings were further confirmed in Nutrition 2018 following a large meta-analysis. These findings are thought to be related to vasodilatory effects and decreased inflammatory markers (31).

Experimental Trials

Blood pressure and insulin sensitivity: The effects of chocolate or cocoa consumption on blood pressure are perhaps the most well documented. A 2012 Cochrane review of 20 short-term randomized controlled trials reported a small but significant reduction in blood pressure associated with consumption of flavanol-rich chocolate or cocoa compared with low-flavanol or flavanol-free control products (32). In the included studies, daily consumption of commercially available dark chocolate for 2 to 8 weeks reduced systolic blood pressure by 4 mmHg and diastolic blood pressure by about 2 mmHg. These blood pressure–lowering effects seem to occur more readily in hypertensive subjects as opposed to normotensive subjects (33).

Grassi et al. (34) showed both blood pressure reduction and enhanced insulin sensitivity following dark chocolate ingestion in a short-term crossover trial of 15 healthy adults. The test dose in this study was 100 g of dark chocolate, providing roughly 500 mg of polyphenols. These investigators also compared 100 g of dark chocolate providing 88 mg of flavanols to white chocolate for 7 days in a crossover trial of 20 adults with untreated essential hypertension (35). The study showed significant improvements in blood pressure, endothelial function, and measures of insulin sensitivity (e.g., HOMA-IR) following dark chocolate treatment. In a randomized, placebo-controlled, double-blind crossover study, flavanol-rich cocoa intake improved postprandial glucose and lipid metabolism in patients with type-2 diabetes when the meal imposed a large metabolic load. This effect did not hold when subjects were offered a diabetic-suitable meal (36). In another randomized, placebo-controlled, double-blind crossover study, researchers showed improved reaction time on a cognitive test in type 1 diabetics compared to their matched controls (37). Population research has found that eating up to 60 g of chocolate per week is associated with a lower risk of developing diabetes overall by improving insulin resistance and insulin sensitivity (38).

Vascular response: Improvement in endothelial function has been seen in healthy adults (39–43), and in smokers (44), medicated diabetic patients (45), hypertensives (35), and adults with cardiac risk factors (46). The author’s lab has demonstrated improved endothelial function with both daily and single-dose ingestion of flavonoid-rich liquid cocoa, as well as with acute ingestion of solid dark chocolate, by otherwise healthy, overweight adults (41,42). Among subjects with established CVD, study findings are

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mixed, but suggestive of beneficial effects of cocoa products. Farouque et al. (47) did not see beneficial effects on vascular function among subjects with established coronary artery disease (CAD) following 6 weeks of daily dark chocolate ingestion. However, Heiss et al. (48) observed improved endothelial function in CAD patients after 30 days of twice daily high-flavanol cocoa ingestion, compared with low-flavanol cocoa ingestion. In a randomized, controlled trial, Flammer and colleagues reported beneficial short-term effects (2 hours after ingestion) of flavanol-rich chocolate on both vascular function and platelet adhesion in patients with congestive heart failure and sustained effects (over a 4-week period) on vascular function (49). Researchers found that cocoa phenols improve endothelial function in patients with NASH (50). Innes et al. (51) found that 100 g of dark chocolate, but not milk or white chocolate, acutely inhibited platelet aggregation in healthy adults. In a study of 32 healthy adults, daily ingestion of 234 mg of cocoa flavanols daily for 4 weeks significantly inhibited platelet aggregation (52). Furthermore, in 2016, Okamoto et al. found habitual cocoa intake reduces central and peripheral arterial stiffness in postmenopausal women. This reduction in arterial stiffness was also seen after 4 weeks of high cocoa consumption in young men and women (53).

Effects of cocoa products on the lipid panel and oxidative stress are somewhat unclear. Engler et al. (54) demonstrated improvement in endothelial function following dark chocolate ingestion by healthy adults but did not observe between-group differences in measures of oxidative stress or the lipid profile. In contrast, Wan et al. (55) showed reduced LDL oxidation, increased high-density lipoprotein (HDL), and increased total antioxidant capacity in serum with a dark chocolate-supplemented diet in 23 healthy adults over a 2-week period. Fraga et al. (56) demonstrated reduction in both blood pressure and LDL cholesterol in young adult male athletes following consumption of flavanol-rich dark chocolate daily for 2 weeks, with no such changes observed when milk chocolate low in flavanols was consumed. A 2010 meta-analysis of eight trials summarized the short-term impact of cocoa consumption on blood lipids (57). The data from these trials indicate that cocoa may significantly reduce LDL cholesterol, and may also reduce total cholesterol in individuals with cardiovascular risk factors but who have normal cholesterol levels. Interestingly, this does not seem to be found when hypercholesterolemic patients were considered. This evidence should allay fears that the high saturated fat content of chocolate would negate the effects of its other health-promoting compounds.

Overall, population research in adults without cardiovascular disease has found that consuming a higher amount of cocoa is associated with a 10% lower risk of CVD and up to 50% lower risk of cardiovascular-related mortality (58).

Other Health Effects

While the effects of cocoa products on cardiometabolic health are well studied, additional health effects are being newly explored. Weisburger (59) has suggested a possible role for chocolate and cocoa in the prevention of cancer, while acknowledging the need for more research before this benefit can be asserted with confidence. The potential for cocoa flavanols to influence immune function, (60) inflammation, (61) antioxidant status, (62) and apoptosis (63) has been demonstrated and could at least theoretically influence cancer risk.

Desideri and colleagues have demonstrated improvement in cognitive function among older individuals with mild cognitive impairment after an 8-week high-flavanol cocoa drink intervention, an effect the authors speculate may be mediated in part by improvement in insulin sensitivity (64). A 2016 randomized, controlled trial (65) found that dark chocolate attenuates intracellular pro-inflammatory reactivity to acute psychosocial stress in men, and in 2020, a large systematic review of cocoa-derived polyphenols on cognitive function suggested a positive effect on memory and executive function (66). Finally, two studies

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published in 2019 showed that high cocoa supplementation decreased inflammatory levels while improving mobility and quality of life in the older adults. The study authors hope that the sum of such effects may help to mitigate the extent of frailty development in the older population (67). In another randomized, placebo-controlled, double-blind crossover study, researchers showed improved reaction time on a cognitive test in type 1 diabetics compared to their matched controls (68).

Jenkins et al. (69) have published data suggesting that chocolate-flavored cocoa bran has comparable effects on fecal bulk as wheat bran. The authors propose that cocoa bran might be useful in efforts to increase fiber intake in general. Preliminary clinical research shows that taking two to four sachets containing cocoa husks and beta-fructosans can reduce hard stool by 45% and reduce transit time by 36 hours (70). Several studies have suggested that cocoa flavanols may protect skin from damage from UV light (71–73). Twelve weeks of high-flavanol cocoa consumption decreased erythema induced by UV light by 25% in one study (72). In another study, specially produced high-flavanol chocolate, more than doubled the dose of UV light necessary to produce erythema (71). Preliminary research in women with photoaged skin shows that drinking a cocoa drink containing 320 mg of flavanols daily for 24 weeks seems to improve wrinkle depth and skin elasticity compared to placebo (74).

In studies of patients with chronic fatigue syndrome, consuming 45 g of a polyphenol-rich chocolate daily for 8 weeks can reduce fatigue by 35%, anxiety by 37%, and depression by 45% with an increase of overall function of 30% (75).

A systematic review in 2018 showed that cocoa flavanol may improve vascular function, reduce exercise-induced oxidative stress, and alter fat and carbohydrate utilization during exercise while interestingly not affecting overall exercise performance (76). In another study, polyphenol-rich nutrient supplementation reduced exercise-induced muscular injury in elite football athletes (oxid. 2018). Further studies are necessary to examine the synergetic effects of chronic cocoa flavanol intake and exercise training (77).

There is an emerging body of research on the effects of cocoa products during pregnancy. Triche and colleagues assessed the association between consumption of cocoa or chocolate during pregnancy and subsequent risk of preeclampsia (78). Chocolate intake, measured by self-report and by cord theobromine levels, was inversely associated with preeclampsia risk. Klebanoff et al. conducted a similar study assessing maternal serum theobromine levels, but not diet, and did not confirm these findings (79). Saftlas et al. found that chocolate intake in the first trimester was associated with reduced odds of both preeclampsia and gestational hypertension, whereas chocolate intake in the third trimester was associated with reduced odds of preeclampsia only (80). Two randomized, controlled trials have now been completed to evaluate the effects of regular chocolate consumption during pregnancy (81,82). Di Renzo and colleagues randomized 90 pregnant women at approximately 12 weeks gestation to receive either a 30-g portion of dark chocolate daily or no intervention for the duration of pregnancy (82). They found that the intervention group had significantly lower blood pressure and lower levels of liver enzymes at multiple time points throughout pregnancy, compared with the control group. Despite the additional 160 cal provided by the chocolate, there was no difference in weight gain between the groups. In contrast, Mogollon et al. did not find any effect of daily consumption of 20 g high-flavanol dark chocolate for 12 weeks on endothelial function or blood pressure in pregnant women, compared with low-flavanol chocolate (81). This study was shorter in duration and had a smaller sample size (N = 44) than the study by Di Rienzo et al. A review of 14 studies in the *Journal of Maternal Fetal Medicine* confirmed the aforementioned results. Maternal chocolate intake had chronic blood pressure–lowering effects in mothers (83).

Finally, in a 2017 study in the journal *Appetite*, participants who were instructed to mindfully eat

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chocolate had a greater increase in positive mood compared to participants who were instructed to eat chocolate non-mindfully or crackers (84).

Mechanisms of Action

Kris-Etherton and Keen (85) reviewed the evidence for health benefits associated with antioxidant flavonoids in both tea and chocolate. The literature is suggestive of an array of potential benefits, including reduced inflammation, inhibition of atherogenesis, improved endothelial function, reduced thrombosis, and interference with cellular adhesion molecules. In general, such effects have been seen with between 150 and 500 mg of flavonoids. This translates into between 1 and 3.5 cups of tea and from 40 to 125 g of flavonoid-rich chocolate.

Consumption of chocolate has been shown to reduce oxidation products in human plasma (86). Potent anti-inflammatory effects of cocoa extracts have been demonstrated in vitro, with inhibition of interleukin-2 expression in particular (87).

Dark chocolate purportedly inhibits platelet aggregation by several mechanisms (88). Cocoa polyphenols may increase the concentration of HDL cholesterol as well as modify the fatty acid composition of LDL cholesterol and make it more resistant to oxidative damage (89,90). Theobromine may also play a role in increasing HDL concentrations (91).

Potential Risks

Data from the Zutphen Elderly Study (28) reveal an inverse association between cocoa intake, blood pressure, cardiovascular mortality, and all-cause mortality over 15 years. However, overconsumption of chocolate can lead to tachyarrhythmias, supraventricular tachycardia, atrial fibrillation, ventricular tachycardia, and ventricular fibrillation due to its caffeine content (92) Dose–response meta-analysis suggests a nonlinear association of chocolate consumption with all outcomes. For both CHD and stroke, there was little additional risk reduction when consuming more than three servings per week (one serving defined as 30 g of chocolate). For diabetes, the peak protective effect emerged at two servings per week with no benefit observed with increased consumption. Thus, consuming chocolate in moderation may be optimal to gain its protective effects while limiting caffeine consumption, sugar content, and fats (93).

Among the perennial concerns regarding chocolate ingestion, for adolescents at least, is a link to acne vulgaris, which has been demonstrated in several studies. It appears that in acne-prone males, consumption of chocolate correlates to an increase in the exacerbation of acne (94). Another study found a statistically significant increase in facial acne lesions among college students 48 hours after ingesting chocolate instead of jelly beans (average compared with baseline: 4.8 new lesions vs. 0.7 fewer lesions, respectively) (95). However, the author of a recent review article in *Clinical Dermatology Review* believes that further studies are needed to investigate the effect of glycemic index on acne. Overall, he believes there is insufficient evidence to draw a causal relationship between diet and acne vulgaris (96).

Chocolate is often implicated in the trigger of migraine headaches. However, the results of a double-blind study unequivocally demonstrate the risk of developing a headache after the ingestion of chocolate is as likely as administering placebo in patients with migraines. It can therefore be concluded that the widespread belief that cocoa-containing foods should be absolutely avoided by migraine patients lacks a reliable scientific basis (97).

Of course, the health benefits of chocolate may nevertheless come at a cost. Chocolate of any variety is a concentrated source of calories (see Table 39.1). Whereas dark chocolate may offer four times the flavonoid content of green tea, tea is generally a very low-calorie source of antioxidants (98). This trade-off between nutrient value and energy density should be considered when making room for chocolate in a

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healthful and reasonably apportioned diet. Despite the reasonable concern that the caloric density of chocolate could cause weight gain, there is some preliminary evidence suggesting that chocolate could actually have a beneficial effect on body weight by promoting satiety and suppressing appetite (99). In one study in rats, cocoa prevented weight gain associated with a high-fat diet and favorably influenced the expression of genes involved in lipid metabolism (100). Another study in mice found that cocoa supplementation reduced the rate of weight gain and reduced inflammation, insulin resistance, and the severity of fatty liver disease in mice fed a high-fat diet (101). However, cocoa does not have the high fat and calorie content of chocolate; it is plausible that these negative attributes of chocolate would neutralize or even outweigh the benefits of cocoa. In a small study in women, Massolt and colleagues found that smelling or eating dark chocolate decreased appetite acutely (102). SØrensen and Astrup compared the appetite-suppressing effects of milk chocolate and dark chocolate in a crossover study in men (103). They found that 100 g of dark chocolate decreased appetite and energy intake at an ad libitum meal compared with an equal quantity of milk chocolate. After adjusting for a difference in energy content between the two types of chocolate, energy intake was 8% lower in the dark chocolate condition. The authors speculate that the more intense flavor of the dark chocolate may have contributed to greater feelings of satiety. This explanation is consistent with previous study findings indicating that a chocolate bar rated as intense in flavor produced more sensory-specific satiety than other less intense snack items (104).

Although there is currently little evidence of an antiobesity effect of chocolate, there is also no clear indication that moderate chocolate consumption leads to weight gain. One cross-sectional study found an inverse relationship between frequency of chocolate consumption and body mass index among healthy adults (105). In contrast, Greenberg and Buijsse observed a significant dose–response relationship between higher frequency of chocolate consumption and greater weight gain during a 6-year follow-up period in a large prospective cohort study (106). However, randomized trials have not typically found an increase in weight after sustained consumption of small amounts of cocoa (41,45–47) or dark chocolate (54). In one study, a daily dose of 25 g (125 kcal) of dark chocolate slightly increased body weight after 3 months, but a 6 g dose (30 kcal) was not associated with any weight change. Both doses were effective in reducing blood pressure (107). To minimize the potential for weight gain, identification of the smallest effective dose of chocolate for a particular condition and population group should be a goal of future research.

Environmental Concerns

The impact of cocoa farming practices on the environment and human rights has drawn some attention (108,109). Large forested areas are often cleared to plant cocoa trees that can grow in full sun, increasing short-term yields, but dramatically reducing biodiversity. Shaded growing systems retain some, but not all, of the biodiversity of an undisturbed forest. Full sun growing conditions also contribute to increased fertilizer and pesticide use and produce yields for a shorter period of time than shaded systems. Franzen and Mulder have provided a thorough review of pertinent issues in cocoa production (110). Also of concern is the use of child labor on cocoa farms in West Africa. Child labor and associated exposure to pesticides and other hazards of physical work have been relatively well documented (111,112). Cases of slavery have also been reported (113).

Consumers who are aware of these issues may understandably have reservations about consuming chocolate for health benefits or may be confused about how to find chocolate that has been sourced in a way that is ethical and environmentally responsible. There is no simple solution to these concerns. Some brands of chocolate may carry labels like “Organic,” “Fair Trade” (114), or “Rainforest Alliance Certified,” (115) but no single certification guarantees that the chocolate’s production did not involve any

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child labor, unfair pay to farmers, or harm to the environment. In response to the pitfalls of third-party certification, some companies are turning to direct trade with cocoa farmers, in what has been called a "bean-to-bar" movement (116). This approach allows chocolate manufacturers to ensure that farmers are paid well and are using sustainable farming methods and fair labor practices.

Nutrigenomic and Metabolomic Considerations

At present, there are no known studies of diet–genome interactions pertaining to cocoa and chocolate consumption. However, there is some evidence that individual characteristics may modulate the effects of chocolate. For example, Martin and colleagues observed different metabolic profiles and response to dark chocolate consumption in individuals who reported high levels of anxiety compared with those who reported low anxiety (117). The concentrations of several metabolites in urine were significantly different between the groups at baseline. After the dark chocolate intervention, these differences were reduced such that the metabolic profiles of high-anxiety participants more closely resembled those of low-anxiety participants. Specifically, urine concentrations of catecholamines, corticosterone, and cortisol all decreased during the intervention period in participants who reported high levels of anxiety. In a subsequent study, Martin et al. also identified specific metabolic profiles associated with habitual chocolate consumption, suggesting that long-term exposure to chocolate influences gut bacterial metabolism (118). After 1 week of twice-daily dark chocolate consumption, a significant increase in HDL was observed in both habitual chocolate consumers and nonconsumers. However, only the habitual chocolate consumers experienced reduced triglyceride concentrations. It is now becoming clear that the gut microbiome influences the metabolism of cocoa polyphenols (119). Interindividual differences in the production of metabolites by microbiota from the molecular components of cocoa are relevant because these metabolites may lead to observable health effects. However, the complex relationship between the many phenolic metabolites of cocoa and their physiological effects is not yet fully understood.

CLINICAL HIGHLIGHTS

It is virtually idiomatic for the public at large that foods that taste good are bad for health. Yet accruing evidence suggests that one of the most widely preferred of all foods—chocolate—belies this notion, provided that the chocolate is chosen wisely.

Accumulating evidence of the health benefits of dark chocolate is quite convincing. A dose of 1 to 2 ounces of dark chocolate (60% cocoa content or higher) several times per week appears to be sufficient to confer benefit. Current evidence strongly supports improvement in cardiovascular risk factors, and blood pressure in particular. Recent studies suggest that dark chocolate may reduce blood pressure during pregnancy, when the effects of hypertension are especially perilous. There is also preliminary evidence for a protective effect on cognitive function, metabolic health, immune function, and carcinogenesis. The most salient potential risk of chocolate consumption is weight gain, but such risk is largely theoretical. Additional studies are needed to establish benefits of cocoa and chocolate beyond cardiovascular protection, to confirm a null effect on body weight, and to determine whether the physiological effects of cocoa vary by individual characteristics such as genotype.

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Chapter 40

Health Effects of Ethanol

Anthony Saenz

INTRODUCTION

Ethanol ingestion epitomizes for clinical and public health nutrition the concept of the double-edged sword. The harms of excessive alcohol consumption contribute mightily to the toll of preventable self-inflicted pathology. Worldwide, 3 million deaths are attributable to alcohol each year, which represents 5.3% of all deaths annually (1). Excessive alcohol consumption in the United States costs $249 billion annually, or approximately $750 per adult, or $2 for every drink sold in 2010 (2). But the cardiovascular benefits of alcohol ingestion are also well characterized. This dichotomy is further compounded by the relatively narrow therapeutic window for ethanol and the fact that its dose-dependent risk or benefit ratio varies with circumstance (e.g., driving, medical comorbidities, and pregnancy). There are thus ramifications related to the health effects of alcohol ingestion that pertain to public policy, law, and risk communication. Much of this is beyond the scope and intent of the current chapter. The focus here is limited to the common health effects, salutary and adverse, of dietary alcohol at or near recommended intake levels.

OVERVIEW

Alcoholic beverages vary widely in total nutrient composition. The common ingredient of interest is ethanol. Ethanol, otherwise known as ethyl alcohol, is one of several varieties of alcohol, and it is the predominant one in beverages. Ethanol, represented by the molecular formula C_2H_6O, is a fermentation product of sugar acted upon by several varieties of yeast in the absence of oxygen. Brewing refers to the process of combining yeast with fruits or germinated grains to produce ethanol.

Brewing can produce an alcohol concentration of up to approximately 25% by volume; more concentrated alcohol is toxic to the yeast. Alcoholic beverages are thus divided generally into fermented beverages and distilled beverages (“hard” alcohol). The ethanol concentration of fermented beverages, including beer and wine, is limited by the tolerance of yeast. Distilled beverages, such as whiskey, gin, rye, vodka, and diverse spirits, concentrate alcohol well beyond the tolerance of yeast. The concentration of alcohol in beverages is often expressed in terms of “proof” units. In the United States, proof is twice the percentage of alcohol content. By law, alcoholic beverages in the United States must indicate the percentage of alcohol content on the container.

Epidemiological study suggests that there are net health benefits from modest alcohol ingestion as compared to no intake at all. It is from this comparison that guidance for an advisable intake level derives. The Dietary Guidelines for Americans 2015–2020 advises, for those who choose to drink alcohol and are safe to do so, a daily consumption limit of up to one drink for women and up to two drinks for men and classifies this level of consumption as moderate (3). A drink is defined as 10 to 15 grams of ethanol contained in 12 fluid ounces (fl oz) of 5% alcohol by volume (ABV) beer, 5 fl oz of 12%

ABV wine, or 1.5 fl oz of 40% ABV (80 proof) distilled spirits.

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A meta-analysis of 60 studies from 2010 to 2020 by the Dietary Guidelines Advisory Committee showed an increase in all-cause mortality in those with higher alcohol consumption compared to those with lower average consumption. Most studies found that men who drink up to two drinks per day and women who drink up one drink per day were at lower risk. In studies to determine more precise dose-dependent data it was shown, among men who drink, the lowest levels of risk occurred with the consumption of up to one or one and one-half drinks on average (4). Few studies looked at that risk for women with consumption of less than one drink per day on average.

Evidence for a cardiovascular benefit of alcohol has been available for decades (5) and is strong in the aggregate, although it is lacking in long-term randomized control trial data (6). Human epidemiological data from such sources as the Health Professionals Follow-Up Study in the United States (7) and the WHO's MONICA (Monitoring Trends and Determinants in Cardiovascular Disease Project) trial in Europe (8) suggest a reduction in cardiovascular mortality and morbidity with moderate alcohol intake and a reduction in all-cause mortality more specifically associated with red wine intake. The INTER-HEART study, a case–control study following 27,000 patients from 52 countries, found an association between regular alcohol consumption and a reduced incidence of myocardial infarction in both genders and in all age groups (9). A 2011 meta-analysis of 84 observational studies found a reduced relative risk in cardiovascular disease mortality (0.75) and incidence of coronary heart disease (0.71) with light-to-moderate consumption (10). Alcohol-induced cardiomyopathy is a well-known complication of chronic, heavy alcohol use, while light-to-moderate use may be protective against the development of heart failure (11,12).

Evidence from population studies suggests that moderate alcohol intake may also reduce the risk of type 2 diabetes by as much as 40%, independent of other influences, although excessive intake increases such risk (13,14). This dose-dependent risk increase demonstrates a J-shaped curve as heavy alcohol use has been associated with increased mortality, in part secondary to decreasing cardiac ejection fraction and progressive left ventricular hypertrophy (15–17). Increased levels of adiponectin, an adipocyte-derived plasma protein associated with insulin sensitivity, have been seen with moderate alcohol use (18). Effects on stroke risk are unresolved, with available evidence suggesting neutral effects at recommended intake levels and harm with higher doses (19–22).

Mechanisms for the beneficial effects of ethanol have been elucidated in human, animal, and cell culture studies (23). These include enhanced insulin sensitivity, increases in high-density lipoprotein (HDL) cholesterol, decreases in fibrinogen, increases in plasminogen and endogenous TPA, reduced inflammation, reduced platelet aggregation, reduced Lp(a), and improved endothelial function (8,17,24–26). Ethanol, when consumed by diabetic patients in small-to-moderate quantities with or immediately before the evening meal, has been shown to substantially reduce the glucose release following the meal (27,28). This important biologic phenomenon may play an important role in the epidemic of diabetes and obesity our nation currently faces. The biologic mechanism whereby alcohol improves insulin sensitivity is thought to involve the suppression of fatty acid release from adipose tissue, which decreases substrate competition in the Krebs cycle of skeletal muscles and facilitates glucose metabolism (17,27). Some studies suggest that ethanol is the primary explanation for such effects (26,29,30), whereas others have highlighted the potential importance of nutrients other than ethanol (31–34).

Red wine is one such beverage thought to offer health benefits for reasons other than its ethanol content (35–38). Bioflavonoid antioxidants are concentrated in the skins of grapes and are thus present in red wine. Several such nutrients, including proanthocyanidins and the flavonoids resveratrol and quercetin,

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are thought to contribute to the health profile of red wine. One paper (39) suggests that when highly concentrated, resveratrol, a compound found in red wine, may influence several key enzymes, such as SERT1 and genes involved in senescence, and may slow aging in mice in a manner similar to calorie restriction. One study on the effects of a resveratrol-containing extract found higher levels of adiponectin, an anti-inflammatory compound, and lower levels of thrombogenic plasminogen activator inhibitor type 1 (PAI-1), an inflammatory compound, in the intervention group (40).

Another study found that 1-year consumption of a resveratrol-rich grape supplement improved the inflammatory and fibrinolytic status in patients who were on statins for primary prevention of Cardiovascular disease (CVD) and at high CVD risk (41). Another study randomized 67 men with a high cardiovascular risk and randomly assigned them to consume red wine, dealcoholized red wine, and gin for 4 weeks. Both forms of wine were associated with decreases in markers of insulin resistance between 22% and 30%, while HDL levels in the groups who consumed alcohol (either red wine or gin) were statistically higher than those from the dealcoholized wine (38). Yet another study by Agarwal et al. found significantly decreased expression of proinflammatory markers (endothelial cell intercellular adhesion molecule [ICAM], vascular cell adhesion molecule [VCAM], and interleukin 8 [IL-8]) in patients who took a resveratrol supplement in comparison to placebo (42). The results of these studies collectively indicate that there are independent benefits from both wine (alcoholic or not) and the alcohol consumed (38). Of note, higher HDL-cholesterol levels have been linked to a significantly reduced risk for cancer (43).

Overall, wine consumption at prudent levels has been suggested to lower all-cause mortality rates by as much as 30% (44,45). Some researchers suggest that beneficial changes to hematologic parameters, such as whole blood viscosity and red blood cell deformability, contribute to these effects (46,47).

The harms of excessive ethanol ingestion are well established and are addressed to a limited extent in Chapter 17. There is some potential for harm at the recommended intake level as well (48). Such harms include increased risk for liver disease, pancreatitis, metabolic syndrome, and oropharyngeal, esophageal, colorectal, prostate, colorectal, and breast cancers (49–53). Consistent evidence exists that links even light alcohol use to breast cancer. Overall, it is estimated that up to 4% of all breast cancers diagnosed in developed countries may be attributable to alcohol ingestion (54). Several large epidemiological studies suggest that alcohol increases the risk of estrogen receptor-positive breast cancer in a dose-dependent manner, with a relative risk increase of roughly 30% ascribed to moderate intake (55–57). A prospective observational study of over 105,000 women enrolled in the Nurses' Health Study followed over 28 years evaluated the relative risk of developing invasive breast cancer and found that binge drinking, but not frequency of drinking, was associated with increased breast cancer risk after controlling for total alcohol intake. The authors noted that alcohol intake both earlier and later in adult life was independently associated with risk (58). In another large prospective study of over 87,000 women, Li et al. found an association between alcohol intake and hormone receptor-positive breast cancer of lobular type but not ductal type, when compared to nondrinkers (59). The Nurses' Health Study also showed a twofold increase in risk of breast cancer in women who consumed more than one alcoholic drink a day in addition to use of postmenopausal hormones for ≥5 years (60). Links to low folate intake in women who drink alcohol have also been made to breast cancer (61). Interestingly, two published reports assessing alcohol intake as a risk factor for breast cancer recurrence and mortality found no increased association between modest alcohol intake and increased breast cancer events or mortality (62,63).

In addition, it has been noted that alcohol consumption is associated with increased prostate cancer risk, and this association is stronger among men with low folate intake (51), whereas a protective effect with light-to-moderate alcohol intake has been noted in association with renal cell carcinoma (64) and

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endometrial cancer (65). The mitigation of cancer risk with high folate levels also occurs with breast cancer risk, with higher folate levels being associated with lower cancer risk (66–69). Therefore, promoting diets rich in folate may be an important strategy for cancer prevention in both men and women who drink alcohol.

Colorectal cancer appears to be influenced by alcohol intake as well, with two meta-analyses showing a 50% increased risk for colon cancer and a 63% increase in rectal cancer in one analysis (70) and a 63% increase in risk for adenomas among higher alcohol consumers in the EPIC cohort (71). On a more positive note, dietary folate intake (but not supplemental folate) was found to have a protective effect on colon and rectal cancer risk among over 56,332 Danish subjects of the Danish Cohort Study who consumed more than 10 g of alcohol per day (72). The dose at which ethanol confers net harm rather than benefit is highly variable, due at least in part to variations in genes for key alcohol-metabolizing enzymes, including alcohol dehydrogenase (73).

A 2013 study by Barrio-Lopez et al. found an increased risk of developing metabolic syndrome in subjects consuming seven or more alcoholic beverages per week. These subjects were found to have elevated risks of hypertriglyceridemia as well as impaired fasting glucose. Beer consumption was independently associated with a higher risk for metabolic syndrome and hypertriglyceridemia (53). There are also individuals for whom any ethanol intake at all is more likely to do harm than good; these include anyone with a family history, and presumably the associated genetic polymorphisms, that predispose to alcoholism. Genetic polymorphisms likely also influence the probability of health benefit from moderate alcohol consumption (74).

Heavy alcohol use carries an increased likelihood of developing pancreatitis, though mild-to-moderate use may also lead to a slightly elevated relative risk (75). Moderate consumption may lower the risk of gallstones (76) with a proposed mechanism of reduction in biliary cholesterol saturation index based on animal models (77). Alcohol intake carries a dose-dependent increase risk of gout (78), though moderate wine drinking may not confer the same probability (79). Alcoholic liver disease describes a spectrum of disorders from fatty liver to alcoholic hepatitis, cirrhosis, and hepatocellular carcinoma. A dose-related relationship between alcohol ingestion and development of alcoholic liver disease has been reported (80). In heavy drinkers, 90% to 100% have steatosis, 10% to 35% have alcoholic hepatitis, and 8% to 20% have alcoholic cirrhosis (81).

Long-term effects aside, the consumption of alcohol is associated with a greater risk of morbidity and mortality from trauma (82), violence (83), and suicide. In a prospective study of over 128,000 Californians, those who drank six or more alcoholic beverages in a day were 6 times more likely to die from suicide, seven times more likely to die from homicide, and two times more likely to die by motor vehicle accident (84). Light drinking did not confer the same risk. Though the link is complex, the lifetime risk of alcohol use disorder is higher in those with major depressive disorder (85).

Both the quantity and distribution of ethanol intake have health implications. Intermittent binges, even when the average daily intake is at recommended levels, have potentially adverse effects (49). Among these, the holiday heart syndrome, the induction of potentially lethal cardiac rhythm abnormalities following an alcohol binge (86,87), is noteworthy.

Overall, alcohol is a proverbial double-edged sword with regard to health effects, with potential to do both good and harm (49,13,19,88,89). The cumulative evidence of its effects has led many authors to recommend it with some enthusiasm (90,91) and others to urge caution (24).

CLINICAL HIGHLIGHTS

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The 2015–2020 Dietary Guidelines for Americans (3) do not specifically recommend the consumption of alcohol as part of a health-promoting diet but rather specify the intake level advisable for those adults who choose to drink. That level is up to one drink per day for women and up to two drinks per day for men on days that alcohol is consumed. They do not recommend that individuals who do not drink alcohol start drinking for any reason. Some recent evidence points to increased mortality at lower levels for both men and women, so future updates will be necessary to follow (4). Globally in 2016, alcohol use was the leading risk factor in premature death and disability among those of age 15 to 49 years, leading some to believe that potential health benefits are outweighed by the detriment to a population as a whole. In this article published in *The Lancet*, the author proposed that the level of alcohol consumption that minimized health loss was zero drinks per week and called for revised global policies for alcohol consumption control (92).

The case against a clear recommendation for alcohol consumption is predicated on several salient considerations. First, alcohol intake is neither recommended nor in many cases even legal for children. Second, alcohol is not an essential component of diet, nor does it, in its various forms, provide nutrients known to be essential and unavailable from other sources (93). Third, the toxicity of alcohol at excessive intake levels is clearly established, the therapeutic window separating healthful and harmful doses is relatively narrow, and the toxic dose varies substantially with individual vulnerability, predicated in part on variability in the activity of alcohol dehydrogenase and related enzymes (94–96). Fourth, the potential toxicity of alcohol varies with circumstance, and thus even a healthful intake level might be acutely harmful if ill-timed. In lieu of high obesity rates and an ever-increasing caseload of patients with metabolic syndrome, the energy density of alcohol might contribute a fifth indictment (53,97). Lastly, excessive alcohol intake has increasingly become a problem and binge drinking is on the rise (98), leading to difficulties in less individualized recommendations.

Despite these issues, however, a case can be made for the inclusion of alcohol in a health-promoting diet. Alcohol is featured along with fish, dark chocolate, fruits, vegetables, garlic, and almonds in a “polymeal” with the purported potential to reduce heart disease risk by more than 75% (90,40,41). Alcohol is prominent in the healthful Mediterranean diet and often invoked as a full or partial explanation for the “French paradox” (99).

Given the diverse implications of alcohol consumption for health, individualized clinical guidance is clearly warranted. In specific cases, some self-evident (e.g., a history of alcoholism or liver disease) and some less obvious (e.g., a family history of breast cancer in a female patient), arguments against alcohol consumption will carry the day. Some argue that the potential for harm exceeds any potential benefit for the population at large (92,100). This view notwithstanding, a cautious recommendation for moderate intake of alcohol for those who choose to drink and are safe to do so is reasonably well justified for the average adult patient (91,101).

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Chapter 41

Health Effects of Coffee

Julet O. Baltonado

INTRODUCTION

Coffee is one of the most widely consumed beverages around the world, and caffeine from coffee, tea, and chocolate constitutes the world's most popular psychoactive substance. Although known mostly for its caffeinated properties, coffee contains multiple bioactive compounds with potential health effects. Recent evidence supports an inverse association between coffee consumption and total as well as cause-specific mortality, including deaths from heart disease, respiratory disease, stroke, injuries and accidents, diabetes, and infection. Coffee consumption also has an inverse association with risk of a wide variety of chronic diseases, including type 2 diabetes mellitus, Alzheimer's disease (AD), Parkinson's disease (PD), and alcohol-related liver disease. Moderate coffee consumption appears to be safe for most individuals, but caution is advised for pregnant women, the elderly, and those with cardiovascular disease. Further research is warranted to help elucidate the precise mechanisms and extent of the potential health benefits of coffee.

OVERVIEW

Coffee contains several components with potential impact on human health (1), including caffeine, antioxidants, magnesium, potassium, and niacin (2). The major active ingredient in regular coffee is caffeine, a xanthine alkaloid compound. The main dietary sources of caffeine include coffee, tea, soft drinks, chocolate, and increasingly a wide variety of energy drinks (see Table 41.1). Though known to be mildly addictive, caffeine is considered by the Food and Drug Administration as a multiple-purpose GRAS (generally regarded as safe) substance (3).

Caffeine acts as a stimulant to the central nervous system, primarily through antagonism of adenosine receptors (4), leading to increased activity of dopamine and the experiential effects of enhanced alertness and reduced physical fatigue. Caffeine is rapidly absorbed from the gastrointestinal tract, and maximum serum caffeine concentrations peak within 90 minutes after ingestion. Caffeine metabolism is carried out by the liver's cytochrome P450 1A2 enzyme (CYP1A2). Variations in individual's response to caffeine may be explained by genetic polymorphisms in the CYP1A2 gene. People with defects in CYP1A2 may have impaired metabolism and prolonged effects, both desired and undesired (5). It is estimated that mean dietary caffeine consumption among adults in the United States is approximately 106 to 170 mg per day (6), with coffee being responsible for 64% of caffeine intake (7). This is well within the daily limit of 400 to 450 mg proposed by the members of the Canadian Bureau of Chemical Safety (8).

There has been a beneficial association between coffee and all-cause mortality, consistent across large cohort studies and meta-analyses. Compared with no consumption, coffee consumption is associated with lower risk of all-cause mortality, even after adjustment for potential confounders (9–11). The most recent meta-analysis found that the largest reduction in relative risk is associated with the consumption of three cups of coffee a day (12).

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High-dose caffeine consumption and withdrawal from regular consumption can lead to adverse effects. Consumption of caffeine in excess of 250 mg at one time (approximately two to three cups of brewed coffee) may lead to a distressing set of symptoms that include palpitations, insomnia, anxiety, psychomotor agitation, and gastrointestinal distress. The *Diagnostic and Statistical Manual of Mental Disorders* includes diagnostic criteria for four related psychiatric disturbances: caffeine intoxication, caffeine-induced sleep disorder, caffeine-induced anxiety disorder, and caffeine-related disorder not otherwise specified (NOS) (13). In contrast, caffeine withdrawal can induce headaches, drowsiness, depression, and irritability. Both caffeinated and decaffeinated coffee may cause or exacerbate symptoms of peptic ulcer disease, erosive esophagitis, and gastroesophageal reflux disease (see Chapter 19). Moderate to high amounts of caffeine intake in those with bladder symptoms may be associated with an increased risk of detrusor instability and urinary incontinence (14,15), with newer studies suggesting that caffeine activates micturition centers in the brain (16).

TABLE 41.1

Amounts of Caffeine in Common Sources of Dietary Caffeine

Product (Serving Size)	Caffeine Content per Serving (mg)
Brewed coffee (8 oz)	96
Espresso (2 oz)	127
Instant coffee (8 oz)	62
Hot black tea (8 oz)	48
Caffeinated soft drink (12 oz)	34
Dark chocolate, 70%–85% cacao (1 bar, 101 g)	81
Milk chocolate (1.55 oz bar)	9
Hot cocoa (12 oz)	8–12
Energy Drinks (8–16 oz)	50–300

Adapted from US Department of Agriculture, Agricultural Research Service, 2020. Data obtained from the USDA FoodData Central. https://fdc.nal.usda.gov/index.html.

Caffeine appears to cause a slight negative shift in calcium balance (17). High caffeine intake in older adults with preexisting vitamin D or calcium deficiencies may increase the risk of hip fractures (18). However, there continues to be conflicting evidence on the overall effect of coffee consumption on bone mineral density and the development of osteoporosis (19–22) (see Chapter 14).

Coffee consumption was first associated with increased blood pressure in the 1930s (23). Both caffeinated and decaffeinated coffee have been shown to raise blood pressure acutely by as much as 10 mmHg in nonhabitual caffeine consumers (24), with greater effects seen in individuals with preexisting hypertension (25); however, these effects are all but eliminated with regular caffeine consumption (24).

Results from long-term studies are showing that chronic coffee intake may not increase the risk for hypertension over time, as was previously thought (26). A meta-analysis of six prospective cohort studies totaling 172,567 participants found that habitual long-term coffee intake was not associated with an increased risk of incident hypertension (27). Of note, in a subgroup analysis of individual classes of caffeinated beverages, investigators did find an increased risk of hypertension associated with consumption of sugared or diet cola beverages (28) (see Chapter 8).

Case reports have documented the development of clinically significant cardiac arrhythmias following

the ingestion of extremely high doses of caffeine, especially in those with underlying cardiac disease (29). Reports of adverse events related to energy drinks and supplements, including hospitalizations and several deaths, continue to be collected by the Food and Drug Administration. Over the recent years, there have been a growing number of case reports linking energy drinks to cardiac arrhythmias in adolescents and young adults. These adverse outcomes are attributed to the high concentration of caffeine paired with other supplements and stimulants in these energy drinks (30–32). Energy drinks should be consumed with caution, especially in children and teenagers.

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The evidence to date does not support an association between moderate doses of caffeine and increased risk of atrial (33–35) or ventricular (36) arrhythmias, even among patients with existing arrhythmias (37). One large meta-analysis including over 115,000 individuals found that low-dose caffeine may even have a protective effect (38). A prospective long-term cohort of 18,960 male physicians found a lower risk of atrial fibrillation only among those who drank one to three cups daily (39).

Current evidence does not support a clear association between coffee intake and increased risk of coronary heart disease (40,41). In fact, a recent umbrella review of multiple meta-analyses found that coffee consumption was consistently associated with a lower risk of mortality from both cardiovascular disease and coronary heart disease (42). However, coffee consumption may be associated with increased incidence of cardiovascular risk factors, which may indirectly affect cardiovascular health. For example, two substances in unfiltered coffee, kahweol and cafestol, have been shown to raise serum total cholesterol levels, low-density lipoprotein levels (43), and triglyceride levels. This effect was more significant with caffeinated unfiltered coffee, even after excluding participants who already had hyperlipidemia (44). The difference in preparation method has become more relevant as unfiltered coffee has increased in prevalence. More studies distinguishing preparation method, comparing boiling, filtering, French press, and brewed are warranted. The effects of cafestol and kahweol can generally be avoided by switching from unfiltered to paper-filtered coffee (45).

Caffeine crosses the placenta, and there is some evidence suggesting possible adverse effects on fetal growth and development (46). Evidence for an association between caffeine consumption and increased risk of spontaneous abortion is mixed (47–49); Signorello and McLaughlin (50) reviewed the evidence in 2004 and concluded that although many studies to date had found evidence of an association between caffeine intake and miscarriage, the methodological limitations and biases inherent in a majority of the studies precluded clear causal inferences. The 2015 Cochrane review also found insufficient evidence from randomized trials to either confirm or refute the potential for caffeine avoidance or consumption to affect pregnancy outcomes (51). The American College of Obstetricians and Gynecologists developed an updated consensus statement in 2013 that less than 200 mg of caffeine, classified as “moderate intake,” was not associated with miscarriage or preterm birth. They concluded that data regarding more than moderate intake were inconclusive (52). Of note, a 2017 meta-analysis of 27 studies found a significantly increased risk of spontaneous abortion at caffeine intakes of 300 and 600 mg per day, consistent with current guidelines (53).

Similarly, there is some evidence that high caffeine intake during pregnancy may be associated with infants born with low birth weight or considered small for gestational age (54,55), though other studies have not observed clinically significant differences (56). One randomized controlled trial by Bech et al. (57) found no effect of reducing caffeine consumption during pregnancy on mean birth weight or length of gestation. The authors speculated that previous nonexperimental studies may not have been able to adequately account for known association between caffeine intake and smoking and alcohol intake, both of which may influence birth weight (56). A meta-analysis in 2015 did find an inverse relationship

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between caffeine and low birth weight, suggesting a dose–response increased risk of low birth weight of 3% for every 100 mg of caffeine consumed per day during pregnancy (58).

A systematic review of studies examining the potential teratogenicity of caffeine concluded that there is no evidence that maternal caffeine exposure causes large increases in congenital anomalies, but the data are insufficient to rule out small risks for certain congenital anomalies (59). The few studies available on caffeine's effect on fertility have had varying results. One study found that high caffeine consumption may have had an effect on time to conception among women trying to conceive (60), although another found that caffeine consumption had no effect on the overall rates of conception (61). Regardless, more studies are needed to verify this link.

Caffeine does have several documented health benefits. Caffeine can be used as an ergogenic aid (62), improving performance and delaying fatigue in long-duration physical activity (63) (see Chapter 32).

Perhaps the most intriguing evidence to emerge in the past few years related to the potential health benefits of coffee stems from multiple prospective epidemiological studies demonstrating that long-term consumption is associated with a statistically significant reduction of risk of type 2 diabetes mellitus (64,65). A recent systematic review of 28 studies with over 1.1 million participants demonstrated a robust inverse association between coffee consumption and the risk of developing type 2 diabetes. The authors found that coffee consumption of six cups per day was associated with a 33% lower risk of diabetes compared with no consumption. This association held true for decaffeinated coffee and was similar regardless of geographic region and sex (66).

The mechanisms by which coffee could potentially improve insulin sensitivity are not well understood, although several hypotheses exist. Coffee has been found to increase plasma adiponectin levels, leading to decreased insulin resistance (67). Caffeine has also recently been found to increase plasma levels of sex hormone- binding globulin (SHBG), a key modulator of sex hormones' effects on glucose homeostasis (68). Another interesting possibility is that long-term caffeine consumption has an upregulating effect on insulin-like growth factor 1 signaling, effectively increasing insulin sensitivity (69). A 2019 study of two large cohorts found similar results when comparing those who drank four or less cups of coffee per day with non-drinkers, finding them to have higher concentrations of total adiponectin and SHBG. Furthermore, the study found that coffee drinkers in these cohorts had lower levels of well-known inflammatory biomarkers including C-reactive protein (CRP), interleukin 6 (IL-6), and soluble tumor necrosis factor receptor 2 (sTNFR-2) (70). These findings support previous evidence on the role of chronic inflammation in the pathophysiology of insulin resistance (71).

Of particular note, a modest inverse association between coffee and diabetes has also been found with decaffeinated coffee (72). Initially, these findings were surprising because caffeine and caffeinated coffee were known to impair glucose metabolism acutely following ingestion (73,74), primarily through impairment of glucose uptake by skeletal muscle (75). However, one randomized trial with crossover design found that intake of pure caffeine led to greater increases in plasma glucose than did equivalently caffeinated coffee (76), suggesting both that certain components in coffee may antagonize caffeine-induced glucose impairment and also that decaffeinated coffee may be most useful for diabetes prevention (77). Investigation has now turned to chlorogenic acid, an antioxidant present in coffee, to better understand the precise mechanisms underlying this association.

Coffee is the major dietary source of the antioxidant phenol chlorogenic acid, and it is a major contributor to the overall antioxidant capacity of the diet (78). Chlorogenic acid and other coffee-derived antioxidants may counter the oxidative forces that are thought to contribute to the development of insulin resistance and diabetes (79). In addition, chlorogenic acid has been shown to enhance intestinal glucose uptake (80), inhibit the glucose-6-phosphatase system (81), and stimulate glucose transport in skeletal

muscles (82), all of which may represent potential mechanisms for enhanced glucose control (83).

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Caffeine intake has been found to be protective against the development of both AD and PD (84). In a 21-year follow-up study, moderate consumption (three to five cups of coffee per day) was found to substantially reduce the risk of AD to 65% compared to low consumption (zero to two cups per day) (85). This same protective association was noted in a case–control study of 54 patients (86) and in a larger population-based cohort in Canada of 4,615 participants (87). The possible mechanisms for this effect of caffeine suggested by animal studies include normalizing protein kinase A levels, reducing amyloid β production and increasing its clearance, and caffeine's antioxidant properties in reducing oxidative stress and apoptosis (84).

Several human studies outlined by Kolahdouzan and Hamadeh have found that caffeine consumption reduces the risk of developing PD in men; however, the effect was equivocal in women. The authors postulate that caffeine may prevent adenosine-mediated neuroinflammation via adenosine antagonism (84). A randomized-control trial of 61 patients found that treatment with caffeine (200 mg/d for the first 3 weeks and 400 mg/d for the second 3 weeks) improved the total unified PD rating scale by 4.7 points and the motor manifestation by 3.2 points (88). Another meta-analysis of 1.4 million participants found a 17% decreased risk of developing PD for every 200 mg/d increment of caffeine consumed. Drinking three cups of coffee per day offered the maximum protection against this risk (89). While caffeine's application as a therapeutic agent has undergone continued exploration, the current data do not support its use for treatment of the symptoms associated with PD (88).

For gastrointestinal diseases, there are robust observational data that suggest a protective effect of caffeine consumption against symptomatic gallstones (90,91). Other studies found this same association in women but not in men (92,93).

The effects of coffee consumption on uric acid levels and the risk of gout have also been studied in a recent meta-analysis (94). Coffee intake was associated with lowering serum uric acid and a significantly reduced risk of gout in both men and women (94,95). Caffeine, a methylxanthine, has been shown in animal models to competitively inhibit xanthine oxidase (96,97) and so might theoretically behave in humans in a manner similar to allopurinol.

Evidence to date does not support a relationship between coffee consumption and the overall risk of cancer, including pancreatic, renal cell, bladder, ovarian, breast, gastric, and prostate cancers (98–101). However, emerging evidence suggests that coffee intake may actually reduce the risk of liver cancer across many populations and in a dose–response manner, regardless of hepatitis virus infection history (102,103).

Coffee consumption has been inversely associated with the risk of cirrhosis (104) and with the risk of death from alcohol-related cirrhosis (105). A recent umbrella review of numerous retrospective, observational, and cross-sectional studies supports the previous data and, furthermore, demonstrates an association between coffee consumption and improved levels of liver enzymes and the lowered risk of nonalcoholic fatty liver disease (NAFLD). Authors caution that the reported beneficial effects were for more than two cups of coffee per day (106). The coffee-derived antioxidants cafestol and kahweol have previously been implicated as contributing to the ability of coffee to prevent liver disease (107). Recent molecular studies have found that caffeine inhibits hepatic stellate cell activation via adenosine receptor blockade and that the antioxidant compounds within coffee reduce oxidative stress within the liver (108).

Another possible health benefit of coffee consumption is decreased risk of endometrial cancer. A recent comprehensive meta-analysis of 12 prospective cohort studies found a significantly decreased risk of endometrial cancer with coffee consumption, including postmenopausal cancer (109). Consuming four cups of coffee per day was associated with a relative risk of 0.80 (95% confidence interval [CI], 0.72–

0.89) in developing endometrial cancer.

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Evidence from earlier case–control studies suggested an inverse association between coffee drinking and risk of colorectal cancer, although there was no consistent dose response (110). Data from prospective studies are inconsistent (111). While earlier studies found no relationship (112), others suggest a risk reduction for colorectal cancer in women but not in men (113). Similarly, a recent meta-analysis found a protective effect from coffee specifically in European men and Asian women only, while consumption of decaffeinated coffee demonstrated a protective effect with regard to colorectal cancer in both men and women (114). While evidence of preventative effect is weak at best, there is strong evidence of no harmful effect.

Coffee contains compounds shown to inhibit absorption of both iron (115,116) and zinc (117). Adequate intake of these nutrients to compensate for these effects in habitual coffee drinkers may assume some importance.

CLINICAL HIGHLIGHTS

Moderate amounts of coffee appear to be safe and may confer several health benefits. Concerns about potentially harmful cardiovascular effects of coffee or caffeine intake have been largely unsubstantiated. However, energy drinks that may contain significant amounts of caffeine should be avoided in adolescents and young adults. Pregnant women are advised to limit caffeine consumption to no more than 200 mg per day (roughly one cup of coffee) as a precautionary measure against the possibility of spontaneous abortion or impaired fetal growth. Coffee consumption may offer modest protection against type 2 diabetes and the development of symptomatic gallstones. There is emerging evidence on the possible protective effects of coffee against AD and PD. Coffee intake may have significant liver protective effects by reducing the risk of cirrhosis, nonalcoholic fatty liver disease, and hepatocellular cancer. Finally, coffee has been shown to decrease the risk of endometrial cancers. Coffee and caffeine-containing beverages may exacerbate symptoms of GERD; susceptible individuals are advised to reduce or eliminate intake for a trial of 3 to 6 months to see whether symptoms are alleviated. For most people, moderate coffee consumption may certainly be sanctioned as part of a healthful dietary pattern.

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Chapter 42

Macronutrient Food Substitutes

Alice Figueroa

INTRODUCTION

Macronutrient substitution is commonly used in the food industry to reduce the amount of added sugars (carbohydrates) and fat in food. The main purpose of macronutrient substitution is to reduce ingested calories from fat and added sugars, limit intake of added carbohydrates and fat, prevent dental cavities, and manage chronic disease related to diet including dyslipidemia, hypertension, hyperglycemia, diabetes, prediabetes, obesity, and coronary heart disease among others. Carbohydrate-based nonnutritive sweeteners (NNSs) and sugar alcohols (polyols) are popular in our food system and used to replace added sugars (white table sugar, corn syrup, or other calorie-rich sweeteners) in processed foods. These processed foods are typically labeled and advertised as low-calorie, sugar-free, no-sugar-added, and diet products. In recent years, natural sweeteners like honey, maple syrup, and agave among others have gained popularity as replacements for white table sugar and high fructose corn syrup (1). Although natural sweeteners provide calories and carbohydrate amounts similar to white sugar, they became popular since they are less processed, contain minerals, and have lower glycemic indexes than white table sugar. Fat replacers are carbohydrate based, protein based, or fat based. These fat replacers are synthetically produced to mimic the creaminess, texture, mouthfeel, and palatability of fat. Fat replacers provide fewer calories or no calories derived from fat and lower the total number of grams of fat in food. Despite claims made about the health benefits of macronutrient replacers, research is inconclusive on the long-term benefits of consuming foods produced with macronutrient replacers.

OVERVIEW

Safety

Currently, eight high-intensity sweeteners, also known as NNSs or sugar substitutes, are commercially available for consumption and purchase in the United States (2,3). The Food and Drug Administration (FDA) is responsible for regulating the safety of high-intensity sweeteners. Six high-intensity sweeteners are approved by the FDA as food additives: acesulfame potassium (Ace-K), advantame, aspartame, sucralose, neotame, and saccharin. According to the FDA, food additives “undergo premarket review and approval by the FDA, before it can be used in food.” High-intensity sweeteners, as well as other food additives, go through a strictly regulated process in order to be approved by the FDA. Typically, producers or sponsors of a food additive must provide evidence that the food additive is safe in the amount and form it will be used. The FDA also considers the following in its approval process: (a) the composition and properties of the substance, (b) the amount that would typically be consumed, (c) immediate and long-term health effects, and (d) various safety factors (4). Evaluations conducted by the FDA have a “built in safety margin,” meaning that the high-intensity sweeteners levels which are approved for consumption are low enough to reduce the risk of having negative side effects from its

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consumption (3). Nevertheless, it is important to note the FDA does not guarantee that there is absolutely no risk involved in the consumption of NNSs or other food additives. The FDA uses the scientific research available to approve high-intensity sweeteners based on the notion that there is "reasonable certainty of no harm" when these food additives are consumed (3).

Two high-intensity sweeteners are generally recognized as safe (GRAS): steviol glycosides derived from the Stevia plant (*Stevia rebaudiana* [Bertoni]) and extracts derived from Luo Han Guo or monk fruit (*Siraitia grosvenorii* Swingle fruit). A GRAS substance used as a food additive, such as steviol glycosides, did not undergo a premarket review and approval by the FDA, but it is considered safe for consumption. Under the Federal Food, Drug, and Cosmetic Act, a food additive is GRAS if it is "generally recognized, among qualified experts, as having been adequately shown to be safe under the conditions of its intended use...through scientific procedures or, for a substance used in food before 1958, through experience based on common use in food" (5).

Consumption of NNSs increased between 2002 and 2018 (6). While the purchase of caloric sweeteners decreased, consumers are purchasing more products containing NNSs and products containing a mixture of NNSs and caloric sweeteners. Beverages contain NNSs and a mixture of nonnutritive and caloric sweeteners have increased in popularity in the United States and make up a large percentage of the "per capita purchases of products containing" high-intensity sweeteners.

Are Nonnutritive Sweeteners Health Supportive?

NNSs are widely recommended by health professionals in clinical practice for weight loss, blood glucose reduction, and metabolic syndrome management (7). Individuals managing diabetes, obesity, or other diet-related condition switch products containing white sugar (or other caloric sweeteners) for sugar-free sodas, candies, jams, and other products sweetened with NNSs in hopes to reduce caloric intake, lose weight, and balance blood glucose levels. Although NNSs are deemed to be safe for consumption, there is no scientific consensus on whether consumption of NNSs is health supportive and beneficial to weight, metabolic syndrome, and glucose management. This chapter will review the safety and characteristics of NNS and nutritive sweeteners (sugar alcohols and natural sweeteners) that are commonly used to replace table sugar (sucrose) and examine whether NNS and other sugar alternatives are associated with improved health outcomes and diet-related disease management.

Nonnutritive, High-Intensity Sweeteners Are Approved by the Food and Drug Administration as Food Additives (8–10) (Table 42.1)

Acesulfame Potassium

Acesulfame K (5,6-dimethyl-1,2,3-oxathiazine-4(3H)-1,2,2-dioxide) is approved by the FDA to be used as a tabletop sweetener, beverage sweetener, and most recently as a general use sweetener (can be used in food and beverages). It is 200 times sweeter than table sugar (sucrose). Ninety-five percent of it is excreted through urine; therefore, it does not provide calories from carbohydrates.

Advantame

Advantame is 20,000 times sweeter than table sugar (sucrose) and it provides zero calories. It was approved as a general purpose sweetener in 2014. It is heat stable and does not become bitter at high temperature; therefore it may be used in baking or high-heat cooking.

Aspartame

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Aspartame (L-aspartyl-L'Phenylalanine methyl ester) was approved by the FDA in the 1980s to be used in foods and drinks. Aspartame is intensely sweet and a small amount is required to sweeten food. It provides 4 kcal/g, but because only small amounts are required to sweeten food, it is classified by the FDA as nonnutritive (providing a negligible amount of calories). Patients with phenylketonuria (PKU) must be advised to not consume aspartame, since it produces phenylalanine when hydrolyzed in the small intestine. The FDA requires that foods containing aspartame be labeled as "Phenylketonurics: contains phenylalanine." The following brands of NNS contain aspartame: Nutrasweet®, Equal®, and Sugar Twin®.

TABLE 42.1

High-Intensity Sweeteners

Sweetener	FDA Regulatory Status	Acceptable Daily Intake Defined by the FDA (mg/kg of Body Weight)	Sweetness Intensity in Comparison to Sucrose (White, Refined Table Sugar)	Caloric Content (kcal/g)	Popular Brands	Effects on Blood Glucose and Insulin Levels	Culinary Uses
Acesulfame Potassium (Ace-K)	Approved as a food additive to be used as a sweetener or flavor enhancer (except in poultry and meat)	15	200x	0	Sweet One® Sunett®	None	Used in baking and cooking, but does not provide bulk and texture.
Advantame	Approved as a food additive to be used as a sweetener or flavor enhancer (except in poultry and meat)	32.8	20,000x	0	Not yet branded	None	Heat stable and can be used in baking and cooking.
Aspartame	Approved as a food additive to be used as a sweetener or flavor enhancer in foods in	50	200x	4	Nutrasweet® Equal® Sugar Twin®	None	May lose sweetness and become bitter when heated.

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	general						
Neotame	Approved as a food additive to be used as a sweetener or flavor enhancer (except in poultry and meat)	0.3	7,000–13,000x	0	Newtame®,	None	Heat stable and may be used in cooking and baking.
Saccharin	Approved as an additive in certain foods and as sweetener for in “special dietary foods.”	15	200–700x	0	Sweet and Low® Sweet Twin® Sweet’N Low® Necta Sweet®	None	Heat stable and may be used in cooking, baking, and canning. It does not provide the volume and texture of sugar. Therefore, some sugar may need to be kept in the recipe to achieve desired texture.
Siraitia grosvenorii Swingle (Luo Han Guo) fruit extracts (SGFE)	Generally recognized as safe	not specified since there is evidence of the Luo Han Guo safety above the amount needed to achieve desired sweetness	100–250x	0	Nectresse® Monk Fruit in the Raw® PureLo®	None	Heat stable and suitable for cooking, baking, and canning.
High purity steviol glycosides purified from the leaves of Stevia rebaudiana (Bertoni)	Generally recognized as safe	4	200–400x	0	Truvia®** PureVia® Enliten®	None	Heat stable and may be used for cooking, baking, and canning. It does not provide the texture or

Bertoni https://nhathuocngocanh.com

							browning of sugar. It is recommended that at least ¼ cup of sugar is kept in the recipe.
Sucralose	Approved as a food additive to be used as a sweetener in foods in general	5	600x	0	Splenda®**	None	Heat stable can be used in cooking, baking, and canning.

**Truvia is marketed as Stevia products but also contains erythritol.*

***Many brands of artificial nonnutritive sweeteners are made using a combination of nonnutritive sweeteners. For instance, Splenda is composed mainly of sucralose, but also contains maltodextrin, which increases its caloric content to 3.36 kcal/g.*

FDA, Food and Drug Administration.

Adapted from U.S. Food & Drug Administration. Additional Information about High-Intensity Sweeteners Permitted for Use in Food in the United States. https://www.fda.gov/food/food-additivespetitions/ additional-information-about-high-intensity-sweeteners-permitted-use-food-united-states

Neotame

Neotame is 3,000 to 7,000 times sweeter than table sugar (sucrose) and provides 0 kcal/g. In 2002, the FDA approved it as flavor enhancer (except in meat and poultry products) and general purpose sweetener. It is heat stable and does not turn bitter at high temperatures. Therefore, it may be suitable for baking. No possible toxic side effects or negative health outcomes were listed by the FDA.

Saccharin

Saccharin is 200 to 700 times sweeter than table sugar (sucrose). It does not contribute any calories (0 kcal/g). In the 1970s, it was linked to bladder cancer after studies conducted in rats showed increased bladder cancer rates in rats fed saccharin. As a result, saccharin products were required to carry a warning level as possibly cancerogenous. In 2000 after evaluating evidence from 30 human studies, the National Toxicology Program of the National Institutes of Health determined that there was insufficient evidence to classify it as a possible carcinogen. It has been removed from the list of potential carcinogens and foods containing saccharin are no longer required to carry a warning label. The following are Saccharin brand names Sweet and Low®, Sweet Twin®, Sweet'N Low®, and Necta Sweet®.

Sucralose

Sucralose (trichlorogalactosucrose) is 600 times sweeter than white sugar. It was approved for use in the

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1990s as a general purpose sweetener, and it is found in numerous processed foods including sodas, energy drinks, baked goods, and frozen desserts. Since it is stable at high heats, it is commonly used in baking. Sucralose's brand name is Splenda®.

Luo han guo

Luo Han Guo, or Siraitia grosvenorii, or Swingle/Monk fruit extract has been recently recognized as GRAS by the FDA. It is 150 to 300 times sweeter than sucrose. For some individuals, it may be unpleasant since it carries a bitter after taste. Overall, it provides 0 kcal/g. More research needs to be conducted to determine its health benefits.

Stevia

Steviol glycosides-rebaudioside is a natural constituent from the *S. rebaudiana* (Bertoni) Bertoni plant, which is native to South America. It is 200 to 400 times sweeter than table sugar (sucrose) and provides 0 kcal/g. The following high purity (95% purity) steviol glycosides derived from the Stevia plant have been deemed as GRAS by the FDA: Rebaudioside A (also known as Reb A), Stevioside, Rebaudioside D, or steviol glycoside mixture preparations with Rebaudioside A and/or Stevioside. The use of fresh Stevia plant leaves and crude Stevia extract is not considered to be GRAS and its import into the United States is not permitted. However, Stevia plants can be successfully grown locally in the United States and can be used as culinary herbs, not as NNSs or food additives.

Nonnutritive Sweeteners and Cancer

Concerns regarding an association between NNS consumption and cancer risk stemmed from animal studies, which found a significant link between consumption of cyclamate in combination with saccharin and increased risk of bladder cancer (11). More recent carcinogenicity studies conducted in humans have not found significant evidence of an association between the consumption of NNS and increased cancer risk (12). In the 1970s, rat studies linked saccharin to development of cancerous bladder tumors in rats. As a result, in 1981, it was classified as carcinogenic to humans. After reviewing human studies which concluded that humans lacked the mechanism that led to increased cancer risk in rats that consumed saccharin, it was determined that there was insufficient evidence to link saccharin with increased incidence of cancer risk. Saccharin was delisted from the US National Toxicology Programs Report on Carcinogens (13). Cyclamate, an NNS not approved for sale in the United States by the FDA, was also linked to bladder cancer in rats. More recent research concluded that cyclamate is not a carcinogenic to humans. As a result, a petition for FDA reapproval of cyclamate has been filed, and it is pending review. Based on FDA data, the National Cancer Institute outlined that there is insufficient evidence to link NNS consumption to increased cancer risk (7).

Effect of Nonnutritive Sweeteners on Weight and Cardiometabolic Health

Research on the effects of NNS intake on body weight is inconclusive. While there are random controlled trial (RCT) and observational studies that link consumption of NNS to weight loss, lower daily calorie intake, and a reduction in waist circumferences, there are also numerous studies including RCT and cohort studies that suggest that intake of NNS does not lead to reduced daily caloric consumption, reduced weight circumference, changes in percentage body fat, or weight loss (14). Various cohort studies found an association between higher consumption of NNSs and increased waist circumference and higher abdominal obesity, while other cohort studies found no significant change in waist circumference or

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percent body fat (6). A meta-analysis and systematic review of randomized control trials and prospective cohort studies on NNS and cardiometabolic health concluded that there is insufficient evidence to suggest that long-term consumption of NNS is beneficial to weight management. Another meta-analysis and systematic review found a significant association between drinking NNS-sweetened beverages and higher risk of obesity (15). There is limited research on the effects of NNS on changes in body mass index (BMI). Three long-term cohort studies found that consumption of NNS is linked to an increase in BMI, but RCT did not support the results (8). Research has linked consumption of NNS to metabolic disorders including weight gain, increased BMI, and higher risk of cardiometabolic diseases.

A recent systematic review published in 2018 in the *British Journal of Medicine* analyzed the effects of NNS on energy intake and appetite. While pooled data from four randomized controlled trials found that energy intake was lower (1064.73 kJ lower) in groups receiving NNS as opposed to those groups receiving sugar, other shorter-term studies and non-randomized control trials found that there was no significant difference in caloric consumption between groups consuming NNS (aspartame or Stevia) and a placebo. There is insufficient evidence to support recommending NNS to reduce energy intake in patients who are trying to manage weight. This may be due to the fact that many of the foods that contain NNS are highly processed foods including sugar-free desserts, soft drinks, juices, yogurts, and energy drinks. Replacing foods that are high in added sugar for highly processed foods sweetened with NNS will not necessarily lead to an overall improvement in nutrition status and increased consumption of health supportive foods like fruits and vegetables, whole grains, lean proteins, and heart-healthy fats.

According to the American Diabetes Association, consumption of NNS may be helpful at reducing immediate intake of excess sugar and calories, and in turn, may lead to lower glucose levels and weight in the short term (16). However, in their recommendations, they acknowledge that there is no clear evidence that using NNS will lead to long-term health benefits including decreased blood sugar and weight and improved cardiometabolic health. In 2019, the *Journal of Family Practice* released practice recommendations for clinicians and medical professionals concluding that NNS are not linked to weight loss. The recommendations state that clinicians should “Advise patients who are trying to lose weight that NNSs are not beneficial for weight loss (6).”

Nonnutritive Sweeteners Consumption and Its Effect on Blood Pressure

With regards to the effects of NNS intake on blood pressure, the research is inconclusive. While three RCTs suggest that individuals assigned to consume NNS instead of sugar or a placebo had lower blood pressure, the evidence was low certainty (17). A meta-analysis of cohort studies found that high consumption of NNS was correlated to higher risk of hypertension(8). Another RCT found that there were no significant changes in systolic or diastolic pressure in individuals consuming aspartame to lose weight (11). Based on the available science, there is insufficient evidence to support the use of NNS for management of hypertension.

Nonnutritive Sweeteners Consumption and Blood Sugar and Diabetes Management

One of the health benefits that is attributed to NNS is the improvement of blood sugar (glucose) management, in particular for diabetic patients. The Academy of Nutrition and Dietetics’ (AND) position paper on the use of NNSs classified NNS as safe and effective at limiting carbohydrate and energy intake. In its recommendations, AND found that NNS are not associated with increased postprandial glucose response and do not affect glycemic response after consumption in diabetes mellitus patients (18). AND recommends that individuals, who wish to consume sweet-tasting foods and drinks without consuming

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excess added sugars and calories, can safely choose to consume FDA-approved and GRAS NNSs. While there is an RCT that shows that levels of fasting glucose were lower in groups consuming aspartame and other NNS when compared to groups consuming white table sugar, there were no significant improvements in insulin levels, insulin resistance, and β cell function measured and assessed using the homoeostatic model assessment for insulin resistance (11). A meta-analysis and systematic review of NNS and health outcomes found that there were no clinical relevant effects and "no significant differences" in glycemic response measures, including HbA1C, plasma glucose and insulin, and C-peptide, between individuals who were assigned to consume NNS versus those assigned to consume sucrose, starch, or a placebo. Pooled data from various cohort studies found that higher consumption of NNS was linked to higher risk of metabolic syndrome and type 2 diabetes and a "3% higher relative risk of type 2 diabetes per additional daily serving of nonnutritive sweetener" (8). Research findings suggest that it is unclear whether long-term consumption of NNS is beneficial to improved glycemic control, insulin levels, and management of type 2 diabetes and prediabetes. For clinical implications, it is important to educate patients that while intake of NNS is deemed to be safe and may help reduce short-term consumption of calories from added sugar, research has yet to find sufficient evidence that NNS consumption is beneficial to blood glucose management in the long term. Furthermore, NNS have not been shown to have any therapeutic blood glucose–lowering benefits or positive effects on glycemic response. Any potential benefits or changes observed in the glycemic response measures after NNS consumption may be the result of replacing added sugar with NNS, not due to therapeutic properties of NNS.

Effect of Nonnutritive Sweeteners on Preference for Sweet Taste

Emerging research seeks to understand the role that NSS have on metabolic and hormonal responses and whether these responses are associated with increased weight, preference for sweet tastes, and other health conditions. Animal research suggests that metabolic and hormonal responses to NNS are triggered by sweet-taste receptors in the gut (13). Current research shows that in order to comprehend the effects of NNS on appetite and sweet preferences, it is crucial to conduct more research on the genetic variation and mechanism of the single receptors (made of the taste receptor type 1 member 2 (TAS1R2 gene) and taste receptor type 1 member 3 (TAS1R3 gene) subunits) responsible for mediating preference for sweet tastes (19–21). Preferences for sweet-tasting foods and drinks appear to be genetically determined and involve the central nervous receptors including dopamine receptors (13). Complex genetic, metabolic, hormonal, and neurological factors, as well as social and cultural preferences, may play a role in individuals' preference for NNS and sweet-tasting foods and drinks. Since there is limited research, it is unclear whether NNS consumption will enhance or diminish preference for NNS and other sweet-tasting foods.

The Effects of Nonnutritive Sweeteners and Sugar Alcohols on the Gut-Microbiota

Research suggests that some NNSs including synthetic, natural, or low-calorie sweeteners affect the composition and health of the microbiomes in the gut. A more detailed discussion of the gut microbiome can be found in Chapter 11. In brief, the gut microbiota is composed of probiotics (yeast and bacteria) that live within our digestive system.

Thus far, research conducted has not found a significant association between consumption of most NNSs with significant changes in the gut microbiota. Animal research studies in rats and some limited human studies indicate that there are three NNSs linked to changes in the gut microbiota: saccharin, sucralose, and Stevia (22).

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Recent studies conducted in both rats and humans have found an association between ingestion of artificial NNSs, in particular saccharin, with dysbiosis which is linked to changes in the metabolic pathway responsible for glucose tolerance (22,23). These changes can lead to glucose intolerance and unintentional weight gain. Consumption of sucralose in rats has been linked to a reduced number of aerobic and anaerobic bacterial probiotics in the gut (22). More studies conducted in human populations are needed to better understand the link between consumption of NNS and dysbiosis in the gut microbiota.

Stevia, a high intensity, NNS, derived from the *S. rebaudiana* plant (*S. rebaudiana*), has been linked to alterations in the human microbiome, some of which may be health supportive. An in vitro study found that Stevia is not completely hydrolyzed and degraded in the digestive tract, which leads to minimal changes in fecal cultures (24). This suggests that Stevia consumption may not have a significant effect on the gut microbiome. For instance, Stevia did not reduce Bifidobacterium and *Lactobacillus* growth (25). Overall, components found in the *S. rebaudiana* plant have been shown to weakly inhibit the growth of both aerobic and anaerobic bacteria including coliforms *(E. coli.) and Lactobacillus reuteri* (25). However, other studies suggest that Stevia may cause a change in the gut microbiota by affecting the number of *bacteroides* in the microbiome (26). *Bacteroides,* gram-negative anaerobic bacteria which may be pathogenic or probiotic, are the most efficient at hydrolyzing Stevia into steviol (27). The relationship between *bacteroides* composition and intake of Stevia is not yet well understood. The root and other parts of the *S. rebaudiana* plant break down into inulins and fructants, which are prebiotic fibers that provide fuel for certain strains of bacteria in the gut microbiome. In particular, a study found that growth of *bifidobacteria* and *lactobacilli* was enhanced by consumption of fructans derived from the *S. rebaudiana* plant, in particular the root. Both *bifidobacteria and lactobacilli* are probiotics that play an important role in promoting digestive health and a diverse microbiome. As previously mentioned in this chapter, fresh whole Stevia leaves and crude extracts are not permitted to be sold as sweeteners by the FDA. However, they are widely used in other countries and individuals in the United States can purchase and grow *S. rebaudiana* to be used as an herb in food preparation. Some Stevia products sold commercially in the United States are mixed with inulin or other NNS. Therefore, it is important to teach patients how to read ingredients labels and make sure that they understand whether they are purchasing pure Stevia or Stevia combined with other ingredients, which may affect microbiome health. For instance, some Stevia products (e.g., SweetLeaf Stevia®) use inulin (oligosaccharides), as a bulking agent, which when fermented by the bacteria in our gut may cause excess bloating, flatulence, and stomach cramping (28). However, most Stevia products commercially available as NNS do not contain high amounts of fructans, a type of oligosaccharides, and are generally considered safe for patients following low fermentable oligosaccharides, disaccharides, monosaccharides and polyol (FODMAP) diets for management of irritable bowl syndrome (IBS) or other gastrointestinal (GI) conditions (29,30). More human subject studies are needed to better understand the association between Stevia consumption and changes in bacterial composition in the gut microbiome.

Natural Sugars

All simple carbohydrates, including natural sweeteners like honey or maple syrup, are digested and absorbed more rapidly than complex carbohydrates like fruits and vegetables (31). As a result, all simple sugars will cause a spike in glucose levels. Simple sugars (simple carbohydrates) including white table sugar, brown sugar, powdered sugar, honey, maple syrup, molasses, and corn syrup are known as added sugars. An added sugars is any caloric sweetener that is added to foods or drinks when processed, cooked, or prepared. Globally, people consume excess amounts of added sugar, which is one of the main

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contributors to increasing rates of diet-related chronic diseases. According to the *Dietary Guidelines for Americans*, on average, Americans consume 17 teaspoons of added sugar per day, which is equal to 57 pounds of added sugar per person, per year (32). Although replacing white table sugar for more natural caloric sweeteners has become a popular way to improve the quality of our diets, our bodies metabolize all added sugars similarly. In fact, all added sugars consumed provide around the same amount of calories and have similar long-term effects on blood sugar levels. One of the possible health benefits of natural sweeteners is that they are less refined than white table sugar and contain nutrients like vitamins, minerals, and antioxidants. Although, it is important to emphasize that consuming added sugars is not the most health supportive way to meet vitamin, mineral, and antioxidant requirements, since excess added sugar consumption can lead to prediabetes, diabetes, and other diet-related chronic health conditions. Some natural sugars like agave syrup or maple syrup have lower glycemic indexes than sugar, which means that they cause a slower, more gradual spike in postprandial glucose levels. There is insufficient evidence to associate consumption of natural sweeteners to improved health outcomes like reduced blood glucose levels or improved diabetes management. For health professionals, it is important to recommend that patients consume no more than 6 teaspoons (25 g) of added sugar per day, regardless of whether the added sugar is white table sugar or a natural sweetener like honey (33,34).

Commonly Used Caloric, Natural Sweeteners (Table 42.2)

Agave Nectar

Agave nectar is extracted from the agave plants native to Mexico. It is composed of the following simple sugars: fructose, glucose, and sucrose. A teaspoon of agave nectar contains around 20 cal and 5 g of simple carbohydrates (40). Agave nectar has a glycemic index of 32, which is considered low (41). A low glycemic index means that agave syrup will cause a more gradual effect on blood sugar levels and lower blood glucose spike. Agave is 1.5 times sweeter than white sugar, as a result, a person may be able to use less agave to achieve desired sweetness. This may help cut back on the amount of calories, simple carbohydrates, and added sugars consumed. Since agave is considered an added sugar and provides calories and carbohydrates, it should only account for less than 10% of our total daily calories. There is limited research on the health benefits of agave. and 5 g of simple carbohydrates (35). Agave nectar has a glycemic index of 32, which is considered low (36). A low glycemic index means that agave syrup will cause a more gradual effect on blood sugar levels and lower blood glucose spike. Agave is 1.5 times sweeter than white sugar, as a result, a person may be able to use less agave to achieve desired sweetness. This may help cut back on the amount of calories, simple carbohydrates, and added sugars consumed. Since agave is considered an added sugar and provides calories and carbohydrates, it should only account for less than 10% of our total daily calories. There is limited research on the health benefits of agave.Agave contains the fiber-rich prebiotic inulin, which may contribute to maintaining a healthy digestive microbiome and help the body absorb the sugar found in agave more slowly.

TABLE 42.2

Glycemic Index of Natural Sugar Alternatives

Food Name	GI (vs. Glucose)	Standard Serve Size (g)	Carbohydrate per Serving (g)	GL**
Agave	11–19	10	8	1–2
Honey	58	25	21	12

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Maple syrup	54	25	18	10
Brown sugar	58–84	10	10	6–8
Molasses	55	10	7.5	4–5
Coconut sugar	54	5	5	3
Yacon syrup	40	10	7.1	1
Dates (*date syrup)	31–50	60	30–46	14–22

**Data on the Glycemic Index and Glycemic Load for Date Syrup is limited.*

***Glycemic Load: GL = GI x carbohydrate/100. It calculates the amount of carbohydrates in a portion of food and how quickly it raises blood glucose levels based on the amount and glycemic index of the food* (*75*).

Low glycemic load (low GL): 0 to 10
Medium glycemic load (med GL): 11 to 19
High glycemic load (high GL): 20 and over
GI, gastrointestinal; GL, glycemic load.

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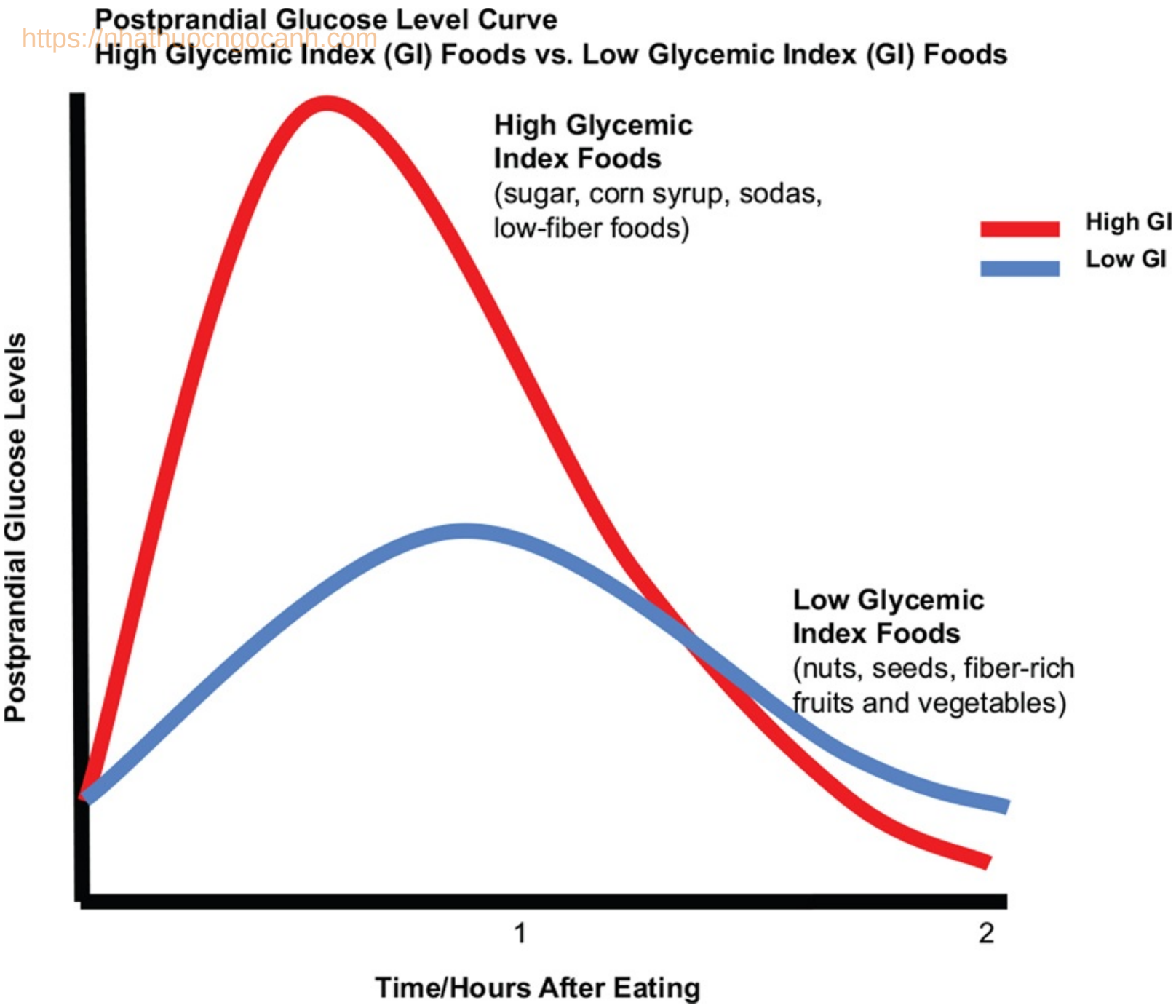

Adapted from Glycemic Index Foundation. The science of GI. https://www.gisymbol.com/what-about-glycemic-load/

Honey

Honey is composed of mostly fructose and glucose. A teaspoon of honey contains about 20 cal and 5 g of sugar (37). When compared to a teaspoon of white table sugar, it contains five more calories and one additional gram of sugar. Honey has a moderate glycemic index of 58 (38). It is rich in phytochemical and antioxidants, which support immune health. Studies have shown that sugar is effective at suppressing coughs (39–41). Because of its moderate glycemic index and its calorie and carbohydrate content, honey is considered an added sugar and should account for no more than 10% of our total daily calories (42).

Maple Syrup

Maple syrup is a product of the sap of maple trees found in North America. It is composed of the following simple sugars: sucrose, glucose, and sucrose. A teaspoon of maple syrup provides 18 cal and 5

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g of carbohydrates. It has a glycemic index of 54, which is considered low. A lower glycemic index means that maple syrup causes a less of a spike in blood sugar levels than white sugar. Maple syrup is a good source of antioxidants and minerals including manganese, zinc, iron, calcium, and potassium. However, it counts as an added sugar and when eaten in excess can contribute to high carbohydrate and calorie intake.

Brown Sugar

Brown sugar has as a similar caloric profile, carbohydrate content, and glycemic as white sugar. Brown sugar has less calories by weight. For instance, 100 g of brown sugar yields 373 cal, while 100 g of white sugar yields 396 cal (43). Brown sugar contains molasses which is a source of calcium, iron, and potassium. Despite its nutrient content, brown sugar is an added sugar just like white table sugar and should be eaten mindfully (see Molasses).

Molasses

Molasses is a sugar cane by-product. It has a moderate glycemic index of 55. One teaspoon provides 19 cal and 15 g of carbohydrates (44). Molasses contains nutritious minerals like magnesium and manganese, which makes it more nutritious than white sugar. However, it still counts as an added sugar. When eaten in excess, it can have an adverse impact on blood glucose levels and weight.

Coconut Sugar

Coconut sugar or coconut palm sugar is produced from the flowers of the coconut palm tree. A teaspoon of coconut sugar contains around 15 cal and 4 g of carbohydrates, equal to the calories and carbohydrates found in white sugar. It has a moderate glycemic index of 54 (45). Although it contains trace minerals, vitamins, and fiber, coconut sugar is an added sugar that contributes calories and carbohydrates and should be eaten mindfully.

Yacon Syrup

Yacon syrup is a natural sweetener that is growing in popularity as a more healthful alternative to white sugar. It is native to South America and produced from the yacon root. Yacon syrup has a low glycemic index of 40 (46). Yacon syrup is rich in fructooligosaccharides (FOS), which are prebiotic fibers. A study found that premenopausal women classified as obese decreased their body weight, BMI, and waste circumference when they were assigned to a group receiving doses of yacon syrup (0.29 and 0.14 g fructooligosaccharides/kg/day) as opposed to a group receiving a placebo syrup (tartaric acid 2.5%, carboxymethylcellulose 1.8%, saccharine 2.5%, and glycerine 10%.) (47). Since yacon syrup is high in FOS, it is not considered low FODMAP and may cause bloating, flatulence, and other digestive symptoms in IBS patients or other individuals who are sensitive to FODMAPs.

Dates and Date Syrup

One date contains about 67 cal and 18 g of carbohydrates. Dates glycemic index is low at about 44 to 53 (25). As study showed that the GI effect of dates was the same in diabetics and nondiabetic individuals. Dates contain trace minerals like potassium, magnesium, manganese, and copper and are a good source of fiber. One date provides 2 g of fiber or about 8% of the daily recommended fiber value (DV) (25). The fiber in dates helps slow down the absorption of carbohydrates (sugars) found in the dates. Date syrup contains minerals, but it is not a good source of fiber-like whole date fruits. Since it does not contain fiber, it may lead to a higher impact in postprandial glucose levels. Manufacturers of date syrup report

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that date syrup has a low glycemic index, but there is no independent research available to verify it. A study found that the consumption of dates did not result in a significant rise in postprandial glucose due to the dates' low glycemic index (48).

Polyols (Sugar Alcohols): Low-Calorie Nutritive Sweeteners

Polyols commonly known as sugar alcohols are used in food products and sold as low-calorie sweeteners. They are marketed as an alternative to decrease consumption of added sugar and calories. The main health benefit attributed to sugar alcohols is that its consumption causes no change or a very slight increase in blood glucose levels. Polyols are often used in combination with other sugar alcohols and NNSs. One the characteristics of polyols is its bulking ability. Therefore, they are used in processed food products as sweeteners or as bulking agents. Sugar alcohols are commonly used in sugar-free, low-carb, low-sugar, or diet beverages (sodas, juices, energy drinks), protein powders and shakes, granola bars, candies, gums, no-calories sweeteners, frozen desserts, and health products advertise as keto-friendly. The amount of calories provided by polyols varies depending on the type of sugar alcohol, since each sugar alcohol is digested, absorbed, and metabolized differently. Generally, polyols are partially digested and slowly absorbed through passive diffusion. Therefore, sugar alcohols provide less calories per gram than sugar and produce a smaller change in blood glucose levels when compared to other nutritive added sugars. Foods that use sugar alcohols as sweeteners are allowed to be labeled as "no sugar added" or "sugar free." Although polyols are found in nature, many of the polyols on the market are manufactured from monosaccharides and polysaccharides. It is important to be aware that although brands of sugar alcohols market themselves as "all natural," the term "all natural" is not regulated, and it does not imply that it is a healthier option. A food labeled as "all natural," "no sugar added," or "sugar free" is not necessarily health supportive, and consuming it may not lead to better long-term health outcomes.

Sugar alcohols are generally recognized as GRAS by the FDA for the general populations' consumption (49). However, high-sugar alcohol consumption is linked to digestive health symptoms including abdominal gas, bloating, and diarrhea. Since sugar alcohols are not completely digested, absorbed, and metabolized by the body, they may be fermented by bacteria in the large intestine causing digestive distress (50). Sorbitol and mannitol, both popular sugar alcohols," must be labeled with a warning that excess consumption may lead to laxative effects. In IBS patients, studies have shown that sugar alcohol consumption may be associated with digestive dysmotility, since sugar alcohol may be high in FODMAPs. More research is needed to better understand the effects of sugar alcohol consumption in IBS patients. However, the research shows the polyol consumption may lead to dose-dependent digestive distress (laxative effects, bloating, flatulence, abdominal discomfort in both IBS patients and healthy patients) (51). Based on available research, moderate consumption polyols appears to not be harmful to metabolic health and may lead to short-term reduction in calories and added sugar. Sugar alcohols have a low glycemic index, meaning that their consumption will not generally cause a spike in glucose levels. More research must be conducted to determine whether consumption of sugar alcohols in place of sugar or other caloric sweeteners is associated with improved cardiometabolic health outcomes like improved diabetes management. Popular sugar alcohols include erythritol, xylitol, mannitol, and sorbitol. Due to its different chemical configuration and smaller molecular weight, erythritol appears to cause little to no GI reactions (52).

Low-Calorie Sweeteners Used Globally

There are several low-calorie sweeteners that are approved for sale globally but are not as widely used in the United States. These sweeteners are considered NNS, since they provide minimal calories.

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Monellin and neohesperidin dihydrochalcone are currently not FDA approved, but are deemed safe in other parts of the world. Monellin is approved as a sweetener in Japan and neohesperidin dihydrochalcone in the European Union (53,54). Thaumatin is classified as GRAS and can be used as a sweetener and flavor enhancer. It is isolated from the West African Katemfe fruit, provides 4 kcal/g, and is 3,000 times sweeter than glucose (55). Thaumatin is used in dairy products, coffee drinks, and savory foods to enhance flavors. Glycyrrhizin is derived from the licorice root, and it is classified GRAS by the FDA as a flavoring agent but not a sweetener. The FDA warns that excess consumption of glycyrrhizin can lead to abnormally low potassium levels, which may cause edema, hypertension, lethargy, and congestive heart failure (56). According to the FDA, consumption of 2 oz of licorice per day for a period of 2 weeks or more can lead to health issues related to abnormal potassium levels (57).

Fat Replacers

Fat replacers are frequently used in the food industry to lower the caloric and fat content of processed foods. The purpose of a fat replacer is to use it as an ingredient that has all or some of the functions and characteristics of fat while not providing the same high-caloric and fat content (58). Although previously fat was mostly blamed as the culprit for diet-related conditions including obesity and heart disease, new research has shown that substituting fat in foods does not promote healthier eating habits and improved health outcomes. Nevertheless, fat substitutes continue to be used in food production and marketed as healthier options. As clinicians, it is important to have an understanding of the possible health effects of consuming fat substitutes. There are four main categories of fat replacers including carbohydrate-based fat mimetics, protein-based fat mimetics, and fat-based substitutes (59). Although there are studies that have linked consumption of fat replacers to weight loss, the most recent recommendations emphasize that it is important for consumers not to replace whole foods rich in healthy fats with processed foods made with fat replacers, that may be lower in calories from fat, but may also be high in added sugar, high in added salt, and low in nutrients (60).

Carbohydrate-Based Fat Mimetics

Fat mimetics imitate one or more physical and sensory features and functions of dietary fat by absorbing water, retaining moisture, and creating a gel. Carbohydrates mimetics are composed of the following carbohydrates: modified starch, cellulose, dextrins, maltodextrins, gums, fiber, pectins, and polydextrose. The caloric content of carbohydrate-based fat mimetics is 1 to 2 kcal/g when mixed with water and 4 kcal/g when not mixed with water (61). Cellulose contributes zero calories, since it is an indigestible fiber. Another example of a popular carbohydrate-based fat replacer is carrageenan. It is used in plant-based milk, sausages, yogurts, dressings, and various products as a thickener. Food-grade carrageenan is deemed to be safe and noncarcinogenic by the FDA. However, studies have found that degraded carrageenan, which is found in trace amounts in food-grade carrageenan, may be cancerogenous and inflammatory (62). The National Organic Standards Board removed carrageenan as an United States Department of Agriculture (USDA) Organic ingredient. Therefore, any foods that contain carrageenan are not able to receive the USDA organic designation. Most carbohydrate-based fat mimetics are used to thicken or stabilize food and preserve the mouthfeel, creaminess, bulk, and moisture in food products that have less fat content. They are mostly used in dressings, frozen desserts, plant-based milk/dairy alternatives, ice creams, frozen yogurts, salads, vegetable spreads (plant-based butter substitutes), baked goods, and processed deli meats. These carbohydrate, plant-based fat replacers lower the fat content of food, the amount of calories derived from fat, and may increase the fiber content (63).

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Protein-Based Fat Mimetics

Protein-based fat mimetics are GRAS by the FDA. They are composed mostly of microparticulated egg and milk-based proteins and occasionally of plant-based protein (64). Their caloric content is 1 to 4 kcal/g. Microparticulated protein mimics the creaminess and smoothness of fats. Protein-based fat mimetics are found mostly in ultra-processed fat-free, low-fat, reduced fat products including fat-free frozen desserts, ice creams, frozen yogurts, reduced fat butter, margarine, plant-based buttery spreads, low-fat dairy products, low-fat cheese, sour cream, yogurt, low-fat salad dressing, mayo, soups, sauces, and coffee creamers.

Protein blends are another type of protein-based mimetics. They combine both plant-based proteins/carbohydrates (gums, scratches, hydrocolloids, inulin), animal proteins, and water. The culinary attribute of protein blends is that they retain the taste, textural characteristics, creaminess, and mouthfeel of foods while lowering the fat content and calories from fat. It is important to note that foods that contain protein-based fat mimetics tend to be ultra-processed and may not necessarily be nutritious or health supportive. While protein-based fat mimetics may contain less fat, it is important for clinicians to inform patients that fat-free or low-fat products may still contain high amounts of added sugar, salt, and calories. Eating fat-free foods does not necessarily mean that individuals are making health-supportive choices.

Fat-Based Substitutes

Fat-based substitutes alter the chemical structure of fatty acids in order to reduce the caloric content of fat. They usually provide 0 to 9 kcal/g depending on the chemical changes made to it (65). Fat-based substitutes include structured lipids, sugar polyesters, and esterified propoxylated glycerol (EPG).

Structured Lipids

Structured lipids are triglycerides made from the hydrolyzation and transesterification of medium-chain triglycerides and long-chain triglycerides. The caloric content of structured lipids is about half of the calories found in edible oil (9 kcal/g of fat) (66). Examples of structured lipids include salatrim (made from hydrogenated vegetable oil), caprenin (made from palm kernels, coconut, and canola oil), and Neobee M-5 (made from coconut oil) (60). Structured lipids are used in pastries, baked goods, nutrition bars, and dairy products to replace coconut oil or coconut butter. Caprenin was removed from the market in the 1990s, since it was shown to increase cholesterol levels. Salatrim is approved for consumption in the United States, Europe, and other countries but studies have linked it to GI distress nausea, diarrhea, and abdominal pain (67).

Sugar Polyesters

Sugar polyesters are made from esterification of sucrose plus long-chain fatty acids derived from edible oils. Although sugar polyesters have some of the same textural and functional properties of fat, they pass through the digestive system without getting broken down and absorbed; and, therefore contribute zero calories. The most popular sugar polyester is Olestra. Gastric and pancreatic enzymes (lipase) are not able to break down or hydrolyze the large Olestra molecules, and the small intestine cannot absorb Olestra's large molecules to produce energy (68,69). In 1996, the FDA-approved Olestra as a food additive that can be used in savory and salty snacks (chips and popcorn). Although the FDA Food Advisory concluded that Olestra is not toxic or carcinogenic to humans, it concluded that its consumption may cause digestive health symptoms including loose stools, diarrhea, and cramping (70). These digestive health systems may occur in certain individuals ingesting Olestra, since it is not possible for humans to

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absorb or metabolize Olestra. It is also important to note that consumption of Olestra at the same time as foods rich in fat-soluble vitamins may result in malabsorption of fat-soluble vitamins (Vitamin A, Vitamin D, Vitamin E, Vitamin K). The FDA requires Olestra to be enriched with fat-soluble vitamins (170 IU vitamin A per gram Olestra, 12 IU vitamin D per gram Olestra, 2.8 IU vitamin E per gram Olestra, and 8 mcg vitamin K per gram Olestra) to prevent fat-soluble vitamin deficiencies (18). In 2003, the FDA approved the removal of a label warning consumers about possible digestive side effects from Olestra consumption. The FDA argued that evidence indicated that Olestra only caused mild digestive health symptoms that did not warrant a warning (71). Furthermore, it stated that consumers were already aware and educated about the possible digestive side effect of Olestra and that the label provided consumers with unnecessary and redundant information that may cause them to mistakenly attribute digestive health symptoms to Olestra consumption (19). Studies have shown that Olestra consumption may lead to a significant short-term reduction in caloric and fat intake. For instance, a randomized, double-blind, placebo-controlled crossover trial of 51 adults found that consumption of Olestra led to reduced intake of fat and calories from fat during a 14-day period (72). However, there is insufficient evidence to associate consumption of Olestra with long-term weight loss and management. A study by Cotton et al. demonstrated that dietary fat reduction through the use of Olestra led to calorie and fat compensation. Participants that reduced 20% to 32% of calories from fat using Olestra, reported compensating for 74% of the energy deficit on the following day (73). Overall participants compensated for 15% of the fat and 20% of the calories that were cut using Olestra. Based on the evidence, it appears that Olestra may not lead to long-term positive health outcomes.

In 2020, EPG sold under the brand name Epogee achieved GRAS status under the FDA. It claims to provide 0.7 kcal/g of EPG, and it is being marketed as a product that will cut the fat content of food by 92%. It can be used in processed foods including spreads, nut butters, candies, frozen desserts, baked goods, and pasta. Despite claims made by the manufacturer, there are a limited number of nonindustry sponsored studies to verify that it does not cause digestive distress and that it is beneficial to weight loss and the management of diet-related diseases.

According to the FDA and AND, GRAS approved fat replacers are safe, nontoxic, and noncancerogenous. In its position statement, the AND states that foods containing fat replacers may be safely used by consumers to achieve the recommended amounts of total dietary fat, saturated fat, and cholesterol. It is important to note that 79% of the population reports consuming low or reduced fat products. Despite widespread consumption of products containing fat replacers, we continue to observe increased rates of diet-related diseases including obesity, hyperlipidemia, coronary heart disease, hypertension, prediabetes, and diabetes. For populations predisposed to the digestive health symptoms, it is important for clinicians to be knowledgeable about the possible side effects of Olestra and to educate patients about the possible adverse reactions. It is crucial to understand that simply because a food product is made with fat replacers, it does not mean that it is lower in calories, salt, or added sugar. Many products that use fat replacers may increase sugar or salt content to make the food more palatable and enjoyable for consumers. Therefore, health professionals should encourage patients to learn how to read and interpret food labels and critically analyze health claims made by food products. Fats are macronutrients that provide essential fatty acids (linoleic and linolenic acid) and fat-soluble vitamins needed for nervous system, hormonal, skin, and hair health. They are also used by the body for energy production and insulation to keep the body warm. Current dietary guidelines do not recommend low-fat diets for the general population and encourage people to eat diets that derive around 35% of calories from fat. The American Heart Association recommends that people eat a diet that prioritizes consumption of whole foods rich in monounsaturated fats (nuts, avocados, olive oil) and polyunsaturated (seeds, walnuts,

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fish) fat. It is recommended that we limit calories from saturated fat (butter, animal-based protein, coconut oil) to 5% or less of our daily diet to promote heart health. Because there is insufficient research on the effects of fat replacers on the health of pregnant women and since fat replacers like Olestra and salatrim are linked to malabsorption fat-soluble vitamins and digestive distress, it may not be ideal to consume these during pregnancy. Given the import function of fat in the body's function, it is important to educate patients about healthy fat consumption and discourage them from replacing whole foods rich in heart-healthy fats and other essential nutrients with processed foods made with fat replacers.

CLINICAL HIGHLIGHTS

Macronutrient replacers began to gain popularity in the post-WWII era. In an attempt to revolutionize our eating habits and promote diets rich in processed foods as healthy, the food industry developed macronutrient replacers to reduce calories, fat, and added sugar in processed foods. Despite the popularity of food produced with macronutrient replacers that promise improved health outcomes, we continue to experience increasing rates of diet-related diseases globally. While there is some research that indicates that consuming foods and drinks made with NNSs and sugar alcohols may lead to short-term reduction in calorie and added sugar intake, the research is inconclusive about the long-term benefits of consuming sugar replacers (NNS, sugar alcohols, or natural sugars). In fact some research links consumption of NNS to obesity and discredits the notion that NNS have a therapeutic effect on blood glucose levels and diabetes management. As it pertains to fat replacers, while some early research linked consumption of fat replacers with weight loss, there is limited evidence to support their long-term health benefits on lipid levels, weight management, or heart health. It is also important to note that certain NNS, sugar alcohols, and fat replacers have been associated with negative health outcomes including digestive distress and increased cancer risk. While the link between bladder cancer and NNS was deemed irrelevant in humans, given that the long-term health benefits of NNS are inconclusive, patients and consumers have the right to know about the possible health benefits and risks of NNS. As clinicians, we must also educate patients about the possible digestive effects of consuming fat replacers and sugar alcohols, especially since the incidence of IBS is growing globally (74). Patients attempting to lead a healthier lifestyle may be choosing to consume alcohol sugars and fat replacers, but may not be aware of the possible side effects of ingesting sugar alcohols and certain types of fat replacers (Olestra). It is important to inform patients about the possible risks associated with consumption of macronutrient replacers.

Based on the research, we can conclude that eating and drinking products made with macronutrient replacers is not necessarily health supportive and may not lead to improved long-term health outcomes. Instead of encouraging individuals to eat highly processed foods made with macronutrient replacers, clinicians should focus on emphasizing the importance of eating a diet rich in fruits, vegetables, whole grains, lean proteins, and heart-healthy fats. The most accessible and effective way to encourage patients to manage caloric intake and achieve a balanced intake of macronutrients is by empowering them to follow MyPlate guidelines at every meal and encouraging them to eat fresh, frozen, or canned vegetables and fruits daily. Patients must also be educated on how to read and understand food labels, so that they are able to make sure that they do not exceed the recommended amounts of added sugar (6 teaspoons [25 g]) of added sugar per day) and saturated fats (10% of daily calories). As clinicians, it is also important for patients to understand that eating ultra-processed foods that are sugar free or fat free will not necessarily improve the quality of their diet. This is especially true if patients are choosing to eat highly processed diet food instead of nutrient-dense whole foods. Furthermore, patients should be encouraged to learn how

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to mindfully consume added sugar and fat instead of seeking ways to replace them using macronutrient replacers. For instance, instead of encouraging a patient to eat sugar-free cookies every night for dessert, we can teach patients to whip up a chocolate smoothie made with real fruits, healthy fats, and lean proteins. Instead of telling patients to drink diet sodas to substitute regular sodas, we can teach patients how to enjoy seltzer water infused with herbs or berries. While eating foods containing macronutrient replacers is safe and may lead to short-term caloric reduction, the research shows that swapping out regular processed foods for low-fat, low-sugar alternatives will not likely lead to improved health outcomes. As clinicians, we can lead the way by educating our patients to adopt an eating and lifestyle philosophy that encourages increased consumption of fruit and vegetables, decreased consumption of ultra-processed foods, and regular physical activity (150 minutes/week). We must also work to create nutrition education and counseling programs that are affordable, accessible, culturally humble, and respectful of food preferences and social traditions.

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Plant-Based Diets

Shireen Kassam

INTRODUCTION

In clinical nutrition, the term "plant-based" is used to refer to a range of dietary patterns that exclude animal-derived foods to varying degrees. In recent years, there has been a marked increase in the number of people following plant-based diets, for reasons generally related to health, animal welfare, cultural/religious beliefs, and environmental concerns. Increasing evidence of the benefits of plant-predominant eating on human health has led to growing consensus on the value of plant-based diets in a clinical setting (1). Clinicians are obligated to have a working knowledge of plant-based eating patterns to ensure their patients/clients are meeting nutritional requirements.

OVERVIEW

Terminology

- **Vegetarian**—excludes meat, poultry, and fish.
- **Lacto-ovo vegetarian**—otherwise vegetarian but permits the consumption of dairy and eggs.
- **Lacto-vegetarian**—otherwise vegetarian but permits the consumption of dairy but not eggs.
- **Pesco-vegetarianism** (a term used less frequently)—otherwise vegetarian but permits seafood.
- **Vegan**—excludes all animal-derived foods, including meat, poultry, fish, eggs, dairy, and honey.
- **Plant-based**—a dietary pattern that is predominately, but not exclusively comprised of plant foods. Although there is no consensus definition, plant-based diets typically include 85% to 90% plant-derived foods.

A fundamental challenge implicit in the use of the above terms in clinical practice and research related to health promotion is the tendency for labels to define what foods an individual is *not eating* without clearly defining what they *are eating*. A case in point is that despite their adverse health effects, many ultra-processed foods are derived exclusively from plants and would therefore meet the criteria for inclusion in a vegan, vegetarian, or plant-based diet. In this chapter, unless otherwise specified, the terms "plant-based" or "plant-predominant" are intended to refer to a dietary pattern that is centered around minimally processed fruits, vegetables, whole grains, legumes, nuts and seeds, herbs, and spices and with minimal (or absent) contributions from animal-derived foods including red meat, poultry, fish, eggs, and dairy products.

NUTRIENTS, NUTRACEUTICALS, AND FUNCTIONAL FOODS

Protein

Despite widespread distribution of essential amino acids in plant foods, it is still widely believed that

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plant-predominant diets pose a risk of dietary protein inadequacy. The source of this misconception lies primarily in the prevailing definition of protein quality, which has historically been based on the distribution and digestibility of the component amino acids in a particular food. As such, protein from animal sources is commonly considered “complete” because it provides all nine essential amino acids to meet human requirements in a readily digestible matrix. Conversely, most plant sources of protein are considered “incomplete” due to relatively lower levels of one or more essential amino acids and a fiber-rich food matrix that decreases digestibility. Commonly cited examples include beans which have low methionine levels and nuts which are low in lysine.

Compared to fat and carbohydrate, dietary protein has a stellar image in popular culture, in the health and wellness industry, and in the media. This reputation, when coupled with the biochemical definition of protein quality, has led to a public perception that plant-based diets are inferior. The evidence suggests otherwise. Isocaloric consumption of a variety of whole plant foods throughout the day, or even over several days, will reliably meet protein requirements with minimal attention to specific food combinations (2). In fact the lower quantities of certain amino acids such as methionine and branched chain amino acids (BCAA), leucine, isoleucine, and valine, in plant-derived protein may actually confer a health advantage (3,4). Furthermore, there are several “complete” plant protein sources, including soybeans, quinoa, chia seeds, and buckwheat. Soy provides protein with a biological value similar to that of animal protein (5). More importantly, several lines of evidence demonstrate that obtaining protein from plant sources rather than animal sources is associated with better health outcomes and can reduce the risk of a number of chronic diseases, including cardiovascular disease, type 2 diabetes, and certain cancers (6,7). Considering the above, a modernized definition of protein quality that considers the health and environmental impacts of dietary protein sources has been proposed (2).

Vitamin A

Preformed vitamin A (retinol) is only found in animal-derived foods, which has led to some confusion about the risk of vitamin A deficiency with plant-based diets. Plants (including many fruits and vegetables) contain provitamin A carotenoids like beta carotene, alpha carotene, and beta cryptoxanthin that can be converted into retinol in the body (8). There are also many other non-provitamin A carotenoids in plants including lutein, zeaxanthin, and lycopene that have no impact on vitamin A status. Beta-carotene is the most abundant provitamin A carotenoid in plant foods and is found in orange, yellow, red, and green vegetables and fruits, including spinach, carrots, sweet potatoes, red peppers, mango, papaya, and apricots. Because of the widespread distribution of provitamin A carotenoids in whole plant foods, vitamin A sufficiency is readily achievable on a plant-predominant or plant-exclusive diet.

Vitamin B_{12}

Contrary to popular belief, the vitamin B_{12} present in meat, eggs, and dairy is not manufactured by mammals or birds but is either absorbed after being consumed by the animal or produced by micro-organisms in the Gastrointestinal (GI) tract (9). A regular and reliable source of B_{12} is essential for any individual whose diet excludes all animal-derived foods. As such, individuals choosing a vegan or largely plant-based diet should be encouraged to obtain B_{12} in the form of a supplement. Furthermore, there is evidence to suggest that the prevalence of B_{12} deficiency is greater than previously thought and can impact both vegetarians and non-vegetarians. Reduced B_{12} absorption occurs with advancing age, so it may be advisable for individuals over the age of 50 years to take a B_{12} supplement, regardless of diet

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pattern (10). Cyanocobalamin is most widely used and most stable form of B_{12} for supplementation although activated methylcobalamin is increasingly popular and may be superior in terms of absorption and tissue retention.

Iodine

Iodine is naturally found in the ocean and in terrestrial soil but concentration and bioavailability of iodine in agricultural soil are generally low, so most plant foods are not a reliable source of dietary iodine (11). Omnivores typically obtain iodine from fish and dairy produced by cows given iodine supplements or enriched diets. When iodized salt is included in the diet, there is little risk of iodine deficiency, but the increasing popularity of non-iodized salt raises the possibility of iodine deficiency. Sea vegetables are a natural source and non-dairy milk alternatives are now commonly fortified with iodine.

Calcium

In Western countries, dairy products are a significant source of dietary calcium, which raises concerns about obtaining sufficient calcium on plant-based diets that exclude dairy. Calcium is widely distributed in plants but absorption and bioavailability are affected by the presence of oxalates. The association between dietary calcium and bone density, and the risk of osteoporosis, is complex and controversial. Current consensus guidelines for healthy adults generally recommend 1,000 mg per day from all sources. Thus, a plant-based diet that incorporates low-oxalate green leafy vegetables, legumes, calcium-set tofu, nuts, seeds, and calcium-fortified milk alternatives can provide sufficient amounts of calcium (12). When calcium and vitamin D levels are maintained on a plant-based diet, there is no reliable evidence for a detrimental effect on bone health (13,14). As such, despite the prevailing narrative that dairy promotes bone health, there is increasing consensus that dairy consumption is not essential for human health (15).

Iron

Iron is naturally occurring in both plant- and animal-derived foods. In animal foods, iron exists is in the heme form which is more concentrated and more efficiently absorbed than in the non-heme form found in plants. Although individuals eating a health-conscious plant-based diet generally consume as much iron as omnivores, iron stores tend to be lower, and the risk of iron-deficiency anemia may be increased (16). Non-heme iron absorption is regulated by physiologic demand. Its absorption can vary greatly, depending upon both the meal composition and the iron status of the individual. The bioavailability of non-heme iron is impacted by the ratio of absorption inhibitors, such as phytates and polyphenols, and enhancers, such as vitamin C, citric acid, and other organic acids. Combining iron-rich foods (whole grain, legumes, nuts, seeds) with foods rich in vitamin C (fruit, vegetables) is the most efficient way to enhance iron absorption from plant foods. This effect is significant, as just 50 mg of vitamin C in a meal can increase iron absorption three to four fold (17).

Zinc

Strict vegan diets have been associated with low serum zinc levels, although well-balanced, plant-predominant diets pose little risk of deficiency. Reliable source of dietary zinc in a plant-based diet include nuts, seeds, legumes, and whole grains although naturally occurring phytates can inhibit zinc absorption. In order to increase the absorption and bioavailability of zinc and other minerals in foods, strategies to reduce phytate levels are commonly employed. These include soaking/sprouting of cereals and beans as well as traditional fermentation methods like those used for sourdough bread, tempeh,

fermented tofu, and miso (18).

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Omega-3 Fatty Acids

The three omega-3 fatty acids that are most relevant to human health are alpha linolenic acid (ALA), docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA). ALA is an essential fatty acid found in plant foods and must be obtained from the diet. In omnivores, DHA and EPA are typically obtained from fish, who obtain it from marine algae. Small amounts of DHA and EPA are also derived by conversion from ALA. There is evidence to suggest that if DHA and EPA are not being obtained from the diet, the efficiency of conversion from ALA increases. In the European Prospective Investigation into Cancer and Nutrition (EPIC) study, DHA/EPA levels in the blood did not differ as much as expected when comparing fish eaters, vegetarians, and vegans (19). Studies also show that vegetarian and vegans have higher blood levels of ALA than omnivores (20). Meeting daily requirements of approximately 2 g of ALA per day would require one tablespoon of chia seeds or ground flaxseeds (linseeds), two tablespoons of hemp seeds, or 30 g of walnuts (21).

There is uncertainty as to whether those choosing a vegetarian or vegan diet benefit from DHA/EPA supplementation to decrease the dependency on conversion from ALA. Given the broad importance of DHA/EPA on human health (see Chapter 2), individuals on plant-based diets with little to no DHA/EPA should consider supplementation. Marine algae provide a reliable source for individuals on vegetarian or vegan diets. Typical dosage for adults is 250 mg DHA/EPA combination per day. Higher doses of 400 to 500 mg daily are routinely recommended during pregnancy and lactation (21).

CLINICAL HIGHLIGHTS

Long-Term Health Outcomes of Vegetarians and Vegans

Observational data suggest that vegetarianism is associated with reduced risk of various chronic diseases and all-cause mortality, although such findings are potentially confounded by other health-promoting behaviors often associated with vegetarianism. The intrinsic nature of a vegetarian diet not only excludes meat products but usually also fosters an increase in the consumption of vegetables and fruits. This invariable adding and subtracting of food groups makes the task determining “cause versus correlation” extremely complex.

There are a small number of prospective cohort studies that have specifically investigated the long-term health of vegetarians and vegans. The two largest cohorts are the Adventist Health Studies-2 (AHS-2) from North America and the EPIC-Oxford study from the UK, both with approximately one third of participants adhering to some form of vegetarian or vegan diets.

The vast majority of the global vegetarian population lives in Asia and two smaller prospective cohort studies investigating the health of Asian vegetarians include the Tzu Chi Health Study and the Indian Migration study. There are some important caveats related to the cohort characteristics and the dietary patterns described in these studies. The foods consumed (and not consumed) on vegetarian and vegan diets vary widely based on geography, personal preferences, and the underlying motivation for adopting these diet patterns. For example, dietary quality may differ substantially in cohorts who avoid animal foods for ethical or religious reasons compared to those who avoid animal foods for health reasons. In addition, many of the studies from these cohorts report on the vegetarian and vegan groups together and therefore the health impact of consuming or avoiding eggs and dairy cannot be reliably reported (22).

In addition to the larger cohort studies mentioned above, there are several smaller prospective cohort

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studies, cross-sectional studies, intervention studies, and meta-analyses that have provided insight about the impact of vegetarian and vegan diets on human health. Below is a discussion of observations from these investigations.

Life Expectancy and Mortality

Observational data suggest a benefit of vegetarianism on both cardiovascular and all-cause mortality, but prospective studies on life expectancy and all-cause mortality have been inconsistent. Vegetarians and vegans combined had a reduced risk of overall mortality compared to non-vegetarians in the AHS-2 study but not in the EPIC-Oxford study (22). In fact, the relatively healthy cohorts in the AHS-2 and EPIC-Oxford studies have lower mortality rates than the general US and UK populations that confound the morbidity and mortality data (23,24).

Cardiovascular Disease

The data on cardiovascular disease (CVD) risk in vegetarians and vegans are consistent with their lower body mass index (BMI), serum lipid levels, blood pressure, and fasting glucose (22). Plant-predominant diets are associated with decreased total cholesterol, low density lipoprotein (LDL), and high density lipoprotein (HDL) levels but not usually with decreased triglycerides (25).

There are several mechanisms by which vegan and vegetarian diets reduce CVD risk factors. Plant-based diets have low (vegetarian) or absent (vegan) cholesterol intake, low saturated fat, and higher unsaturated fat levels. In the AHS-2, there was a strong positive association with the consumption of meat protein and cardiovascular mortality with a strong negative association with protein from nuts and seeds, suggesting that the source of protein may be an important contributing factor in addition to the lower saturated fat consumption (26). This finding was corroborated and advanced in large prospective cohort study published in *JAMA* that concluded that increased dietary plant protein intake is associated with reductions in risk of all-cause and cardiovascular disease mortality (27).

Additionally, the high fiber and plant sterols in well-balanced plant-based diets combine to reduce the absorption of dietary fat and cholesterol. Diets that include a diverse array of plants provide micronutrients and phytonutrients that may impact cardiovascular risk via a range of different mechanisms including effects on lipids, coagulation, inflammation, endothelial function, and blood pressure. Additional benefits from plant-predominant diets may also be related to relative absence of compounds in animal foods known to adversely affect cardiovascular risk such as heme iron and nitrite-based preservatives found in red and processed meats (28).

Emerging research also suggests that the gastrointestinal microbiome, which is influenced by diet, is involved in the pathogenesis of CVD. Choline and carnitine, compounds derived mainly from animal foods (red meat, poultry, fish, and eggs), are converted by gut microbes to trimethylamine (TMA), which is then converted to trimethylamine *N*-oxide (TMAO) in the liver. Higher TMAO levels are associated with increased risk of CVD. TMAO levels are significantly lower in vegetarian and vegans due to lower intakes of precursors and differences in the composition and diversity of the gut microbiome (29).

Stroke

In general, diet patterns that emphasize more fruits and vegetables and lower consumption of meat are associated with a lower risk of stroke (30). However, the results from prospective cohort studies on vegetarian and vegan diets have not been consistent (22). A recent update from the EPIC-Oxford study has reported on rates of stroke and ischemic heart disease in different dietary cohorts (31). The results demonstrated that compared to omnivores, fish eaters, and vegetarians had lower rates of ischemic heart

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disease, but vegetarians had higher rates of hemorrhagic stroke. Possible mechanisms that might account for this finding include the fact that the vegetarian participants had suboptimal levels of vitamin B_{12}, vitamin D, and long-chain omega-3 fat and also the lower LDL cholesterol in vegetarians and vegans. In contrast to these findings, a subsequent publication from the Tzu Chi Health Study reported a significant reduction in the risk of ischemic *and* hemorrhagic stroke in vegetarians (32). This was in spite of lower B_{12} levels in the vegetarians. It should be noted that this cohort differs from the EPIC-Oxford in that the Taiwanese Buddhists don't smoke tobacco or drink alcohol and eat more soy-based foods. Adding to the complexity, a meta-analysis and systematic review of prospective cohort studies published prior to the two aforementioned studies showed that vegetarian diet patterns had no impact on the risk of stroke when compared to non-vegetarian diet patterns (33).

Type 2 Diabetes

Vegetarians and vegans have a consistently lower risk of type 2 diabetes compared with omnivores (22). In the AHS-2 there was a stepwise reduction in risk of diabetes as more meat is removed from the diet. Vegetarians had a 46% decreased risk and vegans a 49% decreased risk of diabetes compared to non-vegetarians. In the EPIC-Oxford study, those avoiding meat had around a 50% reduced risk of diabetes when compared with regular meat eaters. However, the effect was smaller once results were adjusted for body weight. In the Tzu Chi cohort, vegetarians had a greater than 50% lower prevalence of type 2 diabetes (34).

The mechanism by which vegetarian and vegan diets prevent type 2 diabetes overlap with the mechanisms involved in CVD and are related to both benefits of foods that are included and minimization of harm from those that are excluded. This includes the relatively lower intake of various compounds in animal-derived foods that increase the risk of insulin resistance such as nitrites and nitrates in processed meat, advanced glycation end products, BCAA, saturated fat, heme iron, and TMAO. Conversely, the benefits of minimally processed plant-based diets on glycemic control are due to the high fiber content, low levels of saturated fat, and high levels of phytonutrients and antioxidants. Plant-derived polyphenols may inhibit glucose absorption, stimulate insulin secretion, reduce hepatic glucose output, and enhance glucose uptake (28). Dietary fiber reduces postprandial glucose and is fermented by intestinal bacteria to produce short-chain fatty acids, which also improve the glucose response, insulin signaling, and insulin sensitivity. Fiber reduces the energy density of foods, promotes satiety, and has been associated with maintaining a more healthy weight, further promoting insulin sensitivity (35).

Cancer

In general, overall cancer rates are lower in those consuming a vegetarian or vegan diet, although site-specific cancer risk varies between studies. A 2017 meta-analysis reported that vegan diets confer 15% reduced risk of overall cancer (36). In the EPIC-Oxford study vegetarians had an 11% reduced risk and vegans a 19% reduced risk of developing any cancer. For site-specific cancer, vegetarians compared to meat eaters had a significantly lower risk of cancers of the stomach, bladder, and lymphatic and hemopoietic systems but no difference in risk of colorectal, prostate, and breast cancer risk. In the AHS-2 vegetarians had an 8% reduced risk and vegans a 16% reduced risk of developing any cancer. Vegetarians had a significantly lower risk of colorectal cancer and vegans a significantly lower risk of prostate cancer and a trend toward lower risk of breast cancer. Neither the EPIC-Oxford nor the AHS-2 shows an advantage for cancer mortality for vegetarian and vegan diets (22).

Mechanisms by which well-balanced vegetarian and vegan diets may contribute to reduced cancer risk

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are likely related to the relative reductions in foods that increase risk as well as benefits of including foods that reduce risk. Plant-based diets minimize processed and red meat, which are classified as Group 1 and Group 2a carcinogens, respectively, by the WHO (37). Reduced or absent consumption of animal protein results in a lower level of insulin-like growth factor-1 (IGF-1) a growth hormone associated with an increased risk of a number of cancer types (38). The absence of dairy in vegan diets may play a role in reduced prostate cancer risk (39). Conversely, increased consumption of plant foods is associated with decreased cancer risk. Daily consumption of 600 g of fruits and vegetables has been shown to reduce the risk of cancer by 13% (40). Increased fiber consumption is protective (41). Beans, nuts, and soy consumption have also been associated with a lower risk of various cancers (42–44). The impact of diet on cancer risk is addressed in detail in Chapter 12.

Bone Health

A healthy diet and lifestyle play a fundamental role in preventing osteoporosis later in life. Important nutrients for bone health include calcium, potassium, magnesium, folate, vitamin K, and vitamin D (from sunlight), which can all be obtained from a healthy vegan or vegetarian diet. The EPIC-Oxford study showed no difference in the self-reported incidence of fractures between meat eaters, fish eaters, and lacto-ovo vegetarians, but vegans had a 30% higher risk of fracture compared with meat eaters (45). However, when the results were adjusted for calcium intake, those consuming at least 525 mg of calcium per day, regardless of diet pattern, showed no increase in fracture risk. A subsequent 2020 analysis with longer-term follow-up from the same study cohort found that compared to meat eaters, non–meat eaters had increased risk of fractures, with the greatest risk in vegans. This risk is partially (but not completely) attributable to lower BMI found in vegans and may also be related to lower calcium and protein intake. Although additional studies will be necessary to confirm and generalize these results, clinicians should be attentive to BMI, protein, calcium, vitamin D, and other dietary and lifestyle factors influence that bone health in vegetarian and vegan patients (46).

In the Adventist Health studies, vegetarians were not at higher risk of fractures per se, but the studies did report a protective effect of protein consumption, whether from plant or animal sources, for prevention of wrist fractures in older women (47). Consumption of legumes and meat analogues (derived from soy, wheat, gluten, eggs, and milk) was also found to be protective against hip fractures in men and women (48). Interestingly, in a cross-sectional study of Buddhist vegan nuns compared to omnivorous women randomly sampled from monasteries in Vietnam, no difference in bone mineral density or rates of osteoporosis were found between groups despite the vegan nuns having a median daily calcium intake of 330 mg per day (49). A subsequent systematic review and meta-analysis that included 20 studies and over 37,000 participants found that vegetarians and vegans had lower bone mineral density and vegans were at increased risk of fracture compared to omnivores (50). In light of significant study limitations (including lack of information related to dietary quality) and methodological challenges implicit in an analysis of a disorder with a multifactorial etiology, these results should be interpreted with caution. Questions about the impact of plant-based diets on bone density and fracture risk remain, but available evidence suggests that individuals on these diets should be encouraged to ensure adequate dietary protein, calcium, vitamin D, and B_{12}.

Pregnancy, Lactation, and Childhood

The unique nutritional demands of pregnancy, lactation, and childhood raise important questions about the safety of plant-based diets. Available evidence suggests that well-planned vegan and vegetarian diets, with attention to the specific nutrients discussed above, are safe in pregnancy, lactation, and childhood

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(51). When maternal nutrition is wellbalanced, pregnancy outcomes in vegetarians are comparable to outcomes in omnivores. Vegan mothers should be strongly encouraged to supplement with vitamin B_{12}. During pregnancy and lactation, vitamin D supplementation should be considered based on geography, sun exposure, and 25-OH vitamin D levels if available. Iodine supplementation should also be considered, especially if iodized salt consumption is low. In addition, supplementation with long-chain omega-3 fats (EPA/DHA) are advisable to help prevent preterm labor and for fetal neurologic development. Protein requirements increase in the third trimester, so protein-rich plant foods such as beans, legumes, nuts, and seeds should be encouraged. Calcium-rich foods should also be emphasized as increased calcium intake during pregnancy may protect against preeclampsia. With attention to dietary quality and nutritional status, vegetarian or vegan diets are safe and may reduce risk of excessive gestational weight gain, preeclampsia, and gestational diabetes (52).

Multiple studies have attempted to evaluate the impact on plant-based diets in children, but study heterogeneity, small samples, and a bias toward higher socioeconomic status have made firm conclusions elusive. The German VeChi diet study collected data on diet, lifestyle, biometrics, and health status in vegan, vegetarian and omnivorous children recruited between 2016 and 2018. There were no significant differences in height, weight, or daily energy intake of vegan children compared to non-vegan children. Macronutrient intake did vary, with vegan children eating more carbohydrates and fiber and omnivores consuming more protein, fat, and sugar. Available evidence suggests that a well-planned, energy-dense vegetarian or vegan diet in early childhood is appropriate and can support normal growth and development (53). A study in adolescents aged 12 to 18 years old in a predominantly Adventist population in the United States examined the impact of vegetarian versus non-vegetarian diets. The results showed that the diet quality was better in the vegetarians with greater intakes of foods considered to be beneficial to health and an overall better nutrient intake profile, including lower intakes of energy and saturated fats, a more favorable omega-6 to omega-3 ratio, and higher intakes of dietary fiber, folate, iron, calcium, potassium, and magnesium (54).

Vegan mothers who have difficulty or are unable to breastfeed are typically reluctant to use dairy-based formulas for their children. Available data suggest that soy-based formulas are safe to use from birth if breastfeeding is not possible (55,56).

Plant-Based Dietary Index

In response to the challenges in conducting rigorous prospective studies investigating the effects of plant-based diets, especially the issue of controlling for dietary quality, researchers have developed plant-based index (PDI) (57). The PDI is a tool that assigns positive scores to plant-derived foods and negative scores to animal-derived foods. Variations of the PDI that allow for classification of healthy plant foods (vegetables, fruits, legumes, whole grains, nuts, seeds) and unhealthy plant foods (sugar, refined grains, juices) have also been developed. Using the PDI, researchers can analyze the dose–response relationship of animal foods, healthy plant foods and unhealthy plant foods independent of the label (vegetarian, vegan, etc.) applied to a dietary pattern. Table 43.1 shows the components of the PDI, both healthy (hPDI) and unhealthy (uPDI).

The PDI was used in a reanalysis of the PREDIMED study (57), a randomized study of a Mediterranean-style diet compared to a control diet. The reanalysis showed that the benefits of the Mediterranean-style diet were predominantly due to the high consumption of whole plant foods and those that consumed a diet with a high plant-based diet score/index had the lowest risk of all-cause mortality. Subsequently, several prospective cohort studies have shown that participants whose diet has a high PDI have a significant reduction in risk of coronary heart disease (58), cancer (59), type 2 diabetes (60),

kidney failure (61), stroke (62), and weight grain (63). These studies have also shown that a diet with a high uPDI is associated with an increased risk of these chronic diseases, even when animal-derived food consumption is low. Table 43.2 shows the change in risk associated with high adherence to the three PDI indices.

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TABLE 43.1

Components of the Plant-Based Diet Index

Healthy Plant Foods	Unhealthy Plant Foods	Animal Foods
Fruits	Fruit juice	Meat
Vegetables	Refined grains	Fish
Whole grains	Potatoes	Eggs
Nuts	Sugar-sweetened beverages	Dairy
Tea and coffee	Sweets and desserts	Animal fat
Vegetables oils		

Plant-Based Meat Alternatives

The increasing popularity of plant-based diets has led to rapid growth, innovation, and market demand in the plant-based meat industry. Vegetarians have long relied on traditional soy-derived products like tofu and tempeh or "veggie burgers" that combine legumes, grains, and vegetables as alternatives to meat. Although these traditional vegetarian staples are often used to replace meat in a meal, most omnivores agree that they do not accurately mimic the taste or texture of the "real thing." Modern food processing technology has changed that. Plant-based products that look, feel, and taste like meat are rapidly proliferating, and have already become menu items at popular fast-food restaurants. Burgers, sausages, bacon, and nuggets are now being made from wheat, soy, peas, mushrooms, and a long list of other plant-derived ingredients in high-tech food processing plants. Whether these products are better than the meats they are designed to replace in terms of impact on human health remains unknown.

TABLE 43.2

Plant-Based Diet Index and Change in Risk of Chronic Disease; Healthy and Unhealthy

Disease	PDI	hPDI	uPDI
Coronary heart disease	8↓	25↓	32↑
Type 2 diabetes	20↓	34↓	16↑
Total cancer risk	15↓	NA	NA
Renal failure	6↓	14↓	11↑

hPDI, healthy plant-based index; PDI, plant-based index; uPDI, unhealthy plant-based index.

At the time of this writing, there are very little data on the health impacts of plant-based meats. One recent small study suggests that substituting plant-based meat products for 8 weeks improved several cardiovascular risk factors including serum TMAO levels (64). Additional studies are needed to fully elucidate whether these highly processed meat alternatives confer a health advantage over the meat or poultry that they typically replace. In the meantime, given the known adverse health and environmental

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impacts of factory-farmed and processed meats, individuals interested in plant-based diets can be confidently advised to increase their consumption of minimally processed plant foods.

Therapeutic Use of Vegan, Vegetarian, and Plant-Based Diets

Plant-based diets are increasingly popular in both culture and clinic for the prevention and treatment of chronic disease. Observational data suggest that plant-based diets are associated with reduced risk of various chronic diseases and all-cause mortality, although such findings are potentially confounded by other health-promoting behaviors common in individuals who choose plant-based diets. As defined and described here, plant-based diets not only minimize animal-derived foods but also foster an increase in the consumption of vegetables and fruits. The inevitable inclusion and avoidance of food groups makes the task of determining the precise cause of an observed clinical effect extremely complex. Despite the complexity, studies of plant-based diets suggest benefit on cardiovascular risk (65–68), inflammation (69), cancer (70–73), diabetes (74–79), and anthropometric measures such as BMI and waist circumference (80,81) which are especially relevant in the era of epidemic obesity.

A well-balanced, plant-predominant diet is certainly superior to prevailing dietary pattern in the West and increasing evidence suggests that it may be nutritionally optimal. Veganism that relies on processed foods should prompt clinicians to be aware of the risk of micronutrient deficiencies, particularly of zinc, iron, calcium, and vitamins B_{12} and D.

All vegetarian/vegan patients should be interviewed to ascertain their motivations and whether the diet is based on a balanced distribution of plant-based foods or on a preponderance of processed foods. In the latter instance, the patient is subject to the excesses of the Western diet and to nutrient deficiencies as well and should be counseled accordingly. For both reasons, if the patient is not well informed about the protein and nutrient content of plant foods, referring the patient to print and web-based sources of information (see Appendix J) and to a nutrition professional for detailed counseling is warranted.

Plant-based diets that are adopted in adolescence should invite questions about the underlying motivations and to assess the possibility of an eating disorder. Adolescents appear to be at particular risk of unbalanced vegetarian practices and should receive dietary counseling; routine referral to a practitioner with adolescent nutrition expertise is appropriate.

Whether or not they are inclined to renounce animal foods entirely, most patients should be encouraged to shift more toward a plant-based dietary pattern. Recent evidence suggests that the average intake of fruits and vegetables in the United States is well below recommended levels, with roughly 32.5% of the population said to consume fruit two or more times per day and only 26.3% consuming vegetables three or more times per day (82). Increased consumption of fruits and vegetables should be strongly encouraged.

Plant-Based Diets and the Environment

Current global food and agriculture practices are a major driver of climate change, water pollution, land degradation, loss of wildlife and biodiversity, antibiotic resistance, zoonotic diseases, deforestation, and ocean destruction. Animal agriculture produces more greenhouse gas emissions than all forms of transportation combined. A comprehensive analysis of the global farming system concluded that a large-scale shift toward plant-based diets would have a larger impact on planetary health than any other driver of climate change. Meat and dairy production uses 83% of farmland and produces 60% of agricultural greenhouse gas emissions yet only provides 18% of calories and 37% of protein globally. With these statistics, and future generations in mind, it is strongly encouraged for patients and clinicians alike to reduce meat and poultry consumption, replacing lost calories and nutrients with those from plant-based

foods (83–86). A global shift toward plant-predominant dietary patterns has become an imperative for the health of humans and the planet upon which we live (87).

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Diet and Health Promotion: Establishing the Theme of Prudent Nutrition

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Chapter 44

Culture, Evolutionary Biology, and the Determinants of Dietary Preference

Saumya Kumar

If the presence of certain airborne toxins led researchers to conclude that human health would be promoted were we all to breathe underwater, we as clinicians would surely hesitate before offering that advice to our patients. The salient fact that we cannot breathe underwater would, and should, concern us more than the putative benefits of doing so. Even if a science developed that made it possible to distinguish—by virtue of depth, temperature, and content—optimal from less optimal water, the futility of such inquiry would impress us more than any such insights.

The fact is we cannot breathe in water (while other species can) simply because we have not been designed to do so by the forces of evolution. Encouraging our patients to breathe in ways they cannot is not unlike encouraging them to eat in ways they cannot.

Among the environmental forces shaping the adaptation of species, diet has played a premier role (1–3). Although the role of diet in evolution was clear to Darwin and seems self-evident now, much of dietary counseling and nutrition policy ignore its implications.

An approach to human nutrition based in part on evolutionary biology has certain limitations: We have at best imperfect knowledge of what/how our ancestors ate. Our ancestors lived a relatively short lifespan, and we have limited knowledge of the nutrition-related health problems to which our ancestors may have been subject. The diet favored by natural selection for a 40-year lifespan is not necessarily optimal for a lifespan nearly twice as long. Yet, our knowledge of our ancestors' diets is useful in explaining our dietary tendencies and preferences, even if it fails to identify the optimal diet for health promotion.

The conventional practice of nutrition counseling relies principally on an understanding of what patients should be advised to eat. That information becomes essential once we know why people eat as they do and understand what impediments must be overcome to change dietary behavior. But it is of decidedly less value with these questions unanswered. Limited success in the promotion of health and the amelioration of disease through the provision of dietary counseling (4–7) is cause not to renounce responsibilities in this area but rather to reconsider how they can be fulfilled.

The adaptations of our own species are less apparent to us than those of others and consequently are readily overlooked. Consider for a moment a polar bear in its natural habitat. Better still, consider 1,000 polar bears and transplant them all to Morocco. Let their perspicuous demise play itself briefly in your mind, as you consider its cause and obvious remedy. Now consider 1,000 people, or better still several hundred million, in their natural habitat. No particular scene springs readily to mind, for our apparent mastery of the environment has obscured our relationship with it. But although our ingenuity has largely allowed us to overcome the constraints of climate, we have fared less well in our excursions beyond the bounds of the native human diet (3). Much of the chronic disease burden and the majority of deaths in the industrialized world are directly or indirectly linked to a lifestyle and a diet at odds with human physiology (8–10).

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For most species, the limits of tolerance are displayed in anatomic variation: the length of legs, the presence of gills, and the shape of a beak. Humans, no less than any species, are well suited for a particular environment and ill-suited for others. To compensate for incompatibilities between human health and the prevailing environment, those incompatibilities must be understood. To modify human dietary behavior, we must know why we eat as we do (11).

PREHUMAN ERA

Prehuman history, and consequently the origins of human dietary behavior, can be traced back to at least 4 to 6 million years ago (2). By examining fossilized teeth and fossilized human feces (coprolites) and by studying scanning electron microscopy of dental wear patterns, paleo–anthropologists have gained considerable insight into prehuman nutrition.

The earliest identifiable human progenitors in the primate line were arboreal, and they were predominantly, if not exclusively, herbivorous (2,3). Over hundreds of thousands of years, pre-human primates increased in size and descended from the trees. As the cranial vault grew and intellect increased, our ancestors came together in cooperative groups, and began to walk upright and use tools. Some have theorized that early hominins may have added meat to their diets without having the ability to hunt through scavenging. However, early hominins like *Australopithecus* would have had to overcome several obstacles to scavenging, including efficient energy use with walking. The regular consumption of meat likely didn't occur until the development of efficient hunting weapons (12). Rudimentary spears date back to 400,000 years ago, but would not have been effective unless used at close range, which would have been difficult and dangerous. Studies of Neanderthals, who likely thrusted spears at herbivores at close range, demonstrate a high frequency of traumatic injuries on their skeletons and fracture patterns similar to modern-day rodeo riders (13). Advanced hunting tools and tactics, like spear throwers, microliths (stone points for arrows and spears), poison (for arrows), iron-based weapons, and horse-based hunting methods only emerged in the last 100,000 years.

Advanced australopithecines ultimately were supplanted by *Homo erectus*, the first member of the genus *Homo*, which dates back approximately 2 million years; the genus included the species *habilis*, *erectus*, and *sapiens*. *Homo habilis* scavenged more successfully than its predecessors but had limited success in hunting. The greater cranial capacity of *H. erectus* permitted the planning and organizing necessary to ambush large game. Our ancestors became successful hunters in the time of *H. erectus* and continued to refine their skills thereafter. Cooking may have also played a key component in the evolution of human nutrition around the time of *H. erectus* as cooked food is easier to digest and more energy efficient, though of course it contributes to our current obesity epidemic by allowing us to consume a greater amount of calories in a shorter amount of time (14,15). Hunting and cooking became particularly important during the ascendancy of the species *sapiens*, in particular *Homo sapiens neanderthalensis*. The earliest members of *H. sapiens* date back some 300,000 years: *H. sapiens neanderthalensis* approximately 100,000 years, Cro-Magnon humans as much as 50,000 years ago, and modern *H. sapiens sapiens* approximately 30,000 years (16,17).

Whatever the exact prominence of hunting, even a partial dependency on the hunt meant that as soon as prehumans began to eat more than vegetable matter, food supply was always in question. A large kill might supply an abundance of food for a brief period, but invariably it was followed by periods of potential famine. Even with modern weapons and strategies, researchers of 20th-century hunter-gatherer societies noted relatively low success rates of hunting. In July 1964, researchers recorded the Ju/'hoansi of Namibia capturing seven large-game animals over the course of 78 man-days, which confers a 9%

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likelihood of success per man-day of hunting (18). Small game snaring increased the aggregate success rate to 23% using modern techniques and tools. In comparison, the Hadza of Tanzania were successful once every 30 days, conferring a 3% success rate (19). Similarly, ineffective rates have been seen in other hunter-gatherer societies (20–22). In these examples, game animals were scarce and most days hunters return to camp without anything, conferring an actual loss of calories for the day and an opportunity cost of gathering, both of which would render hunting unsustainable if it were not for the large caloric returns associated with each medium-sized carcass and for the caloric contributions from plant foods gathered by their female counterparts.

The cyclical redundancy of feast and famine, or at least the threat of that cycle during human evolution, was among the salient characteristics of the nutritional environment to which our ancestors adapted, characterizing more than 99% of the hominid era on earth (23). A pattern of eating in excess of caloric need and storing fat to endure periods of relative deprivation is observed in modern hunter-gatherers and is thought likely to have characterized the Paleolithic era as well (24). Because of the harsh survival demands of their world, including malnutrition, our ancestors lived a truncated life by modern standards; 19 of 20 Neanderthals (middle Paleolithic) were dead by the time they were 40; 10 of them by age 20 (2).

An increasing reliance on meat in the diet did not expose our ancestors to the type of dietary fat implicated in the chronic disease burden of developed countries. Although at times prehistoric hunters consumed a great deal of meat (25), accounting for up to 30% of calories (23), they consumed very different meat than we do today. Moreover, there is evidence to show that they had very favorable levels of serum cholesterol, blood pressure, and other cardiovascular risk factors, even with very high meat consumptions (26). Modern beef cattle are 25% to 30% fat by weight, whereas the average fat content of free-living African herbivores, thought to be representative of their ancestors, is 3.9% (3). Further, the flesh of wild game contains more than five times more polyunsaturated fat per gram than is found in modern meat, and it contains n-3 (omega-3) fatty acids, which are almost completely absent from domestic beef (3).

HUNTER-GATHERER DIET

The diet of early hominids suggests an uneven divide between meat products and gathered ones. Studies of both the fossil record and modern-day hunter-gatherers shows that early hominids obtained no more than 30% to 40% of total calories from hunting, with the remainder obtained through gathering. The amount of calories obtained from hunting became reliable and substantial only late in human evolution, as discussed previously. This reliable food supply was one of the few ways in which hunter-gatherers began to show differences from their chimpanzee counterparts. Another reason was shown to be the discovery of complex gathered foods, such as honey or hard-shelled fruits. Consumption of these foods required skill and coordination, which the hunter-gatherers were able to do (27,28). The introduction of complex gathered foods that needed effort to process started to illuminate the sexual roles of labor in these communities, as more time and manpower needed to be dedicated. The stereotypical theory was man the hunter, and woman the gatherer. However, studies have shown that the gender roles are more complex than commonly ascribed. Reproductive responsibilities that women have such as childbearing and care for children play a factor, rather than the perceived narrative that women have less strength than men (29). Additionally, it has been shown that as climates and habitats changed, along with food sources, men and women displayed flexibility in sharing responsibilities such as small-game hunting, foraging, and fishing (30,31). Evidence indicates women also introduced early tools, such as wooden digging sticks and carrying devices (12). Further, some have also theorized that grandmothers may have also played an

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important role in child-rearing by contributing valuable calories to growing children through the gathering of underground storage organs, such as tubers and other root vegetables (32). The ethnographic record shows a fundamental aspect of dietary evolution was the complementary aspect of food production among the two sexes, a balance between male-derived proteins and female-derived carbohydrates (27).

MACRONUTRIENT DIFFERENCES: HUNTER-GATHERS THEN VS. MODERN HUMANS NOW

This division of duties between family members could be one of the potential reasons explaining the more controversial topics in paleoanthropology, which is the extent to which our ancestors were hunters versus gatherers. Some experts espouse a larger role for hunting, and thus a greater prominence of meat in our native diet (25). As hunter-gatherers grew into their divided roles and better understood their available food supply, this started to reflect in the breakdown of their diet. Although we see changes in the macronutrient breakdown between a hunter-gatherer diet and that of humans in the United States today, it is probable that diets varied through time and location. There is likely no singular “Paleolithic” diet. One example is the Aboriginal hunter-gatherers in Australia, whose diet was found to be 50% protein, 40% fat, and 10% carbohydrate (33).

Human ancestors consumed far more fiber than modern humans do (as much as 100 g/day), more calcium, one sixth of the current US intake of sodium, and abundant vitamins from the variety of plant foods consumed (23). Of note, modern, cultivated plant foods are likely somewhat less nutrient dense than their wild Stone Age counterparts (24), contributing to the discrepancies between modern and ancestral human diets. In fact, yam, sweet potato, and taro were staple foods in many ancestral diets while grains, dairy, refined fats, and sugar were absent, suggesting that high carbohydrate intake in and of itself is not inherently bad. Fruit was also commonly consumed, which is a more salutary source of fructose than fructose in sucrose and high-fructose corn syrup as it is commonly found today (34). Amazonian Kawymeno foragers in comparison to their neighbor Kichwa agrarians had a diet that was increased in phytochemicals. Tests revealed that local, organic whole-food diets decreased incidence of juvenile-onset vision problems and increased eye health, pointing to increased importance of micronutrients in overall health (35).

There is widespread agreement that the nutrient composition of animal foods consumed in the Stone Age differed substantially from that of domesticated feed animals predominant now. Similarly, the consumption of processed foods did not occur during the times of human ancestors. Evidence has shown that there has been a move away from wild game such as deer and antelope. This has shifted the amount of omega 6 to omega 3 ratio that diets contain, with a previous 3:1 ratio increasing to a current 12:1 ratio (36). Flesh of wild game contains more than five times more polyunsaturated fat per gram than is found in modern meat from farmed animals, and contains n-3 (omega-3) fatty acids, which are almost completely absent from domestic beef (3). Similarly, changes in plant foods through selective breeding have favored changes in fruits and vegetables that are larger in size and with less fiber content to cater to consumer preferences.

Our ancestors generally ate less fat than we do, although the amount varied with time and place (23,25), and they may have even exceeded our intake of cholesterol from consumption of meat, eggs, organs, and bone marrow (2,3). Intake of saturated fat was low, and intake of naturally occurring trans fats was negligible. Western society, over the course of recent decades, has progressively consumed more fat (particularly saturated fat), less unrefined starch, more sugar, and less grain and fiber (37), further distancing us from the diet of our ancestry. There is some encouragement to be seen in a mean decrease in

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the intake of industrially produced trans fats in the United States following the 2003 US Food and Drug Administration rules that established new labeling requirements (38), though individuals with certain dietary choices may still consume high levels of trans fats.

THE USE OF FIRE

The introduction of fire during the *Homo erectus* era brought a massive shift in diet and feeding pattern. Although evidence for fire date back to one million years ago, scholars debate when the controlled use of fire became widespread. Regardless, it is thought that the use of controlled fire may have contributed to the evolution of humans by allowing our ancestors to consume more calories. For example, prior to this point, the consumption of raw meat would have been difficult, dangerous, and energetically taxing. Cooking with fire increased food safety due to lack of pathogens, and broadened the variety of meats used to include wildlife and seafood.

Another positive impact was allowing for an increase in caloric density. Lipid-rich foods, such as peanuts, when cooked (as with fire) can help increase net energy gains. In eating raw peanuts, it has been shown that individuals excrete a larger fraction of the lipids despite the high calorie content of the food (39).

Fires also changed the macronutrient breakdown of meals along with nutritional content. It brought variety to the makeup of both vegetables and meats—they were denatured and broken down, making them easier to digest and resulting in a net rise in energy value (40,41). It increased the accessibility of certain food; for example, with fires it became easier to peel or access certain tubers (42) and grains. It is thought now that humans have become obligate fire users (42).

ENERGY BALANCE: CALORIES CONSUMED VS. CALORIES EXPENDED

Also noteworthy is the dramatic decline in caloric expenditure since the Paleolithic era. It is estimated that hunter-gatherers used a great amount of energy in their day-to-day activities. Some have estimated that males expended about 903 kcal/day on average, and women expended close to 600 kcal/day (43). Men who belonged to the Ache hunter-gatherers of Paraguay would cover up to 10 km daily in their hunting, a mixture of walking, climbing, and sprinting. Hunter-gatherer women would spend hours daily digging, walking, and carrying items from their foraging. This decreased with the introduction of technology in agriculture (44). Studies have shown that simulating this lifestyle can confer some of the benefits in today's humans. Specifically, outdoor physical activity daily can increase daily expenditure but also increase vitamin D synthesis and improve mental health and concentration (43).

Along these lines, data from the Centers for Disease Control Behavior Risk Factor Surveillance system has shown an increase sedentary behavior and a decrease in vigorous activity. The impact of energy-saving devices on caloric expenditure has accelerated over the course of recent decades. Data in Great Britain reveal a 65% decline in work-related caloric expenditure since the 1950s (45); the proliferation of modern electronic devices has doubtless perpetuated this trend. A recent analysis of physical activity worldwide shows that 31% of adults 15 years and older worldwide are physically inactive, with a range of 17% in southeast Asia and 43% in the Americas and eastern Mediterranean (46).

Nonetheless, despite the important of physical activity for maintaining physical and mental health, there is also research that for the Hadza group in East Africa, which has a greater physical activity level than Westerners, total daily energy expenditure was in fact the same, suggesting that energy expenditure may be more consistent than previously thought across a range of lifestyles and cultures. Moreover, it points to

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overeating as a more important contributor to obesity than under-exercising, particularly given that the types of calories more widely available today are less healthy than those eaten by our ancestors (47).

The point of origin of human civilization is subject to debate, but the weight of evidence continues to favor Mesopotamia (2,48). Agriculture developed approximately 12,000 years ago in the delta of the Tigris and Euphrates rivers in what is now Iraq. Sumerians formalized agriculture based on irrigation, permitting the establishment of a reliable food supply for the first time in history.

A predictable food supply gave rise to unprecedented population density. Repeated cycles of irrigation caused salt to precipitate in the soil, destroying its fertility. For the first time, the nutritional needs of a human population exceeded the potential yield from hunting and gathering. The large, concentrated population that agriculture had sustained was compelled to spread out in search of adequate sustenance, giving rise to a human diaspora that ultimately colonized the planet and initiated trade, exploration, and conquest.

The notable nutritional consequence of human dispersion was dietary variation due largely to variations in climate and soil. Each new excursion resulted in the failure of certain established crops and the successful cultivation of new staples. Whereas barley was the principal grain in Mesopotamia, wheat flourished in Egypt, and bread was invented there (2,49).

Naturally, as humanity spread west, it also spread east. The reliance on millet and rice in the diets of eastern Asia reflects the early success of those crops there (50). Each interaction of human population and food supply left an indelible imprint on culture. The need to regulate the distribution of water in irrigation ditches along the banks of the Nile gave rise to centralized regulation that evolved into the pharaonic system of government. Legends developed around the public works of early Chinese leaders committed to producing more arable land to support a growing population.

In ancient Greece, a distinct culture by 1200 BC, olive trees were widely planted to replace trees felled to build houses and ships primarily because olive trees grew well over the superficial limestone characteristic of Greece. A demand for oil in cooking coupled with the increasing availability of olives resulted in reliance on the olive as a principal source because it happened to grow well. The now recognized health benefits of monounsaturated fatty acids (MUFAs) were introduced into the Mediterranean diet by agricultural happenstance. By the fourth century BC, a privileged class in Greece was enjoying a relatively rich diet; this group may have unknowingly benefited from the influence of MUFAs (51).

In ancient Rome, the need to feed a swelling population fostered conquest and further territorial expansion. Greater class distinctions encouraged a taste for the exotic among the wealthy. For the first time, dietary excess became a public health problem, albeit for a select group. The origins of “processing” are traced to Rome and may reflect a preference for heavily seasoned food as a result of nearly universal lead poisoning and a resultant blunting of taste (52).

Medieval Europe with its feudal system was profoundly influenced by food supply. Bread was a mainstay of the diet, and the word “lord” derives from the old English word “hlaford,” meaning “keeper of the bread.” Throughout the medieval period, shortages of food were frequent in late winter, and various pests decimated crops at regular intervals. The dense concentration of European populations, the lack of animal proteins in the diets of serfs, and widespread crop shortages were reflected in human stature. Human beings, in both the new and old world, were on average 6 inches shorter than their hunting ancestors (53). Average height reached the level of the earliest humans again only after the Industrial Revolution. In the Americas, corn thrived and became a staple, and as Michael Pollan has chronicled in *The Omnivore’s Dilemma: A Natural History of Four Meals*, corn has come to dominate the American food system with growing concerns regarding “monoculture” agriculture and genetically modified

organisms (GMOs). The tomato initially was discovered as a “weed” in the cornfields of ancient Central America (54).

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IMPACT OF MIGRATION

The human diaspora has served largely to obscure the link between humanity and dietary adaptations about which generalizations can be made. The marked variations in diets around the globe in the modern era have concealed our common origins and our generally common dietary preferences. An obvious example is the Far East. Traditional Asian diets are quite different from American or European diets, and they have for years been invoked to explain marked differences in the epidemiology of chronic diseases, the most predominant examples of late being T. Colin Campbell and Thomas M. Campbell II’s *The China Study* and Dan Buettner’s *The Blue Zones* (55,56). Buettner argues that the longer, healthier lives of individuals in “Blue Zones” are largely a function of culture, environment, and lifestyle. These factors include a diet rich in beans, regular light exercise, supportive social interaction, a sense of purpose and belonging, and effective stress management, all of which in turn further support healthy eating patterns. But the differences between these populations and others around the world are narrowing in the age of a global economy; fast-food franchises serving hamburgers and French fries populate the planet from Baltimore, to Berlin, to Beijing (57–60). The current ascendancy of the Western or American dietary pattern as the global preference reveals our shared taste for sugar, salt, and fat and is a predictable consequence of our common origins (2,61). These tastes are exacerbated by growing trends toward away-from-home eating, snacking, and increased portion sizes, though of course heterogeneity in these patterns remains as for instance, away-from-home food intake and snacking are as high in the Philippines as in the United States but are rare in Russia and China (62).

Migration has had an increased impact on diets and the burden of chronic disease. There is a concept known as the “healthy immigrant effect,” in which immigrants tend to have less of a burden of obesity and chronic diseases than the native population (63). This is reflective of the original purpose of migration, which an adaptive mechanism following food and more resources (64). However, studies show that over time, the obesity levels of immigrants may match or even surpass their US-born counterparts (65). It is important to differentiate the impact on an immigrant once they move to the United States and the generational impact that acculturation to the United States has on immigrant diet and cultures.

Longer duration of stay (1–5 years) and acculturation in the United States has been shown to be associated with increased body mass index (BMI) and hypertension among immigrant subgroups (66,67). There is no single reason for the devolution in health with acculturation, but likely it is a response to the combination of ubiquitously available calorically dense foods and a decrease in physical activity. Additionally, immigrants have decreased counseling or follow-up with a clinician regarding nutrition, due to language barriers, cultural differences, or lack of access or knowledge (67). Asian immigrants who moved to Canada showed a direct relationship between time spent in Canada and elevated blood pressure. Their hypertension has been attributed to lifestyle changes such as meal patterns and dietary choices (68). These negative changes are mitigated by the positive influences. An example of these are holding onto traditions such as the Chinese collectivist nature of participating in group exercise, or balanced diets with reduced sodium or preservative content (69). An intergenerational impact has been observed among immigrants as well. Keeping the “healthy immigrant effect” in mind, the persistence of an immigrant mother’s health-affirming influences crosses generations to her children. However, in subsequent generations, the health of immigrant children begins to look more like their native counterparts, with an increased BMI (70). US-born Asian Americans have an increased BMI compared to

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foreign-born individuals (71). Additionally, Hispanic adolescents who lived in three-generation houses with their immigrant relatives were found to have lower BMI than those who did not, adding credence to the premise that dietary cultural traditions may have a salubrious effect (72).

In 1962, Neel (16) postulated that genes associated with type 2 diabetes mellitus were too prevalent in the gene pool to comply with conventional paradigms of genetic disease. Invoking the sickle cell gene as an analogy, Neel proposed that the "gene" for diabetes provided a survival advantage in the prevailing nutritional environment of human prehistory. The metabolically efficient individual, able to process and store energy optimally in times of plenty, almost certainly was best suited to endure periods of deprivation. The genotype, which under conditions of dietary excess manifests as obesity and type 2 diabetes, may have been the salvation of our nutritionally insecure ancestors.

This concept has since been embraced more broadly by some, although it remains controversial (see Chapter 6). As stated by Eaton and Konner (73) in an article on Paleolithic nutrition reported in the *New England Journal of Medicine* in 1985, "diets available to preagricultural human beings [determine] … the nutrition for which human beings are in essence genetically programmed." The authors contend that the divergence of humanity from the dietary pattern to which it adapted has significant implications for health, and a subsequent article by the authors 25 years later confirms and further supports this claim (74).

The imprint of evolution remains readily apparent in the idiosyncrasies of modern human dietary behavior and nutritional physiology. Perhaps the single most important example is the nearly universal tendency to gain weight easily and to lose it with considerably more difficulty. Vulnerability to weight gain may be mediated in part through elevated sensory preferences for calorie-dense food (see Chapters 5 and 38). Such a preference, which, like Neel's purported gene for diabetes, promotes obesity under conditions of sustained nutritional abundance, may have conveyed a survival advantage during millennia of subsistence and recurrent privation (16,75).

Recent studies have begun to elucidate the genetic basis for obesity (see Chapter 5). But genes responsible for a condition now affecting some two thirds of the adult population in the United States, and lower but rising proportions in all developed countries, cannot simply be labeled "defective." The same metabolic thriftiness responsible for epidemic obesity was likely essential to the survival of our ancestors in a world of dietary deprivation. Jonathan Wells argues that adiposity is a "complex risk management system" for energy storage responding to multiple ecological stressors, including buffering famine, adaptation to cold, growth, energy for reproduction and immune function, buffering the brain, and aiding in sexual selection (76). This common susceptibility to weight gain has been dramatically revealed in the experience of the Pima Indians of the American Southwest. Adapted to a desert diet unusually low in fat and sugar and unusually high in soluble fiber derived from mesquite, the Pimas had, until the 1940s, a health profile typical of that of other indigent groups. After World War II, the government expanded support for Native Americans and provided the Pimas with, among other trappings of modern society, the typical American diet. Government support also resulted in a decrease in the caloric expenditure required for self-preservation, largely due to the advent of indoor plumbing.

In the ensuing decades, the Pimas have gone on to develop what were for some time the highest rates of obesity and type 2 diabetes of any population known. Although extensive study of this group has advanced our understanding of metabolic rate, the genetics of obesity, and the pathophysiology of the insulin-resistance syndrome, perhaps the most interesting finding is the most intuitive. When the Pimas resume consumption of their native diet, their health problems tend to dissipate (77).

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The tendency to overeat calories may derive in part from the adaptive "feasting" of our ancestors when food was available. According to Dr. Jeffrey Flier and Sharman Apt Russell, we are programmed not only to overeat but also to fail to recognize immediately when we are too full so as to have more energy stores for the next time of famine (78). In rural Cameroon, one study showed the extraordinary rapidity with which weight can be gained through voluntary overfeeding for brief periods, as demonstrated by the Guru Walla ceremony where daily weight gains approaching 0.25 kg were observed in some individuals (79). Modern day overconsumption of calories may be not so much a problem of self-discipline as a problem of unprecedented access to calories. The problem of dietary excess is compounded by the variety of foods constantly available to modern consumers. However, it is important to recognize that obesity was defined in 2013 by the American Medical Association as a chronic disease, with the intention to increase awareness that factors beyond personal choice are affecting it.

Over the last 50 years, the institution of fast food has expanded to meet increasing demand. The number of available offerings in restaurants has increased by over 200%, as well as an increase in portion size of entrees and desserts (80). The most recent USDA data states that 2010 was the year in which the percentage of food consumed away from home surpassed that consumed at home. Across all income levels, the nutritional quality of foods consumed away from home has increased the levels of saturated fat and sodium consumed compared to food eaten at home. An average meal consumed at a fast food establishment contains between 215 and 1,710 cal, which can potentially be a large percentage of an average recommended 2,000 cal/day diet. Humans have evolutionarily adapted to previous famines, and are able to fast when there is no food available and feast when there is an abundance of food. Fast-food chains with their constant availability of calorically dense meals take advantage of this evolutionary nature (81). FDA guidelines in 2018 have required chain restaurants and similar establishments to post calorie content on their menus. Studies done in New York comparing counties which implemented this change and those who did not found a decrease in average BMI in adult residents of counties which disclosed caloric information on restaurant menus (82, USDA).

Sensory-specific satiety is the tendency to become satiated by consumption of a particular food and to consume more total calories when food is available in greater variety (see Chapter 38). Satiety is thought to derive from the interplay of characteristics inherent in food and the concurrent nutritional state of the body. The expression of satiety influences nutrient intake and energy balance.

The potential teleologic advantage of sensory-specific satiety, as posited by Rolls (83), is an incentive for the requisite dietary diversity to satisfy micronutrient requirements. Under current nutritional conditions of constant variety within and between meals, however, the tendency favors caloric overindulgence. Habitual consumption of high-energy foods may decrease sensory-specific satiety, which could lead to higher intake (84). Satiety thresholds are higher for sweets than for other foods, a fact that may account for the consumption of dessert at the end of the meal in most cultures: When satiety is attained, sugar remains desirable (85). Craving for sweetness may have had adaptive value as long as fruits and wild honey were the only available sweet foods, for they are a quick, convenient source of calories. In addition, naturally sweet foods are less apt to be toxic than are foods with a bland or bitter taste (2). The common use of nonsugar artificial sweeteners may further compound the craving for sweetness by dissociating sweetness from energy (86).

OMNIVORE'S PARADOX

The incorporation of new foods into our ancestral diet was contingent on negotiation of the "omnivore's paradox": Although food sampling was essential to prevent nutrient deficiencies, any previously untried

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food represented potential danger. In reaction to these pressures, a natural curiosity developed toward new foods, whereas the degree of preference was associated with familiarity (87). Familiarity remains a profound influence on dietary preference, accounting for, in whole or part, the wide variations in dietary preferences among diverse cultures that are physiologically all but identical. Familiarity also influences expectations about fullness as one study found that children who ate certain foods more often expected those foods to give them greater satiation (88). Changes in dietary habits can establish new patterns of new familiar tastes and new preferences but require a commitment to work through a transitional period. The tendency for children to "dislike" food they have never tried, familiar to every parent, may reflect a deep-seated tendency of the species rather than mere puerile obstinacy.

Hominin have been able to navigate the conundrum of the omnivore's paradox by using the ability to taste. The exquisite ability of humans to taste foods as being sweet, salty, sour, savory, and bitter is thought to have guided our ancestors toward some foods that would have conferred a nutritional advantage and away from others that would have been harmful or devoid of any nutritionally useful substances (89).

In addition to the available research, there is the universally available empirical evidence that diverse human cultures have evolved preferences for a wide range of diets. That the palatability of such diets is often culturally limited and defined suggests that familiarity is significant. Human diets incorporate a spectrum of innately unpalatable tastes. Mechanisms responsible for the development of preference for an innately unpalatable substance remain largely unknown (90). One apparent mediator of preference for a particular taste is its association with a context of appropriate, or familiar, food. Preference for this context, itself, appears to be culturally mediated (90).

FOOD PROCESSING

These ranges of diets are now widening due to the ubiquitous term we know today as "food processing." A proposed definition by Floros et al. (2010) food processing is "any deliberate change in food occurring between the point of origin and availability of consumption." An important example of food processing throughout human history has been with grains. Whereas barley was the principal grain in Mesopotamia, wheat flourished in Egypt, and bread was invented there (2,49). Grinding stones from a Paleolithic site in Israel were found with carbonized starch grains, pointing to the use of these wild cereals as potential dough dating over 12,000 years ago (91). The movement to the agricultural era brought the need to introduce different processing techniques to increase access to these grains.

The newest concept in the evolution of food processing is the idea of ultra-processed foods. Ultra-processed foods are formulations combined of derivatives of foods and additives, via multiple processes such as hydrogenation, extrusion, and pre-processing. Ultra-processed foods have only become available within the past one to two centuries and would not have been part of the fare of our ancestors.

Ultra-processed foods are meant to be convenient, appealing to the consumer, and highly profitable, made with low-cost ingredients (92). This end product is no longer recognizable from its original source (93). Examples of these include reconstituted meat products, soft drinks, frozen prepackaged foods, but also foods that are marketed as low-sugar, vegan, or gluten free (93). These ultra-processed foods embody the definition of "empty calories," meaning energy-rich in macronutrients such as carbohydrates and lipids, but poor in micronutrients and fiber. Empty calories have been shown to increase risk for chronic diseases, and one of the many factors leading to the increase in the prevalence of obesity (93). In many countries today, ultra-processed foods have a lower price than unprocessed foods; however, the price is being paid in increased burden of chronic disease.

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In addition to processing for increased shelf life and convenience, these foods are engineered to take advantage of sensory-specific satiety and the nature of the human palate. Companies that create processed foods hire scientists to research what they call the "bliss point," in which the foods taste good enough to be palatable, but not distinct enough to tell the brain to stop consumption. These researchers aim to find the perfect balance between salt, sugar, and fat along with current consumption trends to optimize sales of their processed foods, essentially creating a product meant to cause overeating (94).

PREFERRED FOODS

Sweet food may have more readily negotiated the omnivore's paradox than food associated with other flavors because of the consistency with which such food proved to be safe (2). The innate preference for sweet taste demonstrated by human infants (90) highlights an involuntary aspect of dietary selection. In addition to sweet foods, other reliable preferences among children include high-fat foods, energy-dense foods, and—at around 4 months of age—salty foods, and there is an innate tendency to reject sour or bitter foods (95). Preferences for these types of food would have been beneficial during human evolution. The boundaries of individual control over dietary selection in an environment of constantly abundant food have not been established, though our primitive preference for sweets and fats goes beyond the allure of taste as opiate-blocking drugs have been shown to decrease sweet cravings, suggesting the potential (yet controversial) role of addictive qualities (96). These addictive qualities are not surprising given that our nervous system and endocrine system evolved to reward us for behaviors that require effort and are required for survival. Classic experiments by Clara Davis (97,98) revealed the ability of human infants to meet metabolic needs by self-selection of diet—but only when a variety of "simple, fresh, unsophisticated foods" was made readily available. Davis and reviewers of her work concur that when children were exposed to less nutritious choices, the quality of their diets suffered (97–99). This idea made sense further in an experimental setting, where infants fed sweetened water exhibited a greater preference for sucrose solutions than others not previously exposed (90). These studies shed some light on the significance of preference for a certain food versus learned preference.

There is evidence that neophobia/pickiness is a strongly heritable characteristic, while specific food preferences are modestly heritable and also influenced by the family environment (95). Unrestricted access to high-calorie, marginally nutritious foods may promote the development of obesity in children (100). Injudicious dietary patterns established early in life may contribute to the later development of heart disease, hypertension, and cancer (99,101). In contrast, promoting the restriction of certain types of foods (e.g., those high in sugar and/or fat) may decrease cravings and preferences for those foods (102).

Our fondness for dietary fat may derive from its prehistoric importance as a dense source of needed calories. Preference for high-fat food apparently is mediated by metabolic, sensory, and sociocultural factors (see Chapter 38). There is evidence that ingestion of sugar and fat may stimulate pleasure by activation of the endogenous opioid peptide system. Consequently, there may be analogies between the intake of dietary fat and addiction (103).

CULTURAL DIETARY PREFERENCES

Food preference is dictated by a variety of aspects, and culture is one of those. The intersection of culture with fondness for certain taste has brought regional differences in diet. The differences between traditional dietary patterns in the United States and Japan, for example, have been ascribed to disparate tastes and preferences (103). As the standard of living among Japanese has risen, however, the popularity

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of meat and imported fast foods has increased in proportion to their accessibility (103). Nutritional differences between the Japanese and American diets, and among diets globally, are waning, as noted earlier. Universal dietary preferences evidently predominate over cultural patterns as nutrient-dilute, energy-dense foods become available (104,105). For the most part, a lower socioeconomic status is associated with a lower-quality (energy-dense, nutrient-poor) diet (106), though similar to the Japanese and American example, higher education and occupation status is also associated with higher sugar and energy intake. Complications of these trends are found in many middle-income and low-income countries like South Africa, where there is a double burden of disease with increasing obesity coexisting alongside still-prevalent undernutrition (107). Food and culture have always interacted, but whether functionally or dysfunctionally has been a matter of circumstance (85,108). A preoccupation with the acquisition of food has clearly resounded through the ages. Success as a hunter was the principal means of gauging status in early tribal societies. In medieval Europe, control of land and the food it could produce gave rise to noble status. To this day, we link status to the acquisition of food, as evidenced by such words and phrases as "earning the dough," "breadwinner," and "bringing home the bacon" (85,109).

As food became equated with currency and success, holidays became times to rest and rejuvenate with mealtimes, and food became central to expressions of love, affection, and celebration. Finding joy in food—even sweets in limited quantities—and showing expressions of love are undeniably positive. However, using expressions of love as a way to continually turn food into unhealthy excess is not. Also prevalent is the belief that more food for less money is a bargain, as epitomized by the all-you-can-eat buffet.

Thus, genetic evolution and cultural history have cultivated human dietary preferences that are well suited for a world in which food is difficult to acquire. The endemic and epidemic health problems of modern societies are in large measure traceable to our lack of defenses against dietary excess (110). Constant nutritional abundance, unknown to both human physiology and human culture for more than 4 million years, has become a modern vulnerability. Yet, we usually wait until our health is "broken" to "fix" it, as opposed to considering—and attempting to change—the very cultural forces that have shaped our dietary behaviors.

Food Industry Influences

The physiologic tendencies endowed by evolution, such as innate preferences for sugar and fat and sensory-specific satiety, are compounded by overt and covert activities of the food industry. Overtly, the food industry spends billions of dollars in advertisements promoting the taste and convenience of fast and processed foods, and it particularly targets children. Research on television advertising shows that exposure affects young people's consumption of the marketed products and influences their food and beverage purchasing patterns even 5 years after the initial exposure (111–113). The basis for preferring fat-dense, sweet, and salty food has already been addressed; other mediators of preference are familiarity and convenience (see Chapter 38). A destructive cycle is created as foods are produced that stimulate our shared preferences for sugar, salt, and fat and then familiarity with such foods is promoted through advertising. The role of healthful foods in the prevailing diet in the United States is increasingly threatened by their marginalization in the popular food culture (114).

Advertising and social media have contributed greatly to the global influence that fast food industries have had. Foods that are heavily advertised, such as high-calorie 24/7 available fast food, are consumed at a greater level than unprocessed foods that are not advertised like fruits and vegetables (115). Recent USDA data found that a one percent increase in fast-food advertising budgets led to a 0.25% increase in demand, showing that advertising has been an effective method for increasing fast-food sales. It has been shown that advertising can even negate positive parenting techniques. A year-long longitudinal study of

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preschoolers showed that targeted fast-food advertising had no impact on the rate of consumption for children whose parents ate fast food regularly; however, consumption was increased in families who ate fast food infrequently (116).

In addition to advertising through the media, the food industry consistently presents information on food package labels to their maximal advantage and often to the detriment of the consumer, our patients. Bold lettering, for example, often implies that the absence of a certain ingredient, such as cholesterol, offers health benefits. Such labeling, however, often appears on products that are naturally free of cholesterol (i.e., all plant-based products) but rich in saturated or trans-fat, sugar, or salt and limited in overall nutritional value. A study looking at 58 “Better-for-You”-labeled children’s products found that 84% did not meet basic nutritional standards as derived from the US Dietary Guidelines and National Academies of Science, with 95% with added sugar, and more than half low in fiber or not containing any fruits or vegetables (117).

Packages boasting an absence of the highly saturated tropical oils often contain products in which those oils have been replaced by partially hydrogenated fat. Fat-modified dairy products indicate how much fat they contain by weight (e.g., 2% milk) rather than how much fat was removed from the original product (e.g., 50% in the case of 2% milk). Whatever nutrient has most recently captured, the public imagination as a means to promote health is named in bold letters on every package of processed foods. At present, front-of-package banner ads for “whole grain” content are in vogue. The marquee nutritional trait on a package generally makes a far more modest contribution to the actual composition of the food (the “contains oat bran” period is a good example) than to the marketing campaign. Many food companies try to promote a healthier image such as McDonald Happy Meals with apple slices instead of fries or Kraft’s promotion of the Oreo as “milk’s favorite cookie” and lower-calorie snack packs while simultaneously promoting even more decadent reformulations (95). A public preoccupation with the health-promoting properties of nature has resulted in widespread labeling of foods as “natural.” Cheese, bacon, whole milk, cream, sugar, and butter may be “natural,” but the benefits in promoting them as such accrue only to their producers, not to our patients.

The food industry exploits vulnerabilities of consumers in a more subtle or covert manner as well. The addition of sugar to such foods as tomato ketchup or processed meats, which would not generally fit into the cultural category of sweet foods, may exert subliminal pressure on the consumer to overindulge because of sensory-specific satiety and resultant undermining of self-restraint (85,118). The addition of salt to such foods as breakfast cereals, often in amounts comparable to those in salty snack foods, may exert a similar pressure, even though the taste of salt in such products is largely masked (119). Whereas an innate preference for sweet and a high associated satiety threshold are thought to have guided our ancestors toward such sources of readily available calories as fruits and wild honey, these traits have been rendered maladaptive by environmental change. With the proliferation of factory-sweetened foods and processed sugar, the guiding hand of evolution is misdirected toward temptation and overindulgence (85). This trend is exacerbated by the fact that more sugary, salty foods are also cheaper. One study showed that in Seattle-area supermarkets from 2004 to 2016. When looking at the average price increase per calorie, unprocessed food such as fruits, vegetables, and meat was 0.41 cents/cal. For processed and ultra-processed foods, the increase was 0.13 cents/cal and 0.14 cents/cal, respectively (120). However, even in supermarkets with reasonably priced healthy options, the average shopper lacks the skill set to reliably identify the more nutritious products (121). In modern Western society, therefore, cultural patterns, economic incentives, and socioeconomic disparities exacerbate physiologic tendencies, further undermining the capacity of our patients to select a health-promoting diet (85,109).

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PUBLIC HEALTH INTERVENTIONS—NATIONAL DIETARY GUIDELINES

Primary care providers must understand the diverse impediments to dietary modification and view that understanding as the basis for more artful counseling rather than as cause for pessimism. The public health stakes are simply too high for us to abandon our efforts at promoting nutritional health (8). Nutrition is of critical importance in the pathogenesis of the most prevalent chronic diseases in the United States, including obesity. National nutrition objectives in the United States for the year 2020 are predicated on the conviction that individualized changes in a person's diet and lifestyle can reduce risks for chronic diseases, keeping in mind the social and physical determinations of diet.

This holistic lens on working on health introduces the many barriers that are present in adopting healthy diets. These include socioeconomic status, access to supermarkets, diet education, lack of time, or lack of willpower (122). There is increasing data showing the importance of access to food and supermarkets and its impact on diet. Studies have shown that neighborhoods with increased access to supermarkets have healthier diets (123). People who are food insecure have been found to have a higher prevalence of chronic disease, and are therefore a high-need population for health behavior intervention. However, the barriers that they face are factors such as lack of high-quality food, unreliable incomes, and lack of education. This highlights the need for sustainable and targeted interventions that can empower people across socioeconomic statuses to eat healthy (124).

An understanding of the determinants of human dietary preference and selection is one of the prerequisites to dietary modification. Only an approach to dietary health that accommodates the physiologic characteristics and cultural predispositions with which humanity has been endowed has meaningful hope of success. As is the case for smoking, changing dietary behaviors likely will require multiple interventions and certainly will require an understanding of the obstacles to such change. Also similar to smoking, the role of stress with overeating is a significant obstacle, even in otherwise healthy eating environments (125).

Although primary care providers can do little to modify the food supply, more effective dietary counseling will contribute to interim progress. There is evidence that the public receives most of its nutrition information from media sources (126–128) but that most people trust nutrition information from a personal physician or health care provider more than from any other source (127). There is also evidence, albeit limited, that dietary counseling by primary care providers meaningfully influences dietary behavior (7).

CONCLUSION

An understanding of why we eat as we do and what impedes and promotes dietary change is an essential element in promoting nutritional health and discussed further in *Disease-Proof: The Remarkable Truth about What Makes Us Well* (129). Such an understanding, shared with patients, alleviates feelings of personal failure in attempts to improve diet. Advising our patients what to eat without addressing the diverse impediments to dietary modification—our shared vulnerabilities, cravings, and aversions—may be comparable to encouraging patients to stop smoking without offering any further assistance. By addressing the obstacles to nutritional health and working with our patients to circumvent them, we may hope to see our efforts at dietary counseling translate into appreciable improvements in the public health, one patient at a time. This practical application of this enterprise is addressed in Chapters 46 and 47.

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Chapter 45

Dietary Recommendations for Health Promotion and Disease Prevention

Erica Oberg and and Wendi Carlock

INTRODUCTION

Food is the fuel on which the human body runs. It stands to reason that the quality of the diet has the potential to influence every aspect of our health. A high-performance body runs best on high-performance fuel. The content of this and other nutrition texts, as well as the primary literature, makes a strong case for this important linkage.

While much can be said about the universal fundamentals of healthful eating, it is important to note aspects of dietary quality that are context specific. In the context of subsistence living, for example, higher-energy-density foods (foods with the greatest amount of potential energy per unit of weight) may offer an advantage by helping to forestall potential caloric deficits when food is scarce. In the context of caloric excess and epidemic obesity, however, foods that provide nutrient density in conjunction with relatively few calories may offer an advantage. The quantity of dietary protein is of primary concern in populations subject to protein deficiency; associated nutrients (e.g., the mix of fats) take on primacy in populations with consistent access to more than sufficient protein. Given that overnutrition now afflicts more of the global population than undernutrition (1), the effects of dietary pattern on weight control are an obligatory consideration in attempting to characterize healthful eating.

Contextualizing the characteristics of a health-promoting diet need not end at the population level. The increased availability of nutrigenomics and laboratory biomarkers invite opportunity to customize guidelines into individualized recommendations for dietary health.

Regardless of whether the target is a population or an individual, the application of diet for health promotion follows two prerequisites. First, the healthful diet recommendations are based on the best available scientific evidence. Second, the recommendations translate the evidence in support of a particular dietary pattern into behavior. While there are certainly controversies and uncertainties concerning the former, the challenges to the latter are considerably more formidable. Nonetheless, the potential benefits of successful dietary health promotion justify a vigorous approach in clinical practice. Knowledge of diet, health, and effective behavioral counseling techniques (see Chapters 46 and 47) continue to evolve, yet the influence of diet on health and the urgency of diet-related disease trends in modern society are sufficiently great to support the implementation of these practices.

Heart disease, the leading killer of adults in the United States, is amenable to dramatic risk reduction through diet by a variety of mechanisms (see Chapter 7). Similarly, obesity in the United States, increasingly a hybrid endemic and epidemic threat to both adults and children, is directly linked to diet and activity patterns (see Chapter 5). The estimate of Doll and Peto (2) that more than one third of all cancers are potentially preventable through dietary manipulations is widely accepted, if not wholly substantiated (see Chapter 12). Stroke, hypertension, diabetes, pregnancy outcomes, degenerative arthritis, and innumerable other diseases, as well as general perceptions of well-being, are responsive to

dietary influences.

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There is currently considerably more consensus than controversy with regard to a health-promoting diet. Controversy persists and arises in areas such as the health effects of specific nutrients or the optimal diet for the prevention or reversal of specific diseases. Therefore, such controversies tend to be nutrient or disease specific. An extensive review of the diverse influences of diet on health serves to mitigate such controversies by providing contiguous lines of evidence that allow for clarification of overlapping recommendations. Elucidating that area of overlap is the principal aim of this chapter.

In the context of established disease, individuals tend to be more motivated and amenable to behavior change and adoption of a health-promoting dietary pattern (see Chapters 46 and 47). For health promotion or long-term risk reduction, the motivation to adopt a new dietary pattern is more difficult to inspire. Prochaska's Stages of Change model is a useful construct for assessing a person's readiness for the adoption of a dietary change.

Dietary recommendations in the setting of clinical disease are similar to those for health promotion, but they may be more extreme both in response to the greater acuity and in response to the patient's greater willingness to adhere to recommendations. The clustering of risk factors for various chronic diseases and of the diseases themselves requires that dietary manipulations for secondary and tertiary prevention not be overly disease specific. An obese patient with type II diabetes, for example, is at increased risk for heart disease, cancer, respiratory disease, and renal insufficiency. Therefore, although specific dietary intervention may be targeted to a single disease like diabetes, the dietary pattern usually remains consistent with recommendations for general chronic-disease prevention and health promotion. Exceptions arise only when disease-specific dietary modifications in the context of organ-system failure require departures from the basic pattern of healthful eating (e.g., protein restriction in liver or renal failure, see Chapters 16 and 17; carbohydrate restriction to reduce the respiratory quotient for pulmonary insufficiency, see Chapter 15).

This chapter characterizes dietary recommendations that may be offered with confidence in the delivery of clinical care to virtually all patients.

DIETARY RECOMMENDATIONS FOR HEALTH PROMOTION

Consensus Recommendations

Diverse bodies of organizations and expert panels make general and disease-specific recommendations for healthy eating. The evidence base, rigorousness of review, and lens of interpretation vary considerably by organization, but there is a good deal of consensus in resultant recommendation statements. Disease-specific organization guidelines are discussed in relevant subsections within this chapter and broad national and global recommendations are discussed later.

The *Dietary Guidelines for Americans, 2015–2020* (3) and the corresponding US Department of Agriculture food guide pyramid (4), now replaced by MyPlate (http://www.choosemyplate.gov), include an emphasis on five overarching guidelines: (a) follow a healthy eating pattern across the lifespan; (b) focus on variety, nutrient density, and amount; (c) limit calories from added sugars and saturated fats and reduce sodium intake; (d) shift to healthier food and beverage choices; and (e) support healthy eating patterns for all. Specific recommendations include an emphasis on abundant intake of whole grains, vegetables, fruits, seafood, and low-fat or nonfat dairy, as well as restricted intake of saturated and trans fat, added sugars, and sodium. The final edition of the *2015–2020 Dietary Guidelines* created controversy because it did not summarily reflect the recommendations in the Scientific Report of the 2015

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Dietary Guidelines Advisory Committee, especially as relates to the recommendations to reduce soda, sugary drinks, and red and processed meat.

Surprisingly, the US Preventive Services Task Force only recommends behavioral counseling regarding a healthy diet and physical activity for patients with cardiovascular risk factors (5). It is prudent for clinicians to be able to respond to patient questions about dietary for health promotion and disease prevention with knowledge of consensus statements.

A recent global review of food-based dietary guidelines compared public health recommendations from over 90 countries (6). The analysis concluded, “Some guidance appears nearly universally across countries: to consume a variety of foods; to consume some foods in higher proportion than others; to consume fruits and vegetables, legumes, and animal-source foods; and to limit sugar, fat, and salt.” Global guidance from the WHO encourages consumption of nuts, whole grains, and healthy fats, but specific national dietary guidelines vary substantially depending on the country. Future iterations of global and national dietary guidelines will likely include an increased awareness of environmental impact of dietary choices and greater attention to sociocultural factors including rapidly changing global dietary trends.

The limitation of any set of guidelines is the facility with which it can be translated into a common sense dietary pattern that is enjoyable, realistic, and sustainable. The Mediterranean diet has become known as the “diet” that is the easiest to adhere to, can be followed as mechanism for preventive medicine through nutrition, and (as is discussed in other chapters) is an effective strategy for the dietary treatment and prevention of diabetes, heart disease, obesity, various cancers, and numerous chronic inflammatory diseases. This pattern of eating is based on the traditional meals, and lifestyle, of the countries surrounding the Mediterranean. It is predominantly plant based, and consists of a daily intake of vegetables, fruits, whole grains, and healthy fats, and weekly intake of fish, eggs, poultry, and beans. It includes small portions of dairy products, and limited intake of meat. The non-dietary lifestyle factors common across these countries include daily physical activity, sharing meals with family and friends, and modest consumption of red wine (7). Similar dietary and lifestyle patterns are observed in the Blue Zones, regions of notable longevity. Regional Blue Zones diets follow the same general pattern, with geographical differences tied to the traditional local foods (8).

In clinical practice, it is important to consider personalizing dietary recommendations based on age, health status, lifestyle, ethnicity, religion, dietary preferences, and any other individual factors that can affect adherence. When appropriate, nutrigenomics or biomarkers can provide additional guidance. Implementation of individualized guidelines often benefit from collaboration with a health care provider with advanced education and training in nutrition and lifestyle medicine. Table 45.1 provides a brief list of healthful modifications to the typical American diet supported by prevailing opinion.

TABLE 45.1

Steps to Improving the Typical American Diet That Are Widely Supported in the Nutrition Community

- Reduce trans fat
- Reduce saturated fat
- Reduce sodium
- Increase fruits and vegetables
- Increase whole grains
- Reduce refined starches and simple sugars
- Replace “bad” fats with “good” fats

- Control portion size and total calories
- Increase physical activity

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Source: From Katz DL. Presentation at TIME Magazine/ABC News summit on obesity. Williamsburg, VA, June 2004.

Recommendations Supported by Confluent Evidence

Weight Control

Whereas dietary deficiencies have long been the predominant nutritional threat to health, caloric excess is now the more significant global risk (9). There are numerous reviews on the subject of diet for weight loss (see Chapter 5), which collectively lend strongest support to diets abundant in fruits, vegetables, and whole grains and relatively restricted in refined starches, added sugar, and total fat (10). Recent studies lend support to the Mediterranean dietary pattern and diets characterized by a low glycemic load (GL) (see Chapters 5–7). Strategies for the achievement of energy balance are beyond the scope of this discussion (see Chapters 5, 38, and 47), but given the increasing global significance of overweight and obesity, portion control and energy balance clearly figure among the key principles of healthful eating. The health and diversity of the gastrointestinal (GI) microbiome is also an emerging area of research interest for application to weight control (11).

Dietary Fat

There is ongoing debate regarding the relative benefits of a diet restricted in total fat as compared to a diet with liberal fat intake, and the relative balance of saturated, polyunsaturated, and monounsaturated fatty acids (see Chapters 2 and 6). A health-promoting diet may derive as little as 10% and as much as 45% of calories from fat, provided that fat is well chosen. The energy density and relatively low satiety index of fat suggest that intake toward the high end of this range may pose difficulties for those struggling with weight control (see Chapter 5).

Studies by Ornish et al. (12) provide support for the extremely low-fat diet, at least for the prevention of cardiovascular events. Another study comparing a low-fat versus high-fat diet in obese people who had reduced energy intake by 25% showed that only the low-fat diet resulted in decreased waist circumference and fat mass, increased flow-mediated dilation, and decreased leptin levels (13).

Estimates of human Paleolithic dietary intake suggest that we are adapted to a fat intake around 30% to 40% of total calories (14). This is near the typical fat intake in the United States today, well below the liberal fat intake of some Mediterranean countries, and well above the intake advocated by Ornish and others. The benefits of a Paleolithic diet may include reductions in weight and cardiovascular risk factors. As reviewed by Kuipers et al., Osterdahl et al. showed that 3 weeks of a Paleolithic-like diet resulted in significant decreases in weight, body mass index, and waist circumference.

Based on the best available estimates, roughly one third to one-half of the fat in Paleolithic diets derived from polyunsaturated fat, with an *n*-3 to *n*-6 ratio between 1:1 and 1:4. The remainder of fat intake is derived principally from monounsaturated fat (and thus the total intake is very low in saturated fat). Although definitive evidence of *n*-3 fatty acid deficiency or of the benefits of supplementation may be lacking for any single disease, the weight of evidence overwhelmingly suggests a prevailing relative deficiency in the modern Western diet. Further, there is some evidence of a benefit of supplementing *n*-3 fatty acid intake in areas ranging from triglyceride reduction to cognitive development (see Chapter 35) to the control of rheumatoid arthritis (see Chapter 20).

Unless consumption of wild fish or game is very consistent, *n*-3 fatty acid intake is sure to be lower

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than optimal, given the near-complete elimination of *n*-3 fatty acids from the flesh of farmed food animals. Nuts and seeds, particularly flaxseed, are good sources of plant-derived *n*-3 fatty acids. For example, 1 tablespoon of flaxseed oil meets the daily *n*-3 target for most adults. Of note, *n*-3 fat from plant sources is generally *α*-linolenic acid, the conversion of which to eicosapentaenoic acid and docosahexaenoic acid (see Chapter 2 and Appendix E) is variable.

Dietary Protein

Available evidence supports protein consumption in the range of 0.6 to 1 g/kg body weight in adults. Intakes up to 2 g/kg may offer some advantages to vigorously active individuals, although this is uncertain (see Chapter 32). Higher intakes appear to be ill advised (see Chapters 3, 16, and 32). High-protein diets advocated for control of insulin resistance and weight loss are not supported by evidence of long-term health benefits and, in general, should be discouraged in favor of the pattern described (see Chapters 5 and 6). While there are studies to suggest cardiometabolic benefits of shifting calories from carbohydrate to protein, those benefits are generally equivalent to a high-carbohydrate but low-GL diet (15). Protein does offer the advantage of a high satiety index (see Table 45.2), and thus a modest increase in the percentage of calories from protein may offer weight control benefits to some (see Chapter 5).

TABLE 45.2

A Comparison of the Energy Density and Satiety Indices of the Macronutrient Classes[a]

Macronutrient Class	Energy Density	Satiety Index	Comments
Fat	Highest; 9 kcal/g	Lowest	The notion seems to prevail that fat is filling, but on a calorie-for-calorie basis, it is the least satiating of the macronutrient classes.
Carbohydrate, simple[b]	4 kcal/g	Intermediate; lower than for complex carbohydrate	The satiety threshold for sugar is higher than that for other nutrients, thus making sugar an important contributor to caloric excess in most people.
Carbohydrate, complex[b]	<4 kcal/g	Intermediate; higher than for simple carbohydrate	Sources of complex carbohydrate—whole grains, fruits, and vegetables—are rich in water and fiber, both of which increase food volume and contribute to satiety yet provide no calories.
Protein	3–4 kcal/g	Highest	Protein is generally more filling, calorie-for-calorie, than other food classes, although this may not be true when compared to complex carbohydrate very high in fiber and/or water content.

[a]*The satiety index is a measure of how filling a food is, based on comparison of isoenergetic servings (see Chapter 38).*

[b]*For purposes of this chart,* simple *and* complex *carbohydrate refer to the metabolic response to foods rather than their biochemical properties. For detailed discussion of this topic, see Chapter 1.*

The evidence is clear that high intake of dietary protein is harmful in the context of impaired renal

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function. High protein intake may accelerate the age-related decline when glomerular filtration is compromised. There is some concern that high intake of protein may accelerate age-related osteopenia (see Chapter 14), but a recent study showed that diets higher in dietary dairy and protein led to favorable effects on bone biomarkers in exercising overweight women (16). If the overall dietary and lifestyle pattern are judicious, a relatively higher protein intake may be tolerated without sequelae. For example, regular, weight-bearing activity in particular attenuates the risk of osteopenia and osteoporosis. Even in studies of competitive athletes, however, there is little evidence of benefit from very high protein intake.

An important consideration in the discussion of dietary protein is the definition of the "quality" of protein sources. Prevailing definitions of protein quality consider the biochemistry and metabolism of the source food without attention to the net effects on human (and environmental) health. A modernized definition of protein quality that includes net effects on health has been proposed and, considering the public's fascination with dietary protein, is an important and timely matter that warrants serious attention (17).

Dietary Fiber

A diet consistent with consensus recommendations will result in considerably greater fiber intake than is typical in the United States (see Chapter 1 and Appendix E). Although recommendations include a fiber intake of approximately 30 g/day, the weight of evidence also supports a specific effort to increase consumption of soluble (viscous) fiber and insoluble fiber. Soluble fiber is found abundantly in vegetables, fruit, beans, seeds, and grains. Consumption of soluble fiber lowers serum lipids and reduces the postprandial rise in both glucose and insulin via changes in intestinal viscosity, nutrient absorption, passage rate, and production of fatty acids and gut hormones (18). Insoluble fiber is often described as "roughage" and does not dissolve in water and is largely indigestible in the human GI tract. It adds bulk to the stool aiding regular bowel movements and preventing constipation. Insoluble fiber can be found in leafy vegetables, whole grains, nuts, and beans (19,20).

The inclusion of fiber rich foods also has a beneficial impact on the health and diversity of the GI microbiome, likely related to their role as "prebiotics" and nutritive short-chain fatty acid metabolites including butyrate (21).

A specific recommendation to consume a variety of beans, lentils, apples, and oat-based products is supported by the available evidence. This is especially important for children as promoting the consumption of fiber-rich foods at a young age may prevent against carotid artery stiffening and related heart disease in adulthood (22).

Micronutrient Supplements

Micronutrient deficiencies persist despite the caloric abundance of the Standard American Diet. A teleological explanation is that humans may be adapted to a higher intake of micronutrients given the higher energy needs of our physically active ancestors and the calorie-dilute, nutrient-dense foods available to them (see Chapter 44).

Research has examined select micronutrients and risk of specific disease. For example, supplements of vitamin B^6 and folate reduce elevated homocysteine levels, a biomarker for cardiovascular disease risk. However, a large clinical trial did not find that supplementation translated into lower cardiovascular mortality (see Chapter 7), although a meta-analysis did suggest benefit of folate and other B vitamins in stroke prevention (23). Folate supplementation before conception and during pregnancy reduces the incidence of neural tube defects. Zinc is involved in various aspects of immune function and supplementation may enhance immunity. Chromium supplements may improve insulin metabolism. Vitamin

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D supplementation, and the combination of calcium and vitamin D (24) in supplement form, have demonstrated benefit in the prevention of osteoporosis (see Chapter 14). The role of calcium supplementation in the protection of bone is controversial, but other benefits of calcium supplementation are convincing (see Chapters 14, 28, and 34). Results from the Women's Health Initiative in 2010 suggest no benefit from calcium and vitamin D supplement on cardiovascular disease and blood pressure (25). Iron supplementation is probably not of universal benefit in the United States but is of potential importance for menstruating women with low intake of red meat.

There is insufficient evidence to support recommending a daily multivitamin for the prevention of chronic disease (26); however, there may be some evidence linking multivitamin/multimineral supplementation with improved cognition and mood (27). A recent study by Haskell et al. demonstrated that 9-week supplementation with a multivitamin in women aged 25 to 50 resulted in improved cognition and multitasking, as well as beneficial effects on mood and reduced homocysteine levels (28). Patients should be discouraged from thinking supplements are a substitute for healthy diet. The benefits of micronutrient supplementation are not nearly as well established as the benefits of a nutrient-dense dietary pattern. While specific supplementation with high doses of single nutrients lacks supporting evidence for primary prevention, it may be appropriate for more targeted disease prevention efforts. For example, a fish oil supplement as a source of *n*-3 fatty acids may be generally advisable for both adults and children who do not routinely consume fatty fish. Dosing recommendations are offered in Appendix L.

Distribution of Meals

There is as much philosophical debate as there is scientific opinion on the relative merits of small, frequent meals versus restricting caloric intake to a defined daily time window. Small, frequent meals create less insulin release compared to isocaloric, larger meals spaced further apart (29,30). Additionally, isocaloric morning versus evening feeding has been studied and been found to be metabolically comparable. Weight loss, accomplished via either pattern, was associated with lower insulin and other metabolic improvements (21). NHLBI data that showed that lower eating frequency predicts greater gains in adiposity in adolescent girls independent from other contributing risk factors such as race, physical activity, and total energy intake (31).

Other trials suggest that apparent benefits may be more related to dietary composition and quality rather than distribution (32,33); which is how most meal decisions are made. For the majority of adults who would benefit from weight loss, frequent snacking may blunt appetite and help prevent bingeing, although this, too, is controversial. As discussed in Chapter 47, the psychological benefits of frequent eating may be considerable for patients working at weight loss or weight maintenance.

Energy Restriction

Evidence that total energy restriction reduces all-cause morbidity and mortality comes primarily from animal models, but there is some human evidence. Long-term compliance with low-energy diets (i.e., calorie restriction) is difficult in all but the most highly motivated individuals; thus human studies are small. Therefore, while of theoretical interest, a recommendation to patients to restrict calories to below normal levels as a health promotion strategy may be of limited practical value. Meta-analyses of intermittent energy restriction, either fasting 2 days/week or limiting caloric intake to 8 to 10 hours/day, were as effective as continuous energy restriction in producing weight loss and positive effects on health biomarkers (34). Intermittent energy restriction may be more feasible for most individuals (35).

Interestingly, for cancer patients undergoing chemotherapy, data support short-term fasting (24–36 hours) on chemotherapy response, tolerability, and quality of life (36). Other condition-specific benefits

may become apparent as evidence accumulates.

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Recommendations for Specific Food Groups

Meat

The question of whether meat consumption has beneficial, harmful, or neutral effects on human health is the source of a volatile, contentious, and seemingly perpetual debate. The most important point to understand is that contemporary meat consumption is strikingly different from that of our Paleolithic ancestors. There were no domesticated animals, factory farms, or processed meats in the Stone Age. The flesh of grass-fed cattle may approximate the wild or ancestral animals but imperfectly. The meats we consume today are higher in calories, harmful varieties of fat, and environmental contaminants that get concentrated as they move up the food chain. In addition, Paleolithic humans likely ate their meats raw so it stands to consider that contemporary food processing (i.e., curing with nitrites) and preparation (i.e., char grilling), both of which add carcinogens, are associated with poor health outcomes (37,38). There is also an environmental impact of factory farming, consolidation of feed lots, and confined animal feeding operations, which may relate back to human health directly (e.g., contaminating field crops and groundwater) and indirectly (e.g., through contributing to climate change) (39). Considering both the health and environmental effect, it is reasonable for clinicians to suggest that factory-farmed contemporary meat consumption be limited, if not avoided entirely.

Eggs

It is important to note that when discussing the impact of dietary fat on health, one must unbundle the effects of trans fat, saturated fat, and dietary cholesterol. While eggs have received plenty of negative popular press, large meta-analyses show no negative effect on overall cardiovascular mortality, except among diabetic patients for whom an increased hazard ratio has been observed (40). Further, comparison of whole egg versus egg white versus egg substitute was equivalent in cardiovascular outcomes; however, egg substitute was slightly beneficial in terms of lipoprotein profile (40). While egg substitute or egg white may be beneficial if caloric restriction is a goal, these processed options can be relatively costly, less palatable, and missing micronutrients like choline and biotin found in egg yolk. Of course, the overall dietary pattern is most important—and the factory-farmed bacon and processed sausage that so often accompany eggs are almost certainly deleterious to health.

Dairy

There is a growing body of evidence that dairy consumption is not only health promoting but also has the capability to lower the risk of cardiovascular disease. One recent meta-analysis showed that increasing dairy consumption to the recommended amount, that is, three servings daily for people greater than 9 years of age, is associated with increased nutrient intake. Further, consuming greater than 3 servings daily leads to even better nutrient status, improved bone health, and lower risk of diabetes and hypertension (41). High intakes of milk, cheese, and yogurt do not appear to be associated with increased mortality, and substituting dairy saturated fat for meat may even lower one’s cardiovascular risk by 25% (42,43). Additional studies have evaluated the impact of dairy consumption on body weight in children, adolescents, and adults. Collectively, current evidence suggest that independent of calories, dairy consumption has minimal impact on BMI, and may be associated with lower risk of abdominal obesity (44–46).

Grains

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Over the past 20 years, grains have been brought under attack (e.g., from low-carbohydrate advocates and those concerned about gluten and lectin sensitivity). Grains are made up of three parts: the bran or hull, the germ, and the endosperm. Whole grains contain all three. Refined grains are principally endosperm, the least nutritious component. From a paleoanthropological perspective, grasses or grains are not native human foods but only entered the human diet with the advent of agriculture about 12,000 years ago, when their domestication led to increases in seed size. The question at hand is whether grains, whole or not, impact our health; and the answer is "most likely."

The National Health and Nutrition Examination Survey analyzed the impact of whole grain intake on various factors in just under 5,000 US adolescents. The study found that whole-grain intake was not associated with body mass index but was related to positive nutrient profiles (i.e., lower fasting insulin levels and higher folate levels) and chronic disease risk factors (47). Further, other studies have demonstrated variously sized reductions in risk of certain cancers, including colorectal cancer (48) and head and neck cancer (49) as well as better overall diet quality and nutrient intake associated with absolute intake of whole grains (50). The relationship between consumption of whole grains and weight is less clear as some studies have demonstrated an association with lower body weight; however, this may be confounded by increased fiber intake (50). Further exploration of carbohydrates is discussed later.

Grain consumption should be considered in the context of GL, a metric that correlates closely with the extent to which grains are refined. A low-GL diet can be achieved by minimizing total carbohydrate intake, but this approach may toss out the baby with the bathwater. High-carbohydrate foods such as most whole grains, beans, legumes, vegetables, and even fruits can contribute to a low-GL dietary pattern. Such foods also provide a diversity of micronutrients of potential importance to overall health, and cardiovascular health specifically (antioxidants flavonoids and carotenoids noteworthy among them). It is most important to limit intake of refined grains, including white breads, pasta, and flour. It is easy to identify "bad" carbohydrates but increasingly more difficult to know what constitutes a "good" carbohydrate. Eating large amounts of whole-grain carbohydrates may not be as health promoting as previously thought. It has been suggested that certain factors determine whether a carbohydrate source is health promoting: the content/ratio of dietary fiber types, glycemic index, whole-grain content, and structure. Aiming for a ratio of total carbohydrate to fiber of less than 5:1 may be helpful (51).

Current discussions of the health effects of grain consumption must consider gluten intolerance (i.e., true celiac disease and non-celiac gluten sensitivity), rising in prevalence in the United States in recent years. The reason for the increase may have to do with genetic vulnerability or hereditability of disease, as well as new-age exposures to gluten (such as genetic modifications to gluten, contamination with pesticides used on conventionally grown wheat, as well as nutrient depletion due to modern agriculture practices and food processing). Gluten itself, however, is not associated with weight gain or loss, and the health benefits of a gluten-free diet are not well supported by research (52,53). While there is a growing population of people truly intolerant or allergic to gluten who would benefit from eliminating it from their diets, the majority of the US population does not have such immune reactions. Eliminating gluten for most individuals will not improve health any more than eliminating refined carbohydrates of any source.

Sugar/Fructose

The preference for sweet has fostered the survival of not only *Homo sapiens*, but mammals in generals. Breast milk is the first exposure to "sweetened beverage" and thus sets our palates preferentially from the beginning. Human breast milk is sweet because we need a fairly concentrated dose of readily metabolizable fuel for our bodies and brains to grow. Our taste buds are geared to help us survive and

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they prefer sugar because we can safely digest it, and it supports our needs for cell growth and repair, hormone manufacture, and fight or flight from predators. Our brain connects sugar with pleasure, rightfully so because this relationship has allowed our survival and procreation.

The problem ensues when we consume sugar in excess. Our Stone Age ancestors lived in a world scarce of food—while we live in an energy-rich environment. For modern humans, sugar is addictive because the more there is (and there is a lot in our world), the more we habituate to it, and the more we desire. One of the contributors to high sugar intake is the widespread use of high-fructose corn syrup (HFCS) that can be derived inexpensively from subsidized corn. An inexpensive sugar source makes it economical for food manufacturers to add copious amounts of sugar to our diets. Qualitatively, HFCS and table sugar (sucrose) are almost identical and consist of pairings of glucose and fructose in a 1:1 ratio. The negative health effects from HFCS are due to the large quantities we consume.

Fructose is routinely demonized for its widespread use an added sweetener in many processed foods. Although clinicians should not condone eating candy and soda, it should be noted that we that fructose is also the primary sugar found in fruit. A diet can contain sugar, including fructose, and be optimal for health. A diet could be low in sugar but still be far from optimal (e.g., low in Ω-3 fat). It is the overall quality, and quantity of food consumption that is important—attacking one nutrient, such as fructose, is incorrect.

Organic Foods

Organic foods may be trendy, but questions remain about whether they are truly beneficial for health or better than their conventional counterparts. For a food to be produced “organically,” there can be no use of synthetic fertilizers, herbicides, pesticides, preventive antibiotics, irradiation, genetic modification, and a range of other agricultural and processing guidelines regulated by the US Department of Agriculture. Consumers of organic foods tend to have healthier diets and lifestyles overall, which leads to significant confounding in studies that attempt to investigate the health impact of organic food consumption. In light of the difficulties inherent in nutrition studies generally and those related to confounding variables, a comprehensive review found benefit of organic food consumption on allergic disease and obesity (54). Additionally, a French study found that organic food consumption was associated with a reduced risk of cancer; again with caveats related to confounding (55). Organic foods have moderately higher concentrations of antioxidants such as polyphenols, and lower residues of pesticide and heavy metals such as cadmium, which have independent health risks. Organic dairy products are higher in omega-3 fatty acids than conventional dairy. Perhaps most significant to human health is the association of antibiotic resistant bacteria related to the widespread use of antibiotics in the conventional (nonorganic) livestock industry.

RECOMMENDATIONS FOR DISEASE PREVENTION

Cardiovascular Disease

The American Heart Association has expressly recognized the importance of diet by calling for dietary assessment in every patient (22). Patients with established coronary artery disease are encouraged to comply with dietary recommendations offered by the American Heart Association (56,57) (see Chapter 7). The American Heart Association offers dietary recommendations that call for efforts to balance caloric intake and physical activity to achieve and maintain a healthy body weight; consume a diet rich in vegetables and fruits; choose whole-grain, high-fiber foods; consume fish, especially oily fish, at least

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twice a week; limit intake of saturated fat to less than 7% of energy, trans fat to less than 1% of energy, and cholesterol to less than 300 mg/day by choosing lean meats and vegetable alternatives, fat-free (skim) or low-fat (1% fat) dairy products; minimize intake of partially hydrogenated fats; minimize intake of beverages and foods with added sugars; choose and prepare foods with little or no salt; if consuming alcohol at all, do so in moderation; and apply these recommendations when eating out as well as when eating at home (58).

American Heart Association also offers Step 1 and the more restrictive Step 2 guidelines to reduce cardiovascular disease but those recommendations do not appear to be doing enough for the prevention of coronary events. Jenkins et al. (59) have demonstrated that restrictive diets can improve lipids as effectively as statin drugs, but sustained adherence to such a diet is challenging in the general population.

Dietary patterns that are well-supported to reduce cardiovascular disease and mortality include both the extremely fat-restricted diet (Ornish program) (12) and the relatively higher-fat Mediterranean dietary pattern (60).

McMillan-Price et al. (15) conducted a trial highlighting the importance of specific food choices as opposed to just macronutrient distribution in the mitigation of cardiovascular risk. For example, GL (see Chapter 6) has been shown in numerous trials to have potentially important implications for insulin metabolism, weight management, and cardiac risk. The percentage of subjects achieving an at least 5% weight reduction was significantly greater on the low-GL diets (irrespective of whether they were high carbohydrate or high protein) than on their higher-GL counterparts. Similarly, body fat loss was enhanced, at least among women, by the low-GL diets. Whereas low-density lipoprotein cholesterol decreased significantly with the high-carbohydrate, low-GL diet, it actually increased on the high-protein, low-GL diet likely due to high animal protein intake. Importantly, a recent meta-analysis concluded high GL and index are associated with increased risk of cardiovascular disease, especially for women (61). By demonstrating that a high-carbohydrate, low-GL diet may offer particular cardiac benefit, the McMillan-Price et al. study points toward a diet in which choice within macronutrient categories is given at least as much consideration as choice among those categories. Cardiac health at the population level will likely be well served when dietary guidance is consistently cast in terms of healthful, wholesome foods rather than competition among the three macronutrient classes from which a diet is composed.

In light of currently available evidence, patients at high risk for or with known coronary artery disease should be encouraged to adopt a basic dietary pattern matching that advocated for general health promotion. Restriction of dietary cholesterol is of lesser importance and may not confer benefit (see Chapter 7). Frequent fish consumption, inclusion of flaxseed in baked goods, and use of flaxseed oil on salad should be encouraged.

Moderate alcohol consumption is widely believed to confer cardiovascular benefits, and prevailing evidence supports this recommendation. Consumption of one alcoholic beverage per day is acceptable for women; men may benefit from up to two drinks; however, the beneficial health effects observed with alcohol consumption may also be related to other compounds in the beverages as well as effects on eating behavior (62,63). Although the benefits of alcohol may pertain to all ethanol, polyphenols in the skins of grapes have antioxidant properties; therefore, red wine may offer additional benefits.

Patients with hyperlipidemia should make a particular effort to increase intake of soluble fiber. They may do so by eating oatmeal, and particularly oat bran, consistently with breakfast; by eating oat-based breads and baked goods; and by eating beans, lentils, and apples. The use of spreads containing plant stanols and/or sterols at a dose of approximately 2 g/day may be advisable for such patients as well.

Cerebrovascular Disease

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Cardiovascular disease and cerebrovascular disease share risk factors. Despite one study suggesting that high fat intake may reduce the risk of stroke (64), the weight of evidence favors comparable recommendations for the prevention of all sequelae of atherosclerotic disease (see Chapters 7, 10, and 20). A recent study found that greater adherence to the Mediterranean diet in older community-dwelling individuals is associated with reduced risk of stroke, or infarct, on magnetic resonance imaging (61). There has been historic concern that patients with a history of intracranial bleeding should avoid fish oil (and possibly vitamin E) to avoid platelet inhibition, although a recent meta-analysis found no increased risk of bleeding (65).[1]

It is worth noting that best-established means of preventing first or recurrent stroke is blood pressure control. The dietary recommendations for the control of blood pressure are provided in Chapter 8. In general, generous intake of calcium-, magnesium-, and potassium-rich foods and restricted intake of sodium are recommended. A diet adhering to the pattern described for health promotion will offer these characteristics and facilitate control of blood pressure (66).

Diabetes Mellitus

The Diabetes Prevention Program (67) provides convincing evidence that a diet conforming to basic guidance for overall health promotion, in combination with moderate physical activity, is an effective intervention for the prevention and control of type 2 diabetes. Specific benefits may be derived from a generous intake of soluble fiber from oats, beans, lentils, apples, and berries. A dietary pattern characterized by a low GL is beneficial as well, and can be readily achieved by adopting a healthful and substantially plant-based diet, with a relatively low intake of processed foods and refined grains. Additional details are addressed in Chapter 6. The American Diabetes Association (ADA) recommends a generous intake of fruits and vegetables, beans, fish, whole grains, and nonfat dairy, along with judicious portion control and restriction of snack foods, sugar, and sweet consumption (68). The dietary pattern recommended by the ADA is congruent with the US Department of Agriculture dietary guidelines differing only in minor details (69).

Cancer

The National Cancer Institute and the Centers for Disease Control and Prevention developed the widely known “5-a-day” program, encouraging fruit and vegetable intake and endorsing dietary guidelines that include 20 to 35 g of fiber per day, with less than 30% of calories from fat (11). The maintenance of ideal body weight, low total energy consumption, and intake of a variety of fruits and vegetables appears to offer protection against many cancers, including but not limited to colorectal cancer, in which case a low-fiber diet is a known risk factor. Vitamins and minerals may also play a role, one such example being the association of high folate intake in postmenopausal women with a reduced incidence of breast cancer. These recommendations are consistent with those for health promotion and the prevention of other leading diseases. One departure is alcohol, which may reduce the risk of cardiovascular disease but appears to promote cancers of the breast, head, neck, pancreas, and other sites. Women at high risk of breast cancer, or individuals with a cancer history, are advised to abstain from alcohol. In such individuals also at risk for or suffering from heart disease, alternatives to alcohol should be sought to provide the additional risk reduction. The antioxidants concentrated in red wine are readily obtained from fruits and vegetables, fruit juices (notably purple grape juice), green tea, and dark chocolate.

The benefits of energy restriction appear to pertain particularly to cancer prevention. Patients at high risk for or with a history of cancer should be encouraged to restrict calories to bring weight down to near

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ideal. In such situations, the use of micronutrient supplements is particularly important. In advanced cancer, nutritional goals should be shifted to weight maintenance, and energy restriction should be abandoned. See Chapter 12 for additional discussion.

Inflammatory Diseases

Chronic inflammation is associated with heart disease, diabetes, obesity, autoimmune disease, neurodegenerative disease, and numerous other chronic illnesses. Although food intolerance may play a role for some individuals in the etiology of chronic inflammatory and autoimmune diseases, there is limited evidence of such an association at the population level. The most promising nutritional approach to the management of chronic inflammation is improving the distribution of fats in the diet by reducing intake of saturated fat, trans fat, and Ω-6 polyunsaturated fatty acids (PUFAs) and increasing consumption of Ω-3 PUFAs (see Chapter 20). Fish containing a high concentration of *n*-3 fatty acids may lower C-reactive protein (CRP) and homocysteine levels, and these effects have been found to be clinically beneficial in patients with ulcerative colitis (70). A generous intake of fruits, vegetables, herbs, and spices is also of likely benefit. As such, dietary recommendations for patients with or at risk for chronic inflammatory conditions are consistent with general dietary recommendations for health promotion.

Infectious Disease

The principal effect of nutrition on the course of infectious disease is mediated through effects on immune system function. A notable exception is in chronic infectious disease, such as HIV and AIDS, where cachexia may become an independent threat to health. A variety of micronutrients serve as cofactors and are essential for immunocompetence, including vitamins A, C, D, E, B^2, B^6, and B^{12}, folic acid, iron, selenium, and zinc (71) Unfortunately, many of these nutrients and the foods that contain them are consumed in suboptimal levels in the typical American diet. Although there is some evidence that supplementation with select nutrients including Vitamins C and D (72), there is no compelling evidence to suggest that the overall dietary pattern recommended for health promotion should be altered for purposes of preventing or managing infectious disease (see Chapter 11).

Renal Insufficiency

The most widely supported dietary manipulation for the management of renal insufficiency is restriction of protein to 0.6 g/kg (see Chapter 16). This intake level falls within the range recommended for health promotion and, therefore, may be advocated without concern of ill effects. The leading causes of renal failure in the United States are diabetes mellitus and hypertension, both of which are amenable to dietary management as described earlier and elsewhere (see Chapters 6 and 8). Notably, once a patient with chronic kidney disease begins dialysis, they must actually increase their protein intake to prevent muscle wasting. According to the National Kidney Foundation Dietary Guidelines for Adults Starting on Hemodialysis, these individuals should eat 8 to 10 oz (or 1.2 g of protein per kg of body weight) of high-protein rich foods, such as poultry, fish, or eggs, each day (73).

Liver Disease

The principal dietary manipulations in patients with chronic liver disease are protein restriction and avoidance of alcohol. Moderate protein restriction relative to levels that prevail in the United States may be advisable for health promotion, whereas the optimal dose of dietary ethanol varies with individual circumstances. Thus, patients with liver disease should, for the most part, adhere to a diet consistent with

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recommendations for health promotion, while abstaining from alcohol. Supplementation with B vitamins generally is indicated and is provided if a multivitamin is taken daily. Nutriceuticals such as silymarin and N-acetylcysteine may play a role, and are discussed elsewhere (see Chapter 17).

Protein restriction is most important in the setting of overt hepatic encephalopathy; however though widely practiced, there is no existing evidence to support its implementation. In a recent review, Kachaamy and Bajaj (74) ascertained that supplementation with branched-chain amino acids may be helpful for patients suffering from encephalopathy despite the usual pharmacologic treatments. They also stressed the importance of preventing starvation in cirrhotic liver disease, which can occur within hours of caloric deprivation versus days in healthy people. Patients with cirrhosis should always eat breakfast and have snacks, and may benefit from probiotic supplementation.

Nutrigenomics

The relatively new field of "nutrigenetics" examines the effects of genetic variation on nutrient–gene interactions, and "nutrigenomics" refers to the impact of nutritional choices on health at the level of gene transcription and metabolism. The potential for nutrigenomics lies in the ability to link personalized dietary guidance to individual vulnerabilities through genetic testing and the identification of specific polymorphisms (75,76). Genetic polymorphisms may account for variable susceptibility to adverse effects of dietary sodium or cholesterol, for example; for variable susceptibility to insulin resistance; and for variable micronutrient requirements. In other words, genetic polymorphisms explain why if two people who follow the exact same diet and exercise regimen may experience very different outcomes.

Nutrient–gene interactions have been studied in patients with inflammatory bowel disease (77), as well as in breast and colon cancer prevention (78).

The particular value of nutrigenomics may reside more in the motivational power of individualized health messaging (see Chapter 47) than in characterizing the dietary pattern conducive to health. While the relative importance of various aspects of diet may vary with alleles, in general, the fundamentals of nutrition that support health at the population level are apt to do so at the individual level as well. The field of nutrigenomics will also likely lead to the development of pharmaceuticals and nutriceuticals, with increasingly specific targets for individual people. When available, accessible, and appropriate, the promise of nutrigenomics should be fully exploited. Genomics may eventually allow for more perfect, individualized dietary guidance, but the anticipation of those advances need not interfere with the delivery of sensible dietary guidance that can be offered based on current evidence.

Evolutionary Biology

There is no denying that the evidence base for dietary recommendations for human health promotion is incomplete. There is, of course, substantially less scientific evidence to guide the development of dietary patterns for species other than our own, yet paradoxically, we seem to be far more confident when doing so. There is little controversy regarding the suitable diets for a wide range of domestic animals or, for that matter, wild animals held in zoos. The guiding principle on which that confidence is based is the "native" diet of each species. Lions in a zoo are not subjected to clinical trials to determine what they should be fed; they are fed something that approximates their diet in the wild. This approach, deemed reasonable and robust for diverse species, deserves application to humans as well. Consideration of our native diet is a useful construct for filling gaps in the science of human nutrition until or unless research advances fill those gaps.

Eaton (79) has made this very suggestion quite persuasively. The approach garners support from the fundamental confluence between dietary recommendations based on modern trials and epidemiological

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evidence and those based on methods of paleoanthropology to estimate our ancestral dietary pattern, which was rich in fruits and vegetables, high in fiber and micronutrients, low in salt and sugar, essentially free of trans fats, and low in saturated fat. The value of considering the dietary pattern to which our species is adapted in confronting the challenges of nutritional health today is addressed more fully in Chapter 44.

Diet and Environment

Although this chapter is primarily concerned with dietary guidelines for human health, it should be noted that human health cannot exist on a ruined planet. As such, the preservation of the health of the planet must be a part of the mission to promote human health. An understanding of the overlap between diets that benefit human and planetary health is therefore in the purview of every health professional.

Current global agriculture and dietary practices are a major driver of climate change, water pollution, deforestation, decreasing biodiversity, antibiotic resistance, and zoonotic diseases. A comprehensive analysis of the global farming system concluded that a large-scale shift toward plant-based diets would have a larger impact on planetary health than any other driver of climate change. With future generations in mind, clinicians should encourage patients to consider their diets as a matter of both personal and planetary health. A global shift toward plant-predominant dietary patterns and sustainable agricultural practices has become an imperative for the health of humans and the planet upon which we live.

SUMMARY

The myriad effects of nutrition on health outcomes are documented in a vast literature of widely divergent quality. In certain vital areas, consensus has yet to develop. Sufficient evidence has been gathered, however, to permit the generation of dietary recommendations for health promotion and disease prevention with considerable confidence. There is overwhelming consensus in support of a diet characterized by a generous intake of vegetables and fruits, if choosing to eat grains, consuming the majority of them in the whole unprocessed form, beans, lentils, nuts, and seeds; an emphasis on fish and poultry or plant foods as protein sources; restriction of trans fat, saturated fat, refined starch, added sugar, and salt; a shift from animal and other saturated fats to unsaturated plant oils; and portion control conducive to energy balance and the maintenance of a healthy weight. Recommendations to include nonfat dairy in the diet are less universal but nonetheless predominant.

The same dietary pattern is appropriate for the prevention of most diseases. This has not always been evident and is worthy of note. Patients with cardiovascular disease often have diabetes, cerebrovascular disease, hypertension, or renal insufficiency, may have had or have cancer, and are constantly vulnerable to infectious disease. If each disease required a different diet, consistent recommendations could not be made to an individual, let alone to a population. The emergence of a “one diet” approach to nutritional health is a logical outgrowth of confluent lines of evidence and the clinical imperative for consistent and practicable advice. The benefits of a health-promoting diet should be combined with regular physical activity for maximal benefit; a sedentary lifestyle may undermine many of the potential health benefits of an otherwise salutary dietary pattern.

All patients, with or without chronic disease or risk factors, should be encouraged to comply with a health-promoting dietary pattern. For many, the Mediterranean diet, and the geographical variants described in the Blue Zones research are the most accessible way to translate the consensus of international health organizations into practical dietary recommendations. Patients with specific risk factors or diseases may benefit from disease-specific dietary adjustments as have been discussed

throughout this book. Although general dietary guidance advice may not significantly change with the development of disease, the conviction and frequency with which counseling, encouragement, and resources are provided should increase.

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An overview of dietary and related lifestyle recommendations for health promotion is provided in Tables 45.3 to 45.6.

TABLE 45.3

Recommended Dietary Pattern for Optimal Health and Weight Control

Nutrient Class/Nutrient		Recommended Intake
Carbohydrate, predominately complex		Approximately 45%–60% of total calories
Fiber, both soluble and insoluble		At least 25 g/day, with additional potential benefit from up to 50 g/day
Protein, predominantly plant-based sources		Up to 25% of total calories
Total fat		Up to 30%, and preferably approximately 25% of total calories
Types of fat	Monounsaturated fat	10%–15% of total calories
	Polyunsaturated fat	Approximately 10% of total calories
	Ω-3 and Ω-6 fat	1:1 to 1:4 ratio
	Saturated fat and trans fat (partially hydrogenated fat)	Ideally, less than 5% of total calories; trans fat intake should be negligible
Sugar		Less than 10% of total calories
Sodium		Less than 2,300 mg/day
Water		8 glasses a day/64 oz/2 L, to vary with activity level, environmental conditions, and the fluid content of foods (e.g., fruits)
Alcohol, moderate intake if desired		Up to one drink per day for women, up to two drinks per day for men
Calorie level		Adequate to achieve and maintain a healthy weight
Physical activity/exercise		Daily moderate activity for 30 minutes or more strength training twice weekly

Note: When absolute amounts are provided, they are referable to a prototypical 2,000 kcal/day diet.

Adapted from Katz DL, Gonzalez MH. The way to eat. Naperville, IL: Sourcebooks, Inc., 2002:213..

TABLE 45.4

Recommended Foods and Overall Dietary Pattern to Meet Nutritional Objectives for

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Food Group	Foods to Choose
Whole grains	At least seven to eight servings per day of whole-grain breads, cereals, and grains with 2 g or more fiber per serving. Include oatmeal, oat bran, brown and wild rice varieties, semolina and whole-wheat pasta, couscous, barley, and bulgur wheat.
Fruits	Four to five servings per day from a rainbow of colors, especially deep yellow, orange, and red: berries, apples, oranges, apricots, melons, mangos, and so on. Select from fresh, frozen, canned packed in juice, and dried varieties. Buy locally grown in season whenever possible.
Vegetables	Four to five servings per day from a rainbow of colors, especially deep yellow, orange, red, and leafy green: yellow, red, and green bell peppers; squash, carrots, tomatoes, spinach, sweet potatoes, broccoli, kale, Swiss chard, Brussels sprouts, eggplant, and so on. Select from fresh, frozen, and canned varieties but be mindful of the higher sodium content of canned. Buy locally grown in season whenever possible.
Beans and legumes	Include three to four times per week. Beans and legumes make a good alternative to meat. Include a variety of beans and legumes in your diet: black, red, kidney, white, cannelloni, garbanzo (chick pea), navy, pinto, lentils, split peas, black-eyed peas, and soy.
Fish[a] (and other seafood)	Include as often as three to four times per week. Fish is generally an excellent, lean source of high-quality protein, and several varieties (e.g., tuna, salmon, mackerel, halibut, and cod) are excellent sources of Ω-3 fatty acids. Seafood, such as shrimp and scallops, tends to be relatively high in cholesterol but is low in fat and also a good source of Ω-3 fatty acids.
Chicken and turkey[a]	Include up to one to two times per week. Skinless breast meat is preferred.
Lean beef, pork, lamb[a]	Moderate intake of meat, working toward a goal of roughly one to two meat-based meals per week, or four to eight per month, if desired. Select lean meats preferentially; the loin and round cuts are the leanest.
Milk and cheese[a]	Choose at least two servings per day from fat-free, skim, or low-fat versions.
Vegetable oils and other added fats	Choose monounsaturated and polyunsaturated sources daily, used in small amounts to avoid excess of calories: olive oil, canola oil, olives, avocados, almond butter, and peanut butter.
Nuts and seeds	Include four to five times per week in small amounts of unsalted raw or dry roasted types: almonds, walnuts, pistachios, peanuts, pecans, cashews, soy nuts, sunflower seeds, pumpkin seeds, and sesame seeds. Mix 1 tablespoon of ground flaxseed daily into other cooked foods.
Eggs[a]	Up to one egg per day on average (more egg white is fine). Preferably, choose an Ω-3 fatty acid-enriched brand.
Sweets	In moderation. Choose low-fat or nonfat varieties whenever reasonable. Dark chocolate (see Chapter 39) offers nutritional benefits.

[a]Optional items. Well-balanced vegetarian and vegan diets would omit these items. Note that fish is recommended for particular health benefits; flaxseed and/or an Ω-3 fatty acid

supplement is especially recommended to those who do not eat fish.

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Source: Adapted from Katz DL, Gonzalez MH. The way to eat. Naperville, IL: Sourcebooks, Inc., 2002..

TABLE 45.5

Portion Size Guide

Food Group	Standard Serving Size
Whole grains	• 1 slice bread • 3/4–1 cup breakfast cereal • 1/2 cup cooked cereal, grains, or pasta
Fruits	• 1 medium piece of fresh fruit • 4 oz 100% fruit juice • 1/2 cup canned, cooked, or chopped fruit • 1/4 cup dried fruit; about one small handful
Vegetables	• 1/2 cup cooked vegetables (about the size of a tennis ball) • 1 cup raw vegetable or salad (about the size of your fist) • 6 oz vegetable juice
Vegetable oils and added fats	• 1 teaspoon oil • 1/8 avocado • 1 tablespoon salad dressing • 1 teaspoon soft margarine
Nuts and seeds	• 1 oz or 1/4 cup • 1 tablespoon peanut or almond butter (about the size of the tip of your thumb)
Beans and legumes	• 1/2 cup cooked beans, lentils, or peas • 1/2 cup tofu • 1 cup soymilk
Fish, chicken, turkey, beef, pork, lamb	• 3 oz cooked (about the size of a deck of cards)
Dairy	• 1 cup milk or yogurt • 11/2 oz low-fat cheese (about the size of four stacked dice) • 1/2 cup ricotta cheese

TABLE 45.6

The theme of optimal eating

	Low-carbohydrate	Low-fat/vegetarian/vegan	Low-glycemic	Mediterranean	Mixed/balanced	Pa
Health	Emphasis on	Emphasis on plant	Restriction	Foods direct from	Minimization of	Mi

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benefits relate to:	restriction of refined starches and added sugars in particular.	foods direct from nature; avoidance of harmful fats.	of starches, added sugars; high fiber intake.	nature; mostly plants; emphasis on healthful oils, notably monounsaturates.	highly processed, energy-dense foods; emphasis on wholesome foods in moderate quantities.	of pro foo Em on pla an me

Compatible elements:	Limited refined starches, added sugars, processed foods; limited intake of certain f emphasis on whole-plant foods, with or without lean meats, fish, poultry, seafood.
And all potentially Consistent with:	**Food, not too much, mostly plants**[a,b,c].

[a]*From Pollan M. In Defense of Food: An Eater's Manifesto. New York: Penguin Press, 2008*.

[b]*Portion control may be facilitated by choosing better-quality foods which have the tendency to promote satiety with fewer calories*.

[c]*While neither the low-carbohydrate nor Paleolithic diet need be "mostly plants," both can be*.

Diverse diets making competing claims actually emphasize key elements that are generally compatible, complementary, or even duplicative. Competition for public attention and a share of weight-loss/health-promotion markets results in exaggerated claims and an emphasis on mutually exclusive rather than shared elements.

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Principles of Effective Dietary Counseling

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Chapter 46

Models of Behavior Modification for Diet and Activity Patterns and Weight Management

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INTRODUCTION

The healthcare setting represents one of the best opportunities for providing nutrition and weight-loss counseling to the majority of people. Approximately 36 million Americans are hospitalized at least once each year (1,2). More than 80% of the US population visits a healthcare provider in any given year for a checkup (3). The utilization of hospital and physician services for diet- and weight-related conditions increased substantially from 1997 to 2015. Shifts in office-based physician visits have reflected the increased need for management of chronic diseases. The total number of individuals with four or more chronic conditions increased steadily from 3.6% in 2002 to 4.5% in 2015. Furthermore, between 1988–1994 and 2011–2014, the overall prevalence of diabetes in the United States increased from 8.8% to 11.9%, with higher physician-diagnosed diabetes (4). When visits for all reasons are considered, the healthcare setting provides annual access to nearly the entire population. This access alone constitutes an important reason why dietary and weight control counseling in the context of routine clinical care should be a priority.

BARRIERS TO COUNSELING BY PHYSICIANS

The potential contributions healthcare providers might make to improving diet and weight control efforts have historically been limited by an array of well-characterized barriers. These include lack of confidence in behavior change counseling due to insufficient provider training, insufficient counseling tools and protocols, lack of time, lack of reimbursement, patient noncompliance, and obesity bias (5–9). Despite an increased awareness for the necessity of nutrition counseling by primary care physicians, the number of office visits that include dietary counseling for patients with cardiovascular disease (CVD), diabetes, or hypertension has actually decreased in recent years (10).

Lack of confidence and insufficient provider training may explain the reluctance of primary care physicians to incorporate behavioral counseling into their practice. A survey of 2,316 students at 16 US medical schools found that only 19% of students believed they had received extensive training in nutrition counseling. Overall, students reported infrequent counseling of patients about nutrition (10). A national survey found that only 53% of physicians felt prepared to counsel patients on diet and exercise (11). Among internal medicine interns surveyed, only 14% felt adequately trained to provide nutrition counseling and a quiz of their nutrition awareness showed notable deficits in their knowledge of nutrition assessment and obesity (12). Physicians who counsel patients with CVD reported that CVD risk factor counseling rates were lowest for behavioral factors such as diet and physical activity, with few physicians reporting feeling confident in their counseling skills (13). Results of a survey of 509 physicians showed that 36% felt knowledgeable about weight management techniques but only 3% were

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confident that they could succeed in counseling effectively in their practice. Similar discrepancies in physician knowledge versus confidence were found for physical activity (53% vs 10%), and nutrition counseling (36% vs 8%), as well as tobacco cessation (62% vs 14%), alcohol reduction (46% vs 7%), and stress management (35% vs 5%). Although physicians realized the importance of healthy lifestyle practices in patient care, they felt that they lacked the training and counseling skills to advise patients about lifestyle behaviors and did not know how to implement these concepts in practice (14).

In another survey of 251 resident physicians, only 15.5% reported counseling more than 80% of their clinic patients about physical activity. While over 93% understood the benefits of physical activity and almost all (96%) felt that it was a physician's responsibility to counsel patients about physical activity, only 29% felt successful at getting their patients to start exercising and only 28% felt confident in their skills to prescribe physical activity for patients. Medical schools and postgraduate programs have only recently started emphasizing communication and counseling skills; however, physicians still do not receive enough training in the essentials of counseling techniques (15,16).

In general, providers who feel more confident in counseling are significantly more likely to provide counseling than those who feel less confident (17). A study of 40 primary care physicians found the majority of physicians felt that both diet (73%) and weight (53%) counseling required too much time. Moreover, 53% of physicians felt "very comfortable" counseling patients on weight, 60% felt "very comfortable" counseling patients on physical activity, and only 43% of physicians felt "very comfortable" counseling patients on diet. Less than half of physicians felt "extremely confident" discussing diet, while over half of physicians felt "extremely confident" discussing weight (70%) and physical activity (63%). However, only a small minority believed their patients would follow their advice on these topics (8%) (18).

Physicians' confidence in lifestyle counseling is influenced both by the degree of counseling training they have received and by the physician's weight status and physical activity habits. A survey of 183 trainees and attending physicians found that physician confidence in counseling for physical activity was greater for those who were habitually active and who reported receiving adequate training in counseling. Interestingly, providers who reported being overweight themselves were more likely to counsel patients regarding physical activity. Overall, up to 83% of the physicians felt limited by their lack of preventive care training (19). Counseling for diabetic patients may be particularly challenging for practitioners who feel inadequately prepared or trained. Internal medicine residents were more likely to provide diabetes patients with counseling on symptoms or medication adherence than dietary counseling. Residents with prior education in chronic disease counseling reported higher comfort with conducting diabetic dietary counseling with their patients (20).

This lack of confidence in counseling skills does not appear limited to American-trained physicians. Among physicians and nurses surveyed in Finland, only slightly more than half reported having sufficient skills in lifestyle counseling (21). General practitioners and nurses in Great Britain reported similar reluctance in addressing weight management when treating children with obesity (22). A survey of family physicians in British Columbia, Canada, found that 82.3% of respondents felt their medical school training in nutrition was inadequate and only 30% reported using nutrition-related services despite recognizing a need in more than 60% of their patients (6).

Insufficient counseling tools and protocols also contribute to physician reluctance. Currently, there are few well-delineated counseling protocols or standardized office instruments designed to address lifestyle behaviors, and often physicians lack awareness of or access to these materials. Physicians do not have clear guidance on which behaviors to target, which counseling techniques to employ, or how to use their counseling time effectively (23). The results are often inappropriate assessment of the individual patient,

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long counseling sessions that conflict with provider time limitations, discussion of a large number of risk behaviors, lack of use of a behavioral change model approach, inappropriate method of advice delivery, poor follow-up, generic advice (as opposed to being tailored to the patient's gender, socioeconomic status, level of education, ethnicity, and readiness for change), and lack of specific recommendations for frequency, duration, and intensity of physical activity.

A review of studies relating to primary care physicians' knowledge, attitudes, beliefs, and practices regarding childhood obesity revealed a large heterogeneity in obesity assessment techniques, despite a promising increase in the use of body mass index (BMI) as an evaluation tool. The authors called for increased uniformity in assessment techniques in order to improve care and physicians' self-efficacy (24). A survey of pediatricians found that 96% chose better counseling tools as the most helpful clinical resource for treating children with obesity, suggesting that practice-based tool kits might improve pediatrician self-efficacy (25). Another systematic review found that physicians who perceived that their patients' health conditions (e.g., obesity) would benefit from lifestyle modification were more likely to provide pertinent counseling (26). This review additionally found that clinicians who were not certain about the effectiveness of physical activity counseling were less likely to provide comprehensive counseling to their patients.

Lack of time is another major barrier in the primary care setting (26). The constraints and realities of a busy primary care practice make it difficult for healthcare providers to devote enough time and resources to counseling, with providers reported feeling there was not enough time to discuss weight management during primary care appointments. Competing priorities in a limited office visit often preclude addressing non-acute conditions, leading to sporadic and unstructured lifestyle counseling (27). One study of physicians' attitudes toward counseling found that a majority of physicians believe that diet and weight-loss counseling require too much time (75%). The study found that 57.7% of physicians spent 3 minutes or less discussing diet and lifestyle with patients (5). The increasing number of services already recommended for preventive care place an unrealistic burden on physician time, as much as 7.4 hours per day. This competition for a physician's time is only expected to grow as we add genetic and other preventive screening tests to our medical arsenal. Already preventive visits are of longer duration than chronic care visits, and physicians need to prioritize which preventive counseling services to provide. Studies have shown that physicians allot insufficient time to nutrition and physical activity counseling, due to the competing need for cancer, cholesterol, and blood pressure screenings (5,28).

Lack of adequate reimbursement has also been a major barrier to physician counseling in the past (26). Doctors have not always been reimbursed for their time spent counseling patients, and they have been reluctant to refer patients to other health professionals such as a dietician whose services would not be covered by insurance. Given that physicians were unlikely to be paid their anticipated hourly rate for counseling, preventive practices recommended by experts have been difficult to integrate into routine clinical practice (29).

In 2010, the Patient Protection and Affordable Care Act mandated that medical insurers must cover preventive care for beneficiaries. Under Title IV of the Affordable Care Act, private insurers are required to compensate physicians for providing weight-loss and nutrition counseling, obesity screening, and counseling to promote sustained weight loss. Cost-sharing for these services is eliminated under this new law, meaning that insurers cannot charge a copay, coinsurance, or deductible to those who enrolled in a new insurance plan on or after September 23, 2010 (29). As of November 29, 2011, Medicare beneficiaries who qualify as having obesity (BMI $\geq$ 30 kg/m^2) are entitled to intensive behavioral therapy (IBT) for obesity in a primary care setting (30). A maximum of 22 IBT for obesity sessions are allowed in a 12-month period. Stipulations are outlined for weekly and monthly visits with a primary care physician,

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which the beneficiary is entitled to only if he or she meets the criteria of losing 3 kg (6.6 lbs) during the first 6 months. Those who fail to meet the weight-loss benchmark must wait 6 months to qualify for another round of counseling.

A key drawback to the regulations in the Affordable Care Act is the stipulation that the weight-loss counseling must be provided by a primary care doctor, nurse practitioner, clinical nurse specialist, or physician assistant. Given that doctors typically receive very little training in lifestyle behavioral changes and medical exams are often limited to brief encounters, patients might receive better results if referred to a registered dietician (RD) or a proven weight management program (31,32). Medicare will only reimburse obesity counseling that is provided by an MD and which takes place in a primary care setting; an RD is reimbursable only if an MD cosigns or if the counseling is specifically related to diabetes or renal disease.

Although the Affordable Care Act is a federal law, each state and each private insurer within each state have different rules regarding what treatment is reimbursable, whether a referral is needed, how many visits are allowed, and the time frame allotted for treatment. The Healthcare Common Procedure Coding System (HCPCS) indicates that Code G0447 is used for billing "Face-to-face behavioral counseling for obesity, 15 minutes." According to the 2020 National Physician Fee Schedule Relative Value File, Code G0447 has a Work Relative Value Unit (RVU) of 0.45. The physician work RVU indicates the relative level of time, skill, training, and intensity to provide a given service; therefore, the RVU codes can be compared for different physician services. For example, the RVU for over 10 minutes of tobacco counseling is 0.50 (Code 99407). This indicates that physicians will be reimbursed slightly less for 15 minutes of obesity counseling than for over 10 minutes of tobacco-cessation counseling. However, the RVU codes are subject to review and revision every 5 years, so it is probable that physician compensation rates will be adjusted as the medical community's perception of obesity counseling changes (31,32).

Patient noncompliance is another barrier to lifestyle counseling. Provider perception that patients will not follow advice or are unable to change habits deters many clinicians from delivering counseling messages (21). Family practitioners reported facing multiple challenges in discussing weight loss with patients with obesity, with a high percentage reporting that patients lack discipline or want an easy solution to weight loss. Despite their reported frustration with treating patients with obesity, practitioners gave high ratings to several strategies for improving care, including having nutrition and exercise therapists as well as community resources readily available (33). A survey conducted at the Children's Hospital of Philadelphia similarly found that over 90% of practitioners cited barriers for pediatric obesity prevention, including lack of parent and child motivation, overweight parents, and the prevalence of both fast food and a lack of physical activity (34). Strategies required to remediate poor compliance (patient education, contracts, self-monitoring, social support, telephone follow-up, and tailoring of counseling messages) require extensive restructuring of primary care procedures and are often too resource intensive.

Finally, obesity bias by physicians, and indeed society at large, may interfere with lifestyle counseling attitudes. Doctors have been shown to display less rapport with patients with overweight and obesity than with normal-weight patients (35), which may be due in part to physicians' feelings of frustrated intolerance in dealing with a problem they perceive as unfixable (36). In fact, a review of the literature found that healthcare providers hold negative stereotypes toward patients who have obesity (37). The result may be a weakening of the patient–physician relationship, diminished patient adherence or avoidance all together, and decreased effectiveness of lifestyle counseling leading to lower quality of care (35,37).

OVERCOMING BARRIERS TO IMPROVE PHYSICIAN EFFECTIVENESS

There is hope, however, that these barriers can be overcome, through improved physician training and time management strategies. A study assessing the effectiveness of an obesity counseling curriculum for residents concluded that residents in the curriculum group provided higher quality of counseling (38). Among family practitioners in New Jersey, those with higher self-reported knowledge of weight-loss diets reported less dislike in discussing weight loss and were less likely to believe treatment is ineffective (33). Brief interventions to change diet and activity patterns in primary care settings have demonstrated some success (39–42). There is evidence that medical student training in nutrition enhances confidence to integrate nutrition counseling into patient care (15). A study of 21 suburban physicians in the Midwestern United States found that when physicians were provided with educational outreach ("academic detailing"), their discomfort with obesity counseling dropped to zero and their patients' clinical outcomes related to weight loss improved (43).

Time constraints can be addressed with both adjustment of the medical system that unburdens the physician and counseling methods tailored to the primary care setting (see Chapter 47) (44). Limited, but nonetheless valuable, dietary (and physical activity) guidance can be offered in as little as 1.5 minutes. When more extensive counseling is required, the time commitment can be spread over a number of office visits, and much of the work can be delegated to a dietary consultant. Welty et al. demonstrated that onsite dietician counseling, concurrent with the physician visit, can help achieve sustained weight loss in patients with obesity (45).

A prominent strategy for improving physician effectiveness in lifestyle counseling is to train physicians in the five As—Ask, Advise, Assess, Assist, and Arrange—as an organizational construct for clinical counseling (46,47). This strategy, promoted by the US Public Health Service and the US Preventive Services Task Force (USPSTF) helps physicians in organizing their approach to behavioral counseling and is suitable for brief, primary care interventions (48,49). The five As approach to counseling has taken on greater importance recently, as the Centers for Medicare and Medicaid Services (CMS) has stipulated that intensive behavioral intervention for obesity counseling of Medicare patients should follow the USPSTF's five As framework (50). Each of the five techniques includes counseling practices aimed at helping patients meet goals such as tobacco cessation, weight loss, and health-promoting physical activity. Physicians are trained in how to assess a patient's current behaviors, risks, and readiness to change, advise on a change of specific behaviors, agree on a collaborative effort to set goals, assist in addressing barriers and securing support for the patient, and lastly, arrange for follow-up treatment or evaluation (38). However, several studies have shown that physicians are often not utilizing the five As adequately (51). In a pilot study in which physicians were trained in the five As, the training intervention slightly improved the quality but not the quantity of the counseling. In addition, 72% of physicians counseled their patients with obesity, regardless of whether they received the training. Physicians who received the training failed to address most of the five As when meeting with their patients (38,52). Jay et al. found that although 85% of patients with obesity received counseling, physicians trained in the five As focused mostly on assessment (38). Physicians who best adhered to the five As model and who utilized more of the counseling techniques had better patient outcomes. Physicians who are trained in the five As appear to have slightly greater success in helping their patients maintain weight loss 12-months post-treatment, possibly because the trained physicians were more likely to refer patients to weight-loss programs (52).

EFFECTIVENESS OF PHYSICIAN COUNSELING

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Healthcare providers in general, and physicians in particular, remain the most trusted source of health-related information. A number of studies have shown that patients readily accept lifestyle counseling from their primary care providers. A study examining lifestyle counseling by primary care residents found that the higher the number of five As counseling practices used by residents, the more the patients were motivated to lose weight and change diet and physical activity behaviors. The study concluded that a higher quality of physician counseling, such as use of the five As, is associated with increased patient motivation and behavior change (38). More specifically, primary care practitioner counseling on weight loss is found to have a significant impact on patients' ability to lose weight. For example, Noël et al. observed that patients who received limited obesity-related counseling were markedly less likely to lose weight over time than those receiving intensive counseling (53). In particular, Petrin et al. suggest that it is both the healthcare provider's and patients' responsibility to make sure they receive counseling pertaining to obesity-related risk factors and subsequent morbidity associated with excess weight. They emphasize that enhanced weight-loss tools will facilitate weight-loss counseling (54). Moreover, a systematic review and meta-analysis of survey data on provider weight-loss counseling and its associated changes in patient weight-loss behavior found patients with overweight or obesity to be four times more likely to attempt to lose weight compared to those who do not receive counseling (55).

Additionally, physician nutrition counseling has the potential to influence patient behavior (47,56,57). An analysis of National Health and Nutritional Examination Survey (NHANES) data found that adults with a BMI over 25 and those with BMI over 30 both perceived themselves as overweight and attempted to lose weight if they were identified as overweight by their physician. Yet only 45.2% of respondents with a BMI over 25, and 66.4% of those with a BMI of 30 or above, were told of their overweight status by a physician (58). A subsequent analysis of the NHANES data found that patients who reportedly discussed their weight status with their physician were more likely to report clinically significant weight loss (17). However, a study by Lorts et al. among low-income adults with obesity in the United States found that physicians' advice to lose weight had limited impact on dietary behaviors (59).

Nonetheless, there is observational evidence that patients are more likely to lose weight when simply told by a physician that they are overweight (60). Patients with obesity might be more receptive to advice from healthcare professionals than from lay sources. One meta-analysis reported that weight-loss advice by physicians had a significant impact on patients attempting to lose weight (55). In another study, patients who received weight-loss counseling in a primary care clinic lost an average of 11 pounds after 1 year, while those who were not counseled on weight loss gained an average of 0.6 pounds after 1 year (61).

It should be noted that the utility of clinical counseling for behavior change has been better established for various behaviors other than those related to diet and weight control, in particular smoking cessation. The importance of physician counseling for smoking cessation has been confirmed through randomized controlled clinical trials that show improved cessation rates when physicians are involved. A systematic review by Stead et al. found that simple advice to quit smoking provided by physicians led to a small impact on cessation rates; however, more intensive counseling was advantageous (62). Specifically, intensive behavioral interventions have resulted in substantial increases in smoking cessation (63); however, less dramatic results are evident in trials utilizing low-intensity interventions (62,64). Despite the importance of physician counseling, data from the National Ambulatory Medical Care Survey found that only 24.5% of current tobacco users received cessation assistance which consists of either tobacco counseling or cessation medication (65).

Physician counseling is equally efficacious as part of routine primary care in reducing alcohol consumption. Jonas et al. systematically reviewed the evidence for the benefits of behavioral counseling interventions in primary care settings to reduce risky and harmful alcohol consumption (66). They

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included a total of 23 controlled trials lasting at least 6 months into the systematic review, consisting of patients who misused alcohol. Results revealed that by using multi-contact behavioral counseling interventions, participants reduced the average number of drinks per week by 3.6 drinks from baseline, and 12% has fewer heavy drinking episodes, compared to the control during a 1-year period (66). An earlier study by Garcia et al. that followed 306 patients who reported excessive alcohol consumption found counseling provided by the family physician to be highly effective (67).

Although physicians have the potential to be influential in promoting weight loss through encouraging healthful eating and physical activity, they too often fail to broach the subject with their patients. While there were 883.7 million physician office visits in 2016, including 54.5% made to primary care, physician lifestyle counseling in primary care settings remained limited (68). In 2010, slightly less than a third (32.4%) of patients who had seen a healthcare provider in the past year received advice to adopt and/or maintain a physically active lifestyle (69). Adult patients with diabetes were the most likely to receive advice to engage in physical activity during that year, whereas patients with cancer were the least likely to receive activity counseling. A large Canadian survey observed that while many patients (69.8%) were verbally encouraged to be physically active, markedly less (15.8%) were provided with written prescriptions (70). In addition, a study by Anis et al. (71) trained students to serve as third-party observers of patient encounters with physicians. Their results showed that counseling about diet or physical activity occurred in only 20% to 25% of visits. Nawaz et al. found that only 50% of adults surveyed reported discussing nutrition during their last routine checkup in the past year, and only 56% reported discussing physical activity with their physician (72). Discussion of diet resulted in an increased likelihood of changes in fat or fiber intake as well as weight-loss success, particularly among patients whose weight status falls within the overweight range.

Overall, it appears that the majority of patients find that their physician neglects to address the issue of weight at all. (73). Multiple studies confirm this observation. According to Healthy People 2020, less than a fifth (19.1%) of adults afflicted for the past 20 years or more with CVD, diabetes, or hyperlipidemia received dietary counseling in 2010. Furthermore, less than a third (28.0%) of adults with obesity were provided with weight loss, diet, or physical activity counseling during the same year (74). Moreover, a study by Bleich et al. examining data from the National Ambulatory Medical Care Survey found that 17.6% of adults with obesity were specifically counseled about losing weight with slightly more receiving counseling regarding their diet (25.2%) and physical activity (20.5%) (75). The study also examined predictors for weight-loss counseling, finding that a diagnosis of obesity, visiting an internist, preventive medicine visits, and extended visit times with physicians were all predictive of having received counseling focused on losing weight (75).

Significant discrepancies exist as to how physicians and patients view weight-loss counseling (76). Patients and their doctors view the necessity for weight loss and the likelihood for weight-loss success very differently. One study analyzing the behavior of 28 primary care physicians found that when doctors were asked about the weight and health status of their patients, they tended to assign their patients to higher weight categories and worse health outcomes in comparison to the self-identification of patients themselves. Moreover, patients were more optimistic about their weight-loss potential and motivation than their physicians (77). A survey conducted in an urban clinic in Bronx, NY, found that 86% of patients with obesity wanted to lose weight but only 17% received dietician referrals, and a mere 36% received a recommendation for weight loss by their physician (78). Only 21% of patients with a weight status of obesity and 11% of patients with a weight status of overweight had this diagnosis documented on their charts. Patients and physicians frequently disagree on the weight-loss goals discussed during office visits. A survey of 29 rural, primary care practices in the Midwest found that physicians and patients even

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disagreed on whether weight loss and physical activity were discussed at all during an office visit, indicating that physicians need to verify that patients have received advice (79).

Gender of both the physician and the patient plays a significant role in how physicians address weight loss with their patients. There is evidence for gender bias in weight-loss counseling, as physicians are more likely to encourage women than men with a BMI ≥25 kg/m^2 to lose weight, possibly due to the greater sociocultural stigma against overweight women (80). Yet an unexpected reverse gender effect was found for patients with a BMI of 32 kg/m^2. In this higher BMI category, physicians were more likely to counsel men to lose weight than women, possibly due to a greater concern about android body fat distribution in men (79). Physician gender appears to play a role as well, as female physicians are more likely to advise patients on weight loss, provide obesity counseling, and refer patients for obesity treatment (81). One study found that physicians endorse greater weight loss for female patients with obesity than for their male patients, though female physicians were less stringent than male physicians in the weight-loss goals proposed for all patients (82). Patient–physician gender concordance appears to play a large role in whether diet/nutrition, physical activity, and weight-loss counseling are provided to patients with obesity. An analysis of the National Ambulatory Medical Care Survey revealed that patients with obesity were significantly more likely to receive diet/nutrition and physical activity counseling when both the patient and physician were male compared to when both were females (83). Locality, age, education level, and socioeconomic status play a role in whether physicians address weight loss with patients as well. Residents of the Northeast are more likely to be counseled than those living in other parts of the United States. After age 60, the likelihood of counseling declines for both men and women. Ironically, persons with a higher education level and socioeconomic status are more likely to receive advice about weight, but low-income patients are more likely to attempt to change their diet and physical activity based on their physician's advice (84).

In sum, the most obvious means by which healthcare settings could make a meaningful contribution to obesity control efforts is through effective behavioral counseling. As noted previously, there is some contact between virtually the entire population and the healthcare setting during any given year. The healthcare system contact, the amenability of the healthcare setting to individualized guidance, and the unique influence of healthcare providers all argue for a dedicated effort to make high-quality dietary, physical activity, and weight management counseling a routine aspect of clinical care.

RECOMMENDATIONS FOR PRIMARY CARE COUNSELING

Several governmental agencies have provided guidelines for behavioral counseling in primary care. The USPSTF recommends intensive dietary and physical activity counseling for adult patients with obesity to be delivered in the primary care setting or via referral to nutritionists or dieticians (85). Specifically, the USPSTF recommends referring adults with obesity to intensive multicomponent behavioral interventions as they have shown a moderate effect (grade B) to achieve weight loss (86). In addition, it recommends that physicians refer patients without obesity or other known cardiovascular risk factors (hypertension, dyslipidemia, abnormal blood glucose levels, or diabetes) to behavioral counseling to promote healthful diet and physical activity. This recommendation is in response to evidence supporting a small but positive effect (grade level C) of behavioral counseling on CVD prevention (87). On the other hand, for patients who already have overweight or obesity and have cardiovascular risk factors, the USPSTF recommends behavioral counseling with moderate evidence (grade B) supporting the beneficial effect for CVD prevention (88). In addition, the Academy of Nutrition and Dietetics recommend that physicians increase

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referrals to dietitians when needed, as nutritional interventions have proven to increase quality of life and decrease healthcare costs. Medicare covers outpatient medical nutrition therapy in patients with diabetes, chronic kidney disease, end-kidney failure, or a kidney transplant (89). The American Academy of Family Physicians similarly recommends that patients should be screened for obesity and offered intensive, multicomponent behavioral interventions with at least one session per month for 3 months (90). Physicians should also assess patients' knowledge of the relationship of their lifestyle to health and provide a clear and customized message about the importance of diet and exercise (91).

Translating such recommendations into counseling that actually influences behavior is a challenge best met through application of the science of behavior modification (92). Eight broad categories of behavioral theories or models have contributed to the understanding of lifestyle change through counseling in medical practice: communication models, motivational interviewing, PRECEDE–PROCEED Model, rational belief models, Theory of Planned Behavior, self-regulative systems models, operant and social learning models, and behavioral economic approaches (93).

Models of Behavior Modification

Communication Models highlight the importance of the generation of the health message, the reception of the message, message comprehension, and belief in the substance of the message (94). In addition, how health messages are framed can significantly influence individual behavior. Prospect Theory demonstrates that individuals respond in a different manner to messaging emphasizing the benefits (i.e., gain-framed) or loses (i.e., loss-framed), even though they are factually the same (95–97). Specifically, when gain frame messaging is used (e.g., emphasizing the benefits of exercise), an individual tends to be risk-averse, whereas loss-framed messaging (e.g., disadvantages of not exercising) facilitates risk-seeking behavior (98,99). Since engaging in health-promoting physical activity and adhering to a healthful diet are perceived to entail few risks and little uncertainty, gain-framed messaging should be employed by healthcare providers (98,99). Additionally, research indicates that health messaging should use simple and positive language such as that used in Michele Obama's obesity prevention initiative (i.e., "Let's Move!") (47,100).

Additionally, *motivational interviewing* (MI) techniques developed by Miller and Rollnick (101) from their work with problem drinkers emphasize the importance of working through ambivalence and developing self-efficacy with the goal of changing unhealthy lifestyle behaviors (102). This counseling style combines warmth and empathy with reflective listening and elicits information by asking key questions. Physicians' use of MI techniques for weight loss has successfully resulted in patients attempting to lose weight and promote sustained, habitual engagement in physical activity (103,104). A systematic review of trials in which MI was utilized by psychologists and physicians as an intervention method found an effect in 80% of the studies. Even one brief session of MI was sufficient to produce an effect in 64% of the cases reviewed (105). A review of studies focusing on nutrition-related behavior change similarly found that MI, in combination with cognitive behavioral therapy, was a highly effective counseling strategy (92). Although MI is patient centered, time-limited intervention, aiming at increasing intrinsic motivation and creating behavior change by addressing ambivalence (106); application of the approach is further explored in Chapter 47. A systematic review of the literature found MI to have the potential to help primary care patients lose weight (106).

Furthermore, the PRECEDE–PROCEED Model, developed by Green, is a framework that has been used to design, implement, and evaluate health promotion interventions, a framework that is pertinent to lifestyle counseling in primary care (107–109). This approach helps determine a patient's needs within a given counseling context by assessing motivational characteristics; physical, manual, and economic

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barriers and facilitators; and specific circumstantial rewards and penalties. This helps the clinician avoid inappropriate techniques, such as trying to persuade an already motivated patient that change is necessary. By skipping unnecessary steps, it frees up time to focus on areas that require modification. For example, the PRECEDE–PROCEED has been successfully applied to developing an intuitive-eating weight management program (110), or an intervention program aimed at increasing physical activity (111).

According to *rational belief models*, objective and logical thought processes determine behavior, provided that the clinician has appropriate information on both the risks and benefits. For example, the Health Beliefs Model emphasizes four perceived predictors: probability of threat, severity of threat, feasibility of benefits, and barriers to adopting the new pattern of behavior (112). This model has been useful in identifying predictors of health behaviors and planning health promotion strategies that have demonstrated improved adherence to self-care behaviors (113).

Another example is the *Theory of Planned Behavior* (TPB) developed by Azjen (114), to discern and predict determinants of volitional behavior. That is, the intention to perform a behavior is viewed as a function of one's beliefs, attitude toward the behavior, and perceived social norms. TPB has been utilized to predict many health-related behaviors and can help explain intentions for physical activity and diet among populations ranging from diabetes patients to healthy adolescents (115,116). An intervention utilizing the TPB in adolescents with obesity found that providing 60 minutes sessions per week for 6 weeks improved attitudes, subjective norms, perceived behavioral control, intention, and behavior. In addition, the intervention led to a significant decrease in BMI ($p < 0.001$), weight ($p = 0.001$), and waist circumference ($p < 0.001$) in comparison to pre-intervention (117).

Self-regulative Systems Models outline a three-part self-regulation process: self-monitoring, self-evaluation, and self-reinforcement. A basic assumption is that people will act in accordance with their interest, once they know it. Prochaska's Transtheoretical Model of behavior change (TTM) assesses an individual's readiness to change according to four core constructs: stages of change (SOC), processes of change, decisional balance, and self-efficacy (118). The main construct, SOC, categorized as precontemplation, contemplation, preparation, action, and maintenance (119), has been applied to a variety of health modification interventions including those targeting physical activity (120). Tailoring of interventions to match a person's stage of change and the use of MI techniques have yielded beneficial outcomes (121). Health educational programs based on TTM have successfully increased transitioning to a higher physical activity behavior change (122). Application of this method is further explored in Chapter 47.

Operant and Social Learning Models focus on the stimuli that elicit or reinforce a specific behavior, such as Skinner's and Pavlov's conditioning approaches to behavior change. Bandura's Social Cognitive Theory emphasizes the immediate social reinforcing consequences related to attempting behavior change; three critical elements are self-efficacy, modeling, and self-management (123,124). The model attempts to link self-perception and individual action and assumes that individuals selectively heed information from four sources: active attainment of goal, vicarious experiences of others, persuasion, and physiological cues (125,126). New ways of behaving occur through imitation and modeling and through observation of the behavior of others (126–128). Social cognitive theory has been used as a basis for interventions aimed at weight gain prevention (129), dietary self-efficacy (130), and physical activity adherence (131) among other health behaviors.

Behavioral Economic Approaches this relatively new field of exploration integrates psychology into economics with the goal of providing insights into "real world" human decision-making (132). Economics traditionally assumed that individuals make rational decisions, such as being forward looking, possessing excellent computational skills, and making consistent choices based on personal preference,

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even when circumstances (or context) change (133). In comparison, behavioral economics acknowledges that individuals have limited computational skills (i.e., bounded rationally) (134) that humans are often nearsighted (myopic) with preferences that might change (particularly when in a "hot" state), and that rules of thumb (heuristics) are often relied on when making decisions (135–137). That is, behavioral economics acknowledges certain behavioral patterns including cognitive biases affect decision-making (138) such as behaving impulsively in an aroused state like Homer Simpson rather than Spock-like calculated decisions (139–141). This field has been introduced to the public via popular books (relying on years of psychological and economic research) by Dan Ariely (e.g., Predictability Irrational), Daniel Kahneman (e.g., Thinking Fast and Slow), as well as Richard Thaler, and Cass Sunstein (e.g., Nudge: Improving Decision about Health Wealth and Happiness) (139,142,143).

More specifically, behavioral economics can increase our understanding with regard to health behaviors and outcomes. The obesity pandemic is a case in point (144). Obesity has nearly tripled worldwide since the 1970s with over 650 million persons with obesity (145), a phenomenon that could be explained by status quo (or default) bias. This bias refers to 'inertia'; that is, the preference to take the "path of least resistance" (140), thereby leading (many) humans in the Western world to have a positive energy balance (i.e., more calories "in" than "out") (146) This is a result of an overabundance of palatable energy-dense foods coupled with energy-saving technology that has "engineered" physical activity out of daily life (47,147). Thaler and Sunstein suggest that choice architecture can facilitate overcoming status quo bias (139). Choice architecture refers to designing the environment in such a way that the more virtuous choice is easier to make over the more harmful one (148). For example, setting fruits and vegetables at eye sight in a lunchroom cafeteria and unhealthful snacks far from sight, thereby facilitating healthful food consumption (139). Furthermore, setting the "default" to one that encourages active living and healthful eating will likely lead to a healthy lifestyle. For example, in countries, such as the Netherlands, where the default is active transport (i.e., cycling), physical activity rates are higher and obesity rates are lower than in countries that rely primarily on motorized transport (47,149,150). Similarly, changing the home environment to one offering nutrient-dense foods will likely lead to healthful eating habits for the entire family (151).

Another known bias in the behavioral economics literature is present time bias, which refers to inconsistent time preferences (152–154). For example, if one sets a goal to avoid fast-food for an entire week only to eat burgers and fries the next day, that is regarded as present time bias. Furthermore, individuals are often myopic when making decisions (140), since the benefits (e.g., enjoying the taste of fast-food) are salient, whereas the future rewards of avoiding fast-food (e.g., obesity prevention) are often not tangible (155). Suggested remedies to this bias are pre-commitment contracts and financial incentives (156,157). Pre-commitment contracts are self-imposed binding agreements where one commits to a "painful" consequence if a-priori goals (e.g., weight loss) are not met (158). For example, a meaningful sum of money (e.g., $1,000) is deposited to a third party prior to beginning a weight-loss program, and if one's goal (e.g., losing 5 kg within 3 months) is not met, then the money is given to charity. Pre-commitment contracts can also take the form of a binding agreement between friends or family to exercise regularly. This approach has been found to be successful in weight-loss programs and smoking cessation interventions (47,158–162), and can be utilized in a primary care setting even via encouraging joining a healthy lifestyle reward program, or even using patients own money to incentivize themselves when meeting health goals (163). Thus, providing financial incentives can promote engaging in desired behaviors (e.g., healthful eating) by shifting future benefits (e.g., enhanced health) into the present in the form of monetary incentives (47,164). These incentives facilitate habit formation, and some studies have observed sustained behavior change even when incentives are taken away (47,157,165,166).

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Indeed, a recent systematic review by Mitchell et al. found that short-term modest incentives ($1.40 per day) may promote sustained physical activity as measured objectively via step counts (167). A randomized controlled trial by Driver and Hensrud observed that individuals receiving financial incentives had higher participation rates and exhibited significantly more weight loss than their counterparts who did not receive incentives (168). Moreover, Mitchell et al. suggest that for incentives to be effective they should be guaranteed (not lottery based) and based on objectively measured criteria (169).

In sum, these and related behavioral modification theories and constructs are largely products of psychology and should guide behavior change interventions (in general) and in the primary care setting, in particular. However, to meet the unique demands of a primary care setting, an effective behavioral counseling model must address the barriers to physician counseling and patient behavior change outlined in the chapter. Elements that can increase applicability and ease of implementation of a model include specific guidance on counseling strategies as well as taking decision-making biases into account; brevity of the counseling script; standardized, validated instruments to assess the patient; and clear delineation of provider response and responsibility.

Several counseling programs have focused exclusively on the primary care setting and have adapted constructs of the behavioral modification theories to fit the primary care context. Most of these programs use a general approach to assisting patients that includes the five As. A majority of these have adapted elements of various behavioral counseling models into a single counseling program. While a recent review has suggested that integrating concepts from behavioral economics into the five As framework can potentially benefit lifestyle counseling in primary care (47), its efficacy has yet to be examined, to our knowledge.

PRIMARY CARE COUNSELING CONSTRUCTS

The efficacy of lifestyle counseling and lifestyle interventions has been well supported by such high-impact programs as the Diabetes Prevention Program (DPP) and the Increasing Motivation for Physical Activity Project (IMPACT) (170,171). Diabetes incidence in the 10-year follow-up to the DPP program was lowest in the group randomly assigned to intensive lifestyle intervention, when compared to the metformin-treated group or the placebo (172). In addition, weight loss was the highest in the lifestyle intervention group versus the metformin and control groups at 1 year (173). Similarly, 1-year results from the IMPACT study found that regular physical activity counseling for sedentary, low-income women resulted in significant increases in estimated total energy expenditure as compared to participants who did not receive telephone counseling (171). Both of these studies demonstrate the powerful impact of effective counseling, which can be successfully applied within a primary care counseling construct as well, as the studies below demonstrate.

Patient-Centered Assessment Counseling for Exercise and Nutrition

Patient-centered assessment counseling for exercise and nutrition (PACE) was designed by physicians, behavioral health scientists, and public health professionals to provide physical activity counseling to healthy adults within a limited time. The program was based on the SOC theory, which postulates that behavior moves along a continuum of change from precontemplation, to contemplation, to action. Accordingly, three distinct counseling strategies relevant to each stage were developed. PACE has been shown to significantly increase physical activity levels. An early efficacy study by Calfas et al. (174) randomized 255 healthy, sedentary participants to an intervention group that consisted of two contacts

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with a health educator and a booster phone call with the control group receiving usual care. Patients receiving the PACE program reported 37 minutes per week in walking compared with 7 minutes in the control group. Green et al. studied the effectiveness of using PACE in a 6-month telephone-based randomized clinical trial designed to increase physical activity in 316 inactive patients (175). The intervention group received physical activity counseling and three 20- to 30-minute phone calls each month to assist in identifying strategies to increase physical activity. The control group did not receive the counseling or the phone calls. The intervention produced higher levels of exercise after the 6-month treatment period as compared with the control (PACE score of 5.37 vs 4.98, $p < 0.05$). Patrick et al. conducted a PACE+ intervention designed to promote improved eating and physical activity behaviors among 878 adolescents, using a computer-supported intervention initiated in a primary care setting (176). The intervention was successful in increasing physical activity and reducing saturated fat intake, although success rates varied by gender. Among women, it was found that more frequent outreach and contacts were beneficial in promoting changes in multiple behaviors. Therefore, it is possible that the beneficial effect of higher frequency of contact might differ by sex. In addition, the PACE+ intervention caused a significant reduction in sedentary time that is paramount as sedentary behavior counseling does not receive enough attention from physicians and is an area that deserves improvement (177).

Activity Counseling Trial

The Activity Counseling Trial (ACT) Research Group reported the results of a randomized controlled trial that compared the effects of two physical activity counseling interventions with standard care (178). The ACT interventions were based on Social Cognitive Theory, which was used to select key personal (self-efficacy), social (social support for exercise), and environmental (access to facilities and resources) constructs. Interventions consisted of advice (physician counseling plus educational materials), assistance (advice plus interactive mail), and behavioral counseling (advice and assistance plus regular phone calls and behavioral classes). At 24 months, VO_2 Max was significantly higher in the assistance and counseling groups compared to the advice group, but no significant differences were reported in physical activity (179). The 24-month effects of the ACT were also assessed for CVD risk factors (180), with substantial improvements found in both men and women who had high risk factors for CVD at baseline; no improvements were found for participants with normal baseline levels. A separate study evaluated the effect of the ACT on health-related quality of life and subjective well-being. A total of 395 women and 479 men who were physically inactive were randomized into one of the following groups: physician advice, advice plus behavioral counseling during primary care visits, or advice plus behavioral counseling that included telephone contact and behavioral classes (181). At 24 months women who received both counseling and assistance had significant reductions in stress and improvements in satisfaction with body function in comparison to those women receiving advice only. Men showed reductions in stress in all arms with no differences between groups (181).

Step Test Exercise Prescription

Petrella et al. compared two methods of exercise counseling by physicians—the first using only American College of Sports Medicine (ACSM) guidelines and the second using the ACSM guidelines along with an office-based assessment to determine fitness levels and prescribe an exercise training heart rate (Step test exercise prescription [STEP]) (182). The assessment consisted of five questions to determine the patient's readiness to start a regular activity program and fitness levels were determined by recording the heart rate after moderate exercise. Patients were offered pedometers as incentives to enhance fitness and increase adherence to the program. Participants in the STEP group reported significant ($p = 0.009$)

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improvement in the extent of physician counseling and knowledge compared to the control ACSM only group. A study of 241 elderly community-dwelling patients found that a STEP intervention consisting of exercise counseling and prescription of an exercise training heart rate improved aerobic fitness levels and exercise self-efficacy in participants (183). STEP benefits were maintained up to 12 months. In addition, a 12-month randomized trial involving 193 participants evaluated the effect of delivering a tailored physical activity intervention using a transtheoretical behavior change counseling program (STEP model) (184). Both groups, intervention and control, provided patients with individualized physical activity interventions based on submaximal step test results but only the intervention provided counseling and based their physical activity prescription on the stage of physical activity behavior. VO_2 max improved in both groups with no significant differences between them; however, the intervention group showed a significant reduction in systolic blood pressure and higher energy expenditure in comparison to the control group (184).

Physically Active for Life

A feasibility study by Pinto et al. (185), called Physically Active for Life (PAL), integrated the constructs of the TTM into a patient-centered model of primary care. The study randomized 12 practices to the PAL intervention group and 12 to standard care. Physicians participating in the PAL program received a training manual, a desk prompt with summary information on counseling, and a poster on activity promotion, and they participated in a 1-hour training session. Patients enrolled in the PAL program received a five-section manual—one section for each stage of change. Cognitive, attitudinal, instrumental, behavioral, and social issues were addressed through a series of questions and statements by the counseling physician. Comparisons between the intervention and control groups showed significant improvements in confidence in the intervention-group physicians, but no significant increase in frequency of physical activity counseling provided to patients. Patients in the intervention group reported satisfaction with the exercise counseling and support materials. In a subsequent paper, Pinto et al. reported the effects of the PAL intervention on the underlying theoretical constructs used in the program. Motivational readiness for physical activity and related constructs of decisional balance (benefits and barriers; see Chapter 47), self-efficacy, and behavioral and cognitive processes of change were examined at baseline, 6 weeks, and 8 months. At 6 weeks, the intervention had significant effects on decisional balance, self-efficacy, and behavioral processes, but those effects were not maintained at 8 months (186).

Pressure System Model

The Pressure System Model (PSM) (187), developed by David Katz, utilizes constructs of the TTM to separate the two fundamental goals of behavioral counseling: raising motivation and overcoming resistance. Traditionally, behavioral counseling has focused on raising motivation by apprising the patient of the risks associated with a particular behavior and highlighting the benefits of changing the behavior. PSM also takes into account impediments to behavior change and offers the patient and provider an opportunity to identify strategies to overcome these impediments. The utility of the model derives from its simplicity. The PSM relies on a two-question algorithm to identify the correct focus for counseling. Chapter 47 details the salient features. It is intended to provide a specific counseling method for use in the primary care setting and resources that can be shared with patients to facilitate adoption of the behavioral changes recommended. Katz et al. assessed the effectiveness of the PSM in a randomized controlled trial in which six Yale University internal medicine programs were randomly assigned to a PSM-based behavioral counseling training program (intervention) or standard curriculum (control) (188). Physicians at these sites received either PSM training or standard residency training. The PSM training program

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consisted of skill building in behavioral counseling, didactic sessions augmented by role-play exercises, use of a simple algorithmic approach to identify patients' counseling needs, a comprehensive list of commonly encountered barriers to physical activity and strategies to address them, and brief counseling scripts. Physical activity levels were measured in 195 patients who received physical activity counseling from a resident trained in PSM counseling methods, while 121 patients were similarly surveyed at the control sites. After 6 and 12 months of intervention, physical activity, as measured by the modified Yale Physical Activity Survey (YPAS), improved significantly from baseline in the intervention sites (1.77 ± 0.84; $p = 0.0376$ and 1.94 ± 0.98; $p = 0.0486$), with no change observed at the control sites (0.35 ± 1.00; $p = 0.7224$ and 0.99 ± 1.52; $p = 0.5160$) (188).

Transtheoretical Model Interventions and Weight Loss

A recent randomized controlled trial evaluating the impact of a weight-loss intervention for women who have obesity (guided by the TTM) found it to be an effective strategy for 6-month weight loss in primary healthcare (189). The intervention group received weight-loss orientation plus counseling based on the TTM versus the control group who only received the weight-loss intervention alone. With regard to long-term weight loss, however, a systematic review observed that there is inconclusive evidence that nutrition and physical activity interventions guided by the TTM lead to long-term weight loss (190). Indeed, for weight loss to remain in effect over the long run, strategies need to be put in place (e.g., social support, self-monitoring) to ensure that the lifestyle changes (e.g., exercise and healthy eating) leading to weight loss are habitual (191,192). In addition to weight loss, lifestyle interventions have been found to reduce metabolic risk. For example, a multicenter, randomized trial of pre- or stage 1 hypertensive adults compared the effects of lifestyle intervention consisting of physical activity, sodium restriction, and weight loss (arm 1), to the same intervention plus the DASH diet (arm 2) to a control group receiving advice only (193). Both arms received a combination of individual and group counseling sessions focused on behavior change and both showed beneficial effects on LDL cholesterol, triglycerides, and total cholesterol at 6 months. In fact, greater benefits were observed among those persons who attended more counseling sessions.

TECHNOLOGY AND BEHAVIORAL INTERVENTIONS TO IMPROVE HEALTH OUTCOMES

Weight-loss and lifestyle counseling in primary care can greatly benefit from structured, preventative programs aimed at helping people live healthier lives, including online weight-loss programs and mobile phone applications (Apps). Apps are useful to remotely deliver an intervention and are now being used by clinicians to self-monitor nutrition and physical activity behaviors, particularly in patients with diabetes and obesity (194). For example, Weigh Forward, a lifelong approach to weight control by RediClinic (195) offers 10 visits with trained clinicians as well as online support. Popular apps that support physical activity maintenance and weight management such as MyFitnessPal (196) allow users to track physical activity and caloric intake with its Calorie Counter and Diet Tracker applications. These online weight-loss tools have the potential to enhance the efficacy of clinical interventions, by empowering patients to manage their own preventive care (197). A randomized controlled trial compared the effect of using a brief in-person counseling plus a physical activity App for 9 months (arm 1) to a brief-in person consultations plus an App for 3 months (arm 2) and to a control group. All groups used accelerometers for the duration of the intervention. After 3 months, both arms utilizing the App observed a significant increase in the number of steps and the time spent in moderate to vigorous intensity physical

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activity. These observations remained after 6 months despite the lack of use of the phone app and counseling in one of the arms (198). This study highlighted the beneficial effect of using phone apps for physical activity habit formation. In addition, a recent meta-analysis evaluating the effect of wearable activity trackers on physical activity participation found a significant increase in daily steps, time spent in moderate to vigorous intensity physical activity, as well as energy expenditure (199). Authors concluded that utilizing activity trackers, either by themselves or as part of a physical activity intervention, is effective at increasing physical activity participation and, therefore, could help clinicians in providing ongoing support to their patients (199). Another meta-analysis examining the impact of mobile phone apps on weight loss and physical activity found significant reduction in body weight and BMI in comparison to the control group. However, in comparison to the previous meta-analysis, authors did not observe significant differences in physical activity levels between the intervention and control groups (200).

CONCLUSIONS

Randomized clinical trials of behavioral interventions have shown modest reductions in BMI, systolic and diastolic blood pressure, low-density lipoprotein, and total cholesterol (87). Due to an increased emphasis on health promotion and disease prevention, the use of behavioral counseling strategies in primary care should become common practice as physicians have a unique opportunity to create an early impact in the lives of their patients (47). The evolution of behavioral modification theories from the provenance of psychology to primary care can be traced in the adaptations and modifications described in this chapter. These revisions address a number of barriers to behavioral counseling commonly cited by primary care physicians such as the lack of training (201), and the short consulting time with patients. For example, behavioral counseling sessions by a psychologist can typically last 15 to 45 minutes, but primary care physicians are unable to devote that much time to counseling for health behavior change. All the programs discussed in this chapter provide brief, time-efficient behavioral counseling scripts for use by clinicians or other healthcare providers. Some of the programs also include instruments that allow the clinician to identify key risk behaviors efficiently and accurately, assess the patient's readiness to change, and track counseling activities. These instruments usually consist of a few questions to help the physician tailor a session to the needs of the patient, focus on the most important issues, and offer specific, personalized advice.

Clearly articulated strategies designed to address the impediments to a particular behavior change further serve to enhance effectiveness of primary care counseling. The majority of these models include a robust physician education component. These training curricula are typically based on principles of adult learning and build physician skills using interactive, sequential learning in workshops, group settings, or individual training sessions. Even relatively brief physician training has led to improvements in physician self-efficacy for counseling (48). This was demonstrated in the PAL study in which physicians rated their confidence in performing a series of eight counseling activities. Physicians in the intervention group showed significant increases in their confidence to offer an individualized exercise plan to their patients, identify resources, and address issues associated with barriers (185). Similarly, physicians participating in the STEP program felt more knowledgeable and confident about the program compared to those in the control group (182). The advancements in technology through the introduction of apps and wearable technology has the potential to support lifestyle counseling in primary care (202–204). To maximize this potential, wearable technology could be integrated into the electronic health record (205). For example, healthcare settings that utilize electronic health records (e.g., Kaiser Permanente) to routinely assess physical activity levels (206) could use wearables to more accurately determine patients' physical

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activity habits and prompt individuals to modify their behavior in “real time” (207). However, the effectiveness of this approach warrants empirical investigation in future research.

Despite these advances, important limitations persist in the routine application of behavior modification to primary care. To date, data to verify the efficacy of such efforts remain sparse and follow-up periods are short. Even the behavior modification interventions designed for the primary care setting can be unclear about the frequency of counseling and/or the content of follow-up sessions after initial counseling. While promising in many regards, the counseling advances to date warrant further evaluation in various practice settings and with diverse groups of patients before their general utility can be affirmed. That said, uptake of such methods into practice settings even as their evaluation proceeds is justified by the high prevalence of obesity, its comorbidities, and the ineffectiveness of prevailing approaches. Of note, there is apt to be an important role for lifestyle counseling even when clinicians turn to pharmacotherapy (208), or bariatric surgery (209,210).

Historic changes in how we view and treat obesity were made on a national level in the United States. Obesity was traditionally treated as a syndrome, not a disease, and as such was not treated as a respected condition (211). However, the American Medical Association (AMA) voted for “Recognition of Obesity as a Disease” at their 2013 annual meeting by approving Resolution 420 “to recognize obesity as a disease state with multiple aspects requiring a range of interventions to advance obesity treatment and prevention” (212,213). The AMA further called for an improved measure of obesity than BMI alone, and better clinical and public health strategies for addressing obesity. Immediately after the AMA’s designation of obesity as a disease, new legislation was introduced into the Senate and House of Representatives called the Treat and Reduce Obesity Act (214); however, it did not progress beyond the committee level (215). This bill (HR 2415) would require Medicare to cover more obesity treatment costs including prescription drugs for weight management and to make it easier for almost 50 million elderly and disabled Medicare patients to receive weight-loss counseling. The bill would allow more providers to offer intensive behavioral counseling and would require the CMS to emphasize the behavioral counseling service to its beneficiaries. The bill was reintroduced in 2015 and then in 2019 as the Treat and Reduce Obesity Act of 2019 (HR 1530/S.595) and has yet to be approved (215–217). The Affordable Care Act mandates that medical insurers must provide free preventive care to beneficiaries. Under Title IV of the Affordable Care Act private insurers are required to compensate physicians for providing weight-loss and nutrition counseling, obesity screening, and counseling to promote sustained weight loss. This mandate has the potential to have far-reaching effects in how the medical community approaches obesity treatment and weight-loss counseling. The AMA designation of obesity as a disease and the concurrent re-introduction of the Treat and Reduce Obesity Act might influence how we prioritize and reimburse physician behavioral counseling in the future.

The fundamental question is whether obesity should be viewed as a cultural or a clinical problem. Our healthcare system is focused on disease care, rather than prevention. Arguably lifestyle changes alone can reduce our risk for heart disease, cancer, stroke, diabetes, dementia, and obesity by 80%, far surpassing the efficacy of any drug or medical intervention (218). The obesity epidemic calls for a comprehensive solution, based upon constructive, compassionate counseling by well-trained clinicians, coordinated with wellness programming available through community interventions as well as pertinent apps. These measures, in turn, must be supported by structural, policy, and environmental changes that promote healthy behaviors and lifestyles conducive to disease prevention, weight management, and wellness. While clinician counseling is an important part of the solution, policy-level changes that lead to a society where the cultural norm is healthy eating and active living at home, at work, and in school are necessary to bring about sustainable change (150,219).

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Chapter 47

Dietary Counseling in Clinical Practice

Jenna Blasi

INTRODUCTION

The information in this and related books is just so much ink unless it is applied in clinical practice. Thus, dietary counseling is the medium of exchange that infuses significance into the study of clinical nutrition and renders nutrition a field directly relevant to health outcomes. But access to and knowledge and understanding of salient nutrition principles are by no means commensurate with the capacity to deliver those principles to patients effectively, persuasively, and productively. Effective dietary counseling requires astute consideration and handling of factors—some under the patient's control and some not—governing behavioral patterns (see Chapter 38); confrontation with traditional impediments to such counseling in the clinical setting; the avoidance of confrontation with a patient; identification of the particular assistance an individual patient needs and compassionate attention to it; the timely and judicious use of supporting materials and resources; an acceptance of the incremental nature of change and delayed gratification; and dedicated persistence. Few worthwhile endeavors are easy, and nutritional counseling is no exception.

But effective dietary counseling is of vital importance, given the impact of dietary pattern on health. The evidence to support the effectiveness of dietary counseling on modifying health outcomes is slowly accumulating, and there is more evidence now to support nutrition and lifestyle counseling than when the last edition of this book was published (1,2) (see Chapter 46). In line with this growing body of evidence, the Centers for Medicare and Medicaid Services have created new regulations that authorize reimbursement for obesity counseling (3) (see Chapter 46). However, the case is still far from ironclad that routine dietary counseling is beneficial. In 2012 and again in 2017, the US Preventive Services Task Force concluded that behavioral counseling for dietary improvement has limited benefits and only recommend routine use of dietary counseling in selected patients with cardiovascular risk factors. USPSTF guidelines suggest that primary care physicians individualize the decision to offer behavioral counseling in the general population (4,5). Similarly, the American Academy of Family Physicians recommends intensive behavioral lifestyle counseling specifically for patients with hyperlipidemia and other cardiovascular risk factors (6). In contrast, for pediatric patients, it is recommended that all children receive lifestyle counseling, with more intensive counseling for overweight and obese patients (7). Despite these recommendations and the rising body of evidence in favor of intensive behavioral counseling, the implementation rate of both screening and counseling remains low (8).

But with over 40% of US adults classified as obese (9), the argument for counseling is compelling. Diet is fundamental to the management and prevention of cardiovascular diseases, diabetes, cancer, and hypertension. Accordingly, the American Heart Association has expressly called for the routine assessment of diet in all clinical encounters. Dietary practices divergent from recommendations, combined with lack of physical activity, have for many years been considered the second leading cause of preventable death in the United States, behind tobacco use (10). However, since the previous edition of

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this textbook, poor diet and lifestyle practices have surpassed tobacco use as the leading cause of preventable death in the United States (11).

Furthermore, everyone eats but only a minority of the population uses tobacco; in the aggregate, the health effects of nutrition are likely to be far greater. Even when not discernibly contributing to the development or prevention of a particular disease, nutrition plays a role in lifelong health, influencing appearance, functional status, self-esteem, socialization, energy level and vitality, mood, behavior, athletic performance, and susceptibility to infection. Therefore, the potential for dietary practices to modify health is tremendous and universally applicable.

When the importance of diet to health is acknowledged, we are duty bound to contend with it in practice, even if the success of our efforts is in question. We are, for instance, obligated to treat pain to the best of our ability, even if our best effort proves insufficient. In much of medical practice, our limitations are inspiration to apply greater effort, not an invitation to abdicate. Dietary counseling deserves and demands its share of this pervasive clinical respect.

Thus, any controversies regarding dietary counseling in primary care should be devoted to how, not whether or why. There is reason to believe, on the basis of both judgment and empirical evidence, that greater commitment to nutrition counseling in clinical practice would lead to greater effectiveness. Once we are committed to dietary counseling as a matter of principle, the remaining choices are about how to make it work for our patients and ourselves. Laid out in this chapter is a framework that is equally respectful of the needs of both groups. Patients need advice that is sound, reliable, personally relevant, and compassionate rather than judgmental. Clinicians need a delivery system that is efficient, comfortable, replicable from encounter to encounter, and mindful of its place in the panoply of clinical obligations. That these disparate objectives can be met is the argument to which this chapter is dedicated.

INTRODUCTION OF THE COUNSELING CONSTRUCT

Chapter 46 provides an overview of behavior modification constructs relevant to dietary counseling and addresses some of the most salient barriers to that counseling, namely, clinician confidence in dietary counseling, insufficient counseling tools and protocols, time constraints, insurance reimbursement, patient noncompliance, and obesity bias. With the five A's framework (Ask, Advise, Assess, Assist, Arrange) applied in conjunction with an understanding of the models related to effective messaging, motivational interviewing, beliefs, operant conditioning, self-regulation, and behavioral economics, clinicians have an array of effective tools to employ for dietary counseling. This chapter is principally devoted to the elaboration of a particular counseling approach predicated on that body of behavior change theory and designed to navigate around those barriers.

The Pressure System Model (PSM), developed expressly to render elements of behavior change theory more amenable to application in the primary care setting, was first published in 2001 (12). Since that time, the model has been applied in a controlled trial of physical activity promotion (13); tailored for use by a large primary care group in Maine (14, unpublished data.); incorporated into a regional obesity control plan for the New England States (15); presented as an example of needed obesity control measures at the National Obesity Action Forum (16); and was incorporated into a clinician-centered, skill-based weight management program.

In brief, the PSM includes a two-question algorithm as the initiation of dietary counseling and then brief, targeted interventions directed to patient need, as determined by the algorithm. The PSM algorithm (see Fig. 47.1) determines whether counseling should be focused primarily on raising motivation, lowering resistance, or both, by placing the patient into one of five categories (see Fig. 47.2). The

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subsequent focus of counseling is category specific (see Table 47.1). The intent of the construct is to facilitate counseling that is productive in increments as brief as 90 seconds per encounter. When detailed and time-consuming dietary counseling is warranted, referral to a dietitian, nutritionist, or other health professional with dietary counseling expertise is generally advised.

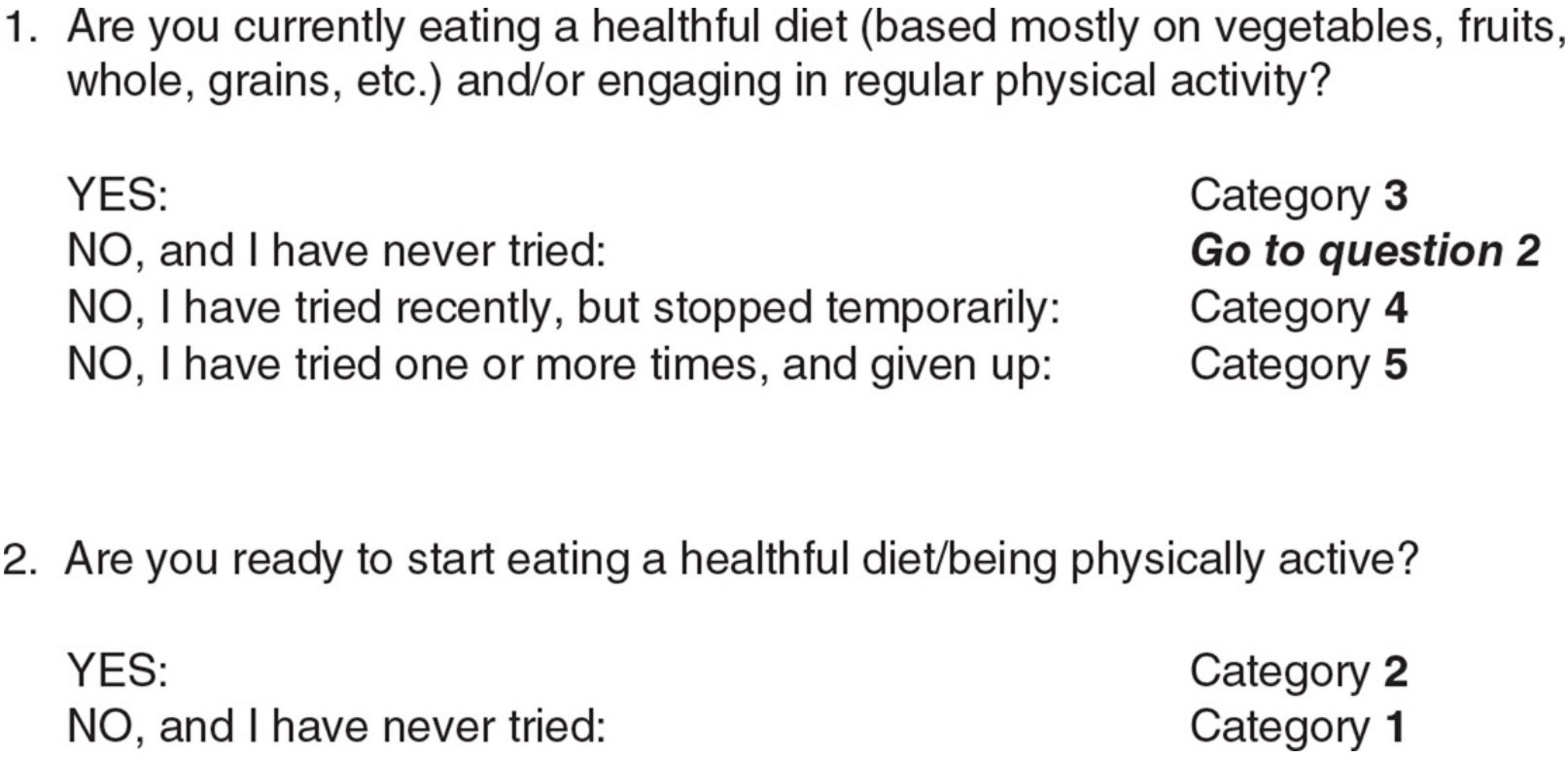

FIGURE 47-1 PSM algorithm. The PSM counseling approach is predicated on just two basic questions that help determine whether a given patient primarily needs help in raising motivation or overcoming resistance/barriers. The categories are explained in Figure 47.2.

Details of the Counseling Construct

Development of the PSM began with an effort to synthesize elements from the various behavior modification models presented in Chapter 46 and to address the most common barriers in order to characterize and influence the processes of change more effectively in the context of primary care encounters. To that end, the governance of behavior maintenance and behavior change were distilled down into two fundamental and opposing forces: (1) the desire for change, or *motivation*, and (2) resistance to change, or *obstacles* (17,18). The potential utility of the model is closely allied to its simplicity: Facilitating behavior for any given patient begins merely by identifying which of these two forces warrants dedicated attention.

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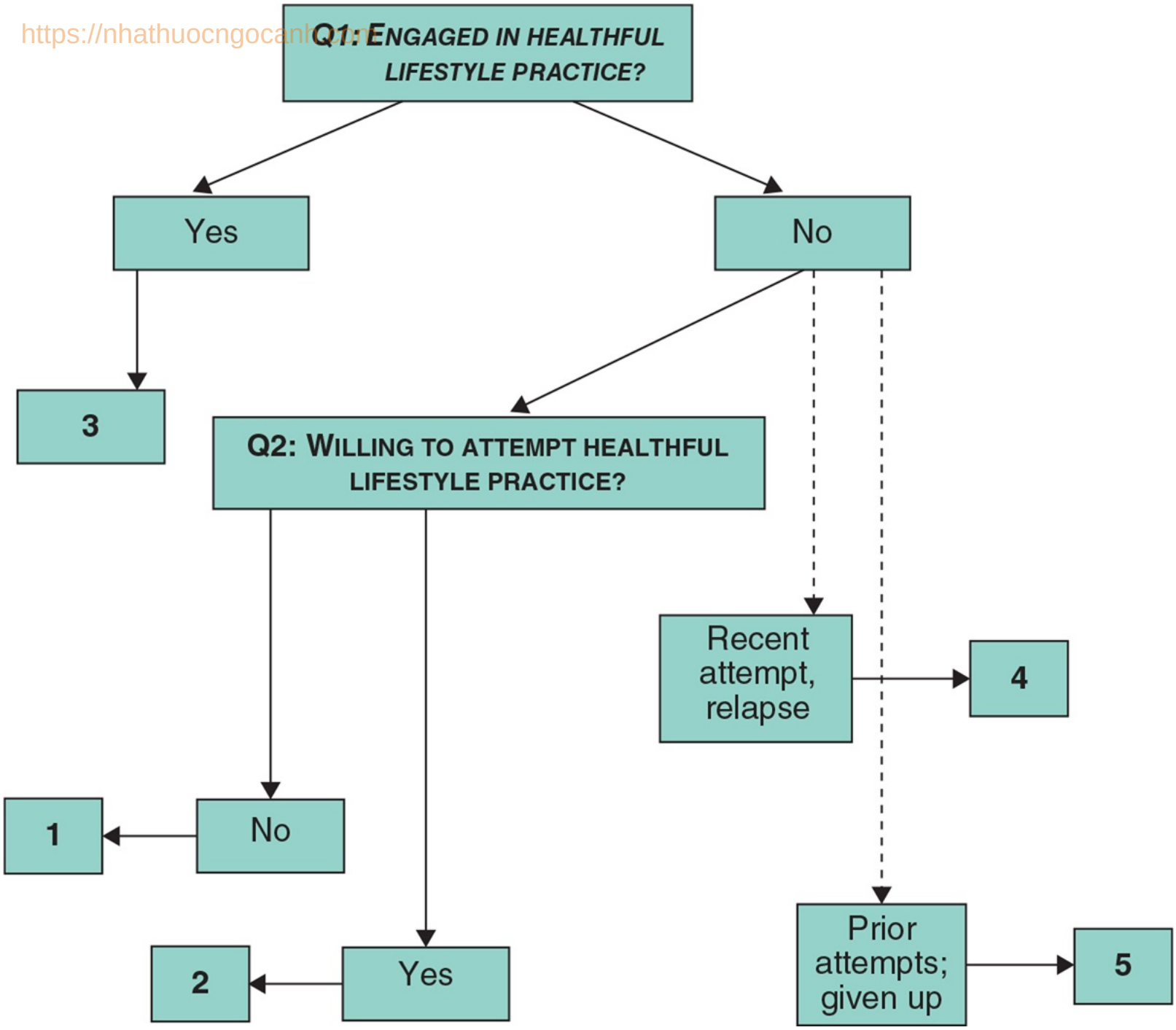

FIGURE 47-2 PSM categories. Solid lines indicate direct questioning; dashed lines indicate various potential patient responses to a given question.

TABLE 47.1

Pressure System Model Categories and Associated Counseling Approaches

Category	Algorithm Responses	Emphasis of Counseling	Special Considerations
1	No/No	Motivation	Patients in Category 1 are "precontemplative," not having thought about the behavior change in question. The goal of initial counseling is to raise awareness, interest, and motivation.
2	No/Yes	Motivation	Patients in Category 2 are considering behavior change and are

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		and resistance	thus “contemplative.” This group will likely benefit from a primary focus on raising motivation to induce change but also some attention to the potential barriers that are fostering hesitation and ambivalence.
3	Yes	—	Patients in the “action” phase generally just need encouragement. However, as new barriers are encountered, troubleshooting assistance may be necessary.
4	No; relapse	Resistance	Patients in this group were motivated enough to attempt change; a relapse suggests that a barrier was encountered. Troubleshooting that barrier and attempting to identify and plan for others are warranted.
5	No; burnout	Resistance	Patients with multiple failed attempts at behavior change are apt to feel “burned out.” This group needs to first understand why failure is not their fault—that it results from encountering barriers—and then needs assistance identifying and troubleshooting those barriers.

Source: Katz DL. Behavior modification in primary care: the pressure system model. Prev Med. 2001;32:66–72.

Believing in the importance of the condition to be avoided, in personal risk, and in the utility of the change are all components, or prerequisites, of motivation (19,20). A change believed to modify meaningfully a substantial, personal risk is desirable. Such a change, however, will occur only if the resultant motivation exceeds the aggregate resistance, whatever the nature or source of that resistance (see Fig. 47.3).

In this regard, the established behavior change models discussed in Chapter 46 are informative. To effect a change, one must be capable of change. Individuals lacking self-efficacy cannot change their behavior until or unless they learn that they have the capacity to do so. The Stages of Change model represents sequential assessments of the balance between resistance and motivation. When the difficulty is perceived to exceed the rewards of change, one is unwilling to change and fails to advance to the action stage. With new information or experience, motivation for change may rise as the perceived difficulty remains constant. As the gap between the two narrows, one perceives the potential for change and becomes contemplative. Change is attempted whenever motivation, at least temporarily, exceeds the recognized resistance. The behavior change is maintained until or unless difficulty overtakes motivation, at which time relapse occurs. A more realistic, or at least more practiced, assessment of both difficulty and motivation are the result of unsuccessful attempts at change. These attempts either serve as the necessary preparation for sustainable change or lead to frustration.

The complexities of diet make behavior change particularly difficult. The well-known slogan of drug control efforts in the United States, “Just say no,” is clearly impertinent when it comes to diet. Diet cannot be avoided, but it must be managed. The need to struggle with the desired behavior change on a continuous basis is more than most people can manage successfully. Consequently, the rate of compliance with dietary recommendations has historically been very low (21–23).

In primary care practice, most (but certainly not all) patients will be fairly motivated to select a health-promoting diet. This is true either because the patients are already sick and therefore motivated by the perception of personal risk, or they are seeking primary care despite being well, in which case they are seeking preventive and health-promotion services. One of the most common nutrition-related problems seen in primary care is obesity, and it is the problem most likely to have led to prior efforts to change

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diet. Obese adults seeking primary care are unlikely to need motivation for dietary change. Failure to change diet in most patients is the result not of inadequate motivation but of excessive resistance. The only ways to produce change under such circumstances are to reduce the difficulty and to increase motivation further.

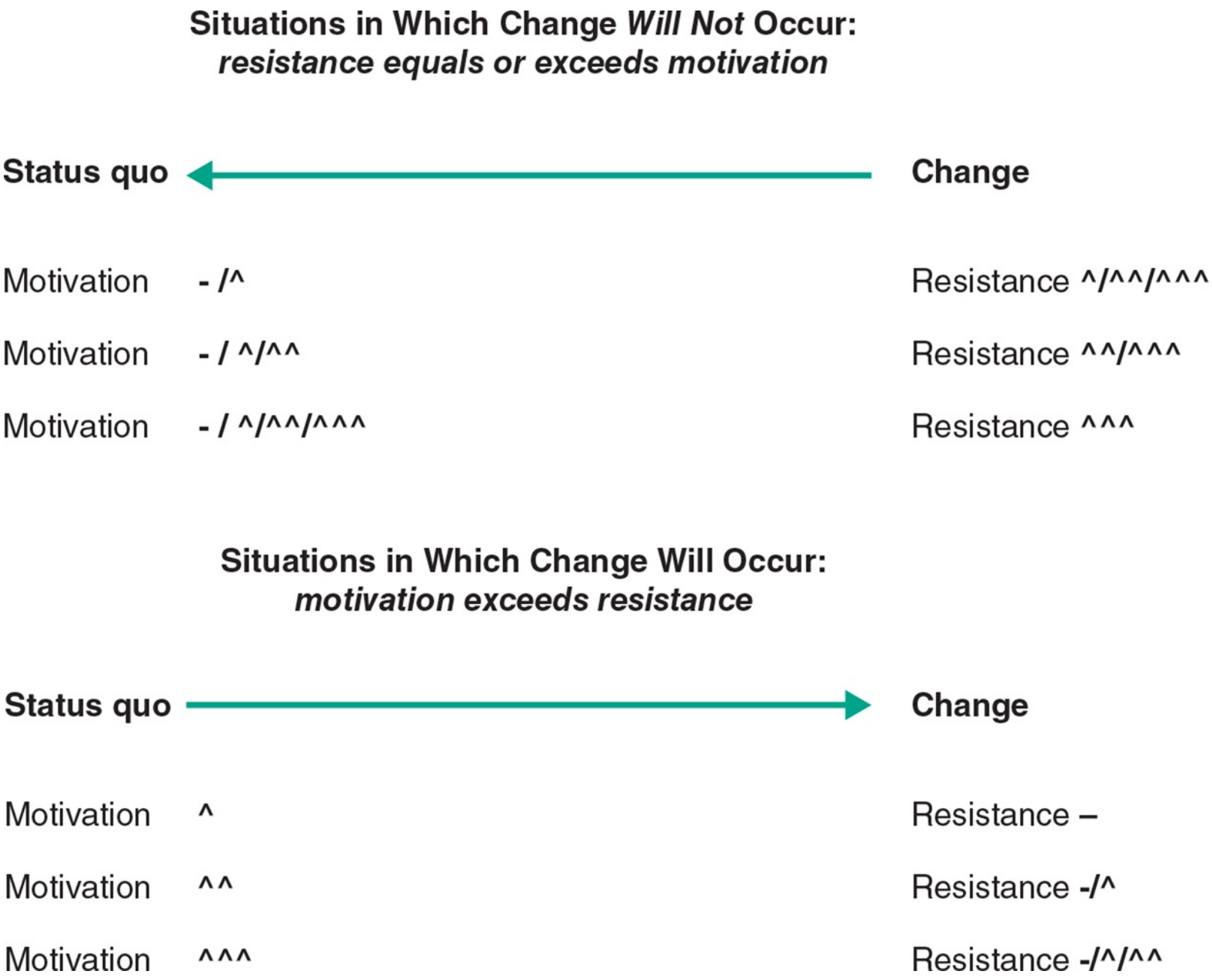

FIGURE 47-3 How gradients between motivation for change and barriers, or resistance to change, determine the outcome of behavior change efforts. The relative force of motivation and resistance, as represented by arrowheads, determines whether desired behavior change occurs or whether the status quo is maintained. A horizontal line represents neutrality, and increasing numbers of upward-pointing arrowheads represent increasing force, or "pressure."

Often, motivation can be raised, and specific methods of motivational interviewing have been developed (19,20). As noted by Botelho and Skinner (20), "advice giving," a relatively ineffective means of raising motivation, has tended to predominate in clinical practice. Minimally, motivation for dietary change requires knowledge of the link between diet and health. This is achieved by informing patients of the hazards of an injudicious diet and the benefits of a more healthful diet as a routine part of primary care

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delivery. Although patients are often informed in this area, they are also frequently misinformed, and important knowledge gaps prevail (24–27). Importantly, patients with better knowledge of nutrition are more likely to eat healthful diets (28), so improving nutrition literacy may ultimately improve diet.

One way of improving nutrition knowledge is via the efforts of government programs like MyPlate by the USDA Center for Nutrition Policy and Promotion. Another, more individualized approach is through nutrition guidance systems such as DietID (29). DietID is a digital tool that helps patients measure and manage diet, utilizing a visual pattern-recognition assessment that establishes a current dietary baseline. Based on that assessment, it offers personalized goal setting, nutritional guidance, behavioral navigation, and tracking directed at sustainable diet and lifestyle improvements. The value of rapid and reliable dietary pattern recognition assessment tools for research and clinical application is compelling and offers several advantages over current methods used to assess diet (30).

There are particular opportunities for motivating patients with existing illness; disease-specific counseling is often more effective than health promotion. This is the “teachable moment” concept salient in preventive medicine practice (31).

An especially important aspect of raising motivation to change is reestablishing self-esteem and self-efficacy when they have been lost. Paradoxically, one of the ways to reestablish a patient’s self-efficacy may be to inform them how much of dietary behavior is beyond individual control. This approach requires that the practitioner and patient distinguish between responsibility and blame and between factors subject to personal control and those beyond it, such as the built environment (32–35). Patients with repeated, unsuccessful efforts at changing diet (usually to lose weight) must be taught that factors beyond their control contrive to prevent such change. These factors include a litany of obesogenic influences from fast food to electronic devices, vending machines to video games, food processing to food marketing, and the fundamental mismatch between a Stone Age metabolism and a Space Age food supply (36) (see Chapter 44). Each of these and many related factors is either the direct product of physiologic adaptations to the forces of natural selection or the result of sociologic, psychological, religious, and cultural evolution.

There are two reasons a brief discussion of these exonerating factors is essential. First, by alleviating patients of their feelings of failure and futility, lost motivation for dietary change can be recaptured. Second, to prevent failure from recurring yet again, the balance between motivation and difficulty must be fundamentally altered. To do this, difficulty in changing diet must be reduced. This can be achieved only if the impediments to sustainable dietary change are recognized by both practitioner and patient and if strategies tailored to overcome them are designed and implemented. A text for patients devoted to this very matter is available (36) and includes a representative list of such impediments and the strategies for overcoming them.

In the PSM, the outcome of attempts to change diet (or other behaviors) is determined by the relative force applied by motivation and resistance, as shown in the following formulae:

1. Capacity to change diet or sustain change = Aggregate motivation – Aggregate resistance, where the difference must be positive
2. Inability to initiate or sustain dietary change = Aggregate resistance – Aggregate motivation, where the difference must be positive
3. Tendency to relapse after change varies directly with resistance and indirectly with motivation; relapse will occur when difficulty meets or exceeds motivation.

The conventional approach to behavioral counseling in primary care is to attempt to raise motivation

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(19), and motivational interviewing seems to enhance weight loss in obese and overweight patients (37,38) (see Chapter 46). Patients are apprised of the health risks associated with the maintenance of smoking, alcohol consumption, illicit drug use, and sedentary lifestyle and of the benefits of changing such behaviors. As shown in Figure 47.3, when motivation can be raised above resistance, behavior change will occur.

Generally, unaddressed in counseling efforts, however, are the fixed impediments to behavior change. A schedule that does not readily accommodate exercise may overcome motivation for physical activity. A fellow household member's smoking may overcome an individual's motivation to quit. The convenience and familiarity of fast food, and uncertainty about how to change patterns of shopping and cooking, may overcome an individual's desire to improve their diet (39). As shown in Figure 47.3, even if motivation is fairly high, change cannot occur if resistance to change is higher still. While counseling may serve to raise motivation, the level may fail to exceed resistance.

The insidious danger in this traditional approach to counseling is the tendency to actually or at least apparently "blame the victim" of behavioral risk factors (40–45a). While an unmotivated patient may be encouraged by a clinician's efforts to motivate, an already motivated patient is apt to experience frustration when change does not occur. That frustration is generally shared by the practitioner, adversely affecting the relationship (46). The PSM serves as a reminder that motivation is not infinitely malleable and that when resistance is great enough, motivation alone cannot produce behavior change. This encourages both patient and provider to engage in the productive process of identifying impediments to change that may be surmountable instead of the unproductive process of self-recrimination.

The second contribution of the PSM is its capacity to define the appropriate focus of counseling efforts based on discrete and easily recognized clinical scenarios. This progression from theoretical construct to clinical algorithm renders the model practical under the constraints of a typical insurance-based primary care practice.

As shown in Table 47.1, each of the five categorical determinations facilitated by the PSM algorithm has specific implications for counseling. Patients for whom motivation is relevant should receive motivational interviewing. The salient principles of this method are shown in Table 47.2. A simple tool to expedite a patient's progress through their own ambivalence—the principal objective of motivational interviewing—is a decision balance, as shown in Figure 47.4. A decision balance enables a patient to map out the sources of ambivalence and modify them over time. The balance may be completed at an office visit or in between visits, and it may be productive for the patient when assessed in private as well as at a clinic visit. Apparent gaps in the balance are an opportunity for the practitioner to offer advice and information that might tip the balance in favor of desired behavior change. But the balance also pushes back and indicates to the practitioner and patient alike when an effort to change is likely to be premature and thus unsuccessful. At such times, continuing to work toward a more favorable balance is the prudent course.

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	Change	Don't Change
Pros		
Cons		

FIGURE 47-4 A decision balance. Cells in the balance are filled in by a patient during or in between office visits. As the balance evolves over time, its implications for behavior change also evolve.

TABLE 47.2

Salient Principles of Motivational Interviewing

Principle	Implications
Express empathy/acknowledge ambivalence	Legitimizes patient's feelings, shows respect.
Develop discrepancy	Reveals disconnect between behavioral pattern and goals.
Avoid argumentation	Conveys that patient is in charge; builds therapeutic alliance.
Roll with resistance	Acknowledges that working through ambivalence is a process that may take time.
Support self-efficacy	Conveys support for patient.
Encourage social contracting	A confidante adds both support for change and a sense of accountability.

Source: Miller WR. Motivational interviewing: research, practice, and puzzles. Addict Behav. 1996;21:835–842.

When the patient's needs, as indicated by the PSM algorithm, relate more to barriers than to motivation, a focus on motivation may be counterproductive. In such encounters, an effort to identify and overcome barriers of personal relevance is most constructive. Many of the strategies used to overcome these impediments were modeled after an approach first tested for smoking cessation, and a related approach applied in one trial of physical activity promotion (12,47–50).

To apply this model, the discrete components of motivation and difficulty must be identified so that they can be targeted as indicated in counseling efforts. Factors influencing motivation are summarized in the following relatively short list, although means of enhancing motivation are more subtle and complex:

1. Risks of not changing
2. Health benefits of changing
3. Body image benefits of change

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4. Social/psychological benefits of change
5. Social support
6. Perceived self-efficacy

Whereas motivation may be inspired by a great many considerations but is ultimately composed of relatively few, the list of actual or potential barriers to dietary change is virtually endless. Only by working with an individual patient can the salient impediments to dietary modification be identified. Individualized assessment of dietary pattern followed by appropriate goal-directed guidance and tracking can facilitate the process of overcoming impediments to sustainable dietary change (29). A notable limitation of the current constructs is the limited ability of tools to accurately assess diet quality. The ability to provide thorough and specific dietary direction requires an accurate starting point. The effectiveness of dietary counseling to achieve a clinical endpoint is only as good as the proper assessment of the starting point. In other words, it is important to accurately measure what we are trying to manage. In the case of dietary counseling, the primary metric to be measured and managed is *diet quality*. Meaningful advancements in the ability to rapidly assess diet quality have been made, which have promise for improving the efficiency and effectiveness of dietary counseling in clinical practice. (30)

Structured Approach to ADEPT Dietary Counseling

One of the likely advantages of a nutrition text written by a primary care practitioner is the author's obligatory acceptance that nutrition in clinical practice will not, and should not, supplant other priorities. Just as clinical practice is deficient if it is inattentive to the profound influences of diet on health, so is clinical nutrition deficient if it is inattentive to the competing demands with which a provider must contend in all too little time.

With these considerations in mind, the approach to nutritional counseling laid out here is willfully streamlined and targeted toward practicing clinicians, for whom efficient use of face to face time is critical. It is also applicable to the various lifestyle practices germane to health, notable among them being tobacco use and physical activity pattern, along with diet. In the context of this book, the guidance offered is cast in terms of dietary counseling preferentially, but it is a matter of clinical judgment that health-related behavior is most deserving of attention at any given time.

The recommended steps for structured dietary counseling, shown in Table 47.3, are as follows:

1. **A**dminister the PSM algorithm.
2. **D**etermine the appropriate **e**mphasis on motivation or resistance.
3. **P**rovide tailored counseling.
4. **T**rack behavior (e.g., dietary intake) over time.

The acronym ADEPT (Apply Algorithm; Determine Emphasis; Provide tailored counseling; and Track behavior) may be useful in remembering the sequence of steps. This acronym is, of course, tailored as a reminder specific to the PSM but is closely related in both its emphasis and sequence to the "five A's": assess, advise, agree, assist, and arrange follow-up (51–53).

The Medical Home and Lifestyle Counseling

The patient-centered medical home is being promoted as a key component in the reform of primary care in the United States. The medical home is a patient-centered care model that involves the primary physician working with a multidisciplinary health care team to provide longitudinal care of the patient (54). Such

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models of care promote improved patient satisfaction and outcomes and decreased staff burnout (5). The medical home opens exciting avenues for the delivery of lifestyle counseling since it will be possible for the primary clinician to provide some lifestyle basic counseling and then refer the patient directly to an on-site dietician or nurse who can provide more intensive counseling.

Technological Innovations in Counseling

Advances in technology have allowed for novel and creative ways of enhancing lifestyle counseling through the use of internet-based platforms, smartphones, digital video, and social networking.

TABLE 47.3

Steps in the Application of Pressure System Model in the Context of Primary Care Visits[a]

Counseling Step	Comment
Apply algorithm	Apply the two-question PSM algorithm to determine current lifestyle/dietary practices and willingness to alter them. (This can be about the individual patient or all members of a household if the patient manages the diets of others.)
Determine emphasis	Determine the appropriate emphasis on raising motivation, lowering resistance, or both, and providing encouragement if current dietary practices are healthful.
Provide tailored counseling	Use motivational interviewing techniques and a decision balance if the appropriate emphasis is on raising motivation. If the appropriate emphasis is on overcoming resistance, work with the patient to identify and troubleshoot barriers.
Track behavior	If patient reports a healthful diet, probe for particulars, such as information about a typical day, and offer guidance for any adjustments deemed important. Regardless of patient's PSM category, ask them to complete several days' worth of food intake diaries and either mail them in or bring them at follow-up to verify habitual dietary intake pattern, as warranted.

[a]*The acronym to recall this sequence of steps is ADEPT*.

PSM, Pressure System Model.

Although patients and providers are rapidly adapting to synchronous telemedicine appointments, the implications of this platform on dietary counseling remains unclear. Video-based telemedicine has advantages and disadvantages to the traditional in-person consultation format. Advantages include: avoids transportation logistics and costs, minimizes need to take time off work, eliminates child or elder care issues, improves accessibility, decreases potential infectious exposures, and often gives providers insight into the home environment all of which may have implications on dietary counseling. Disadvantages of telemedicine that can have an impact on dietary counseling include: limited physical exam capability, technology challenges, privacy and security, insurance reimbursement and the complex social and psychological differences implicit in video-based interactions.

Digital therapeutics is another rapidly evolving area that can impact the delivery and reception of dietary counseling. As a subset of digital health, digital therapeutics are evidence-based clinical interventions that use software applications to treat and prevent a wide range of medical problems, including those that can be influenced by diet and lifestyle change. Advancing evidence in the area of the

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term “m-health” (mobile health) is now being used to describe the ways that mobile phones, monitoring devices, personal digital assistants, wearable technology, and other digital tools are being used by patients and clinicians. Technology can build on clinical counseling efforts by giving patients tools for self-monitoring (food, activity, and biometrics), providing reminders via phone, text, email, and serving as another source of peer support through online communities and social networks (55). Smartphone apps are widely used for dietary tracking, education, clinical intervention, and monitoring. (56). However, though there an abundance of weight-loss and nutrition apps available, formal testing of their efficacy in clinical trials remains limited. A 2016 systematic review provided modest evidence that multi-component interventions that include the use of smartphone apps to improve diet and lifestyle can be effective. (57) More rigorous and extensive research is needed to determine how best to optimize technological tools in dietary counseling.

CONCLUSIONS

The combination of diet and physical activity pattern together have recently surpassed tobacco and become the leading cause of premature death in the United States (10). The health of every patient is influenced, for good, bad, or both, by diet. Given the pivotal role of dietary patterns on health, attention to dietary counseling in the course of clinical care is of universal importance.

Encouraging patients to eat well for the promotion of health and the prevention and/or amelioration of disease should be approached in the context of well-established principles of behavior modification. Some patients need to be motivated before they are willing to consider change, others need help strategizing to maintain change currently under way, and still others need help overcoming the sequelae of prior failed attempts. This latter group, perhaps predominant, may be harmed by counseling efforts focusing only on motivation. The PSM of behavior modification can be used to identify discrete clinical scenarios in which motivational counseling is needed and is likely to be productive. Much effort at dietary modification fails due to the diverse and challenging obstacles to a healthy diet in the modern “toxic” nutritional environment. The clinician committed to promoting the nutritional health of patients must commit to devising strategies, tailored to individual patients, over and around such obstacles.

Dietary and lifestyle patterns are predicated on many social determinants and other considerations besides health (41). Given that human dietary metabolism and preferences are derivatives, largely, of the very different environment of prehistory (see Chapter 44) and that the modern nutritional environment has developed to satisfy preferences, health problems resulting from dietary excess are not surprising.

Given the multiple influences on food selection and the fact that health is often not the dominant concern, professional guidance is clearly required to encourage and guide individual efforts to approximate a health-promoting dietary pattern. Such efforts must play out at the complex interface of medicine and lifestyle, physiology and sociology, anthropology and evolutionary biology, personal responsibility and environmental determinism, psychology, and metabolism. Of fundamental importance to such efforts is the understanding that any effort to change individual behavior requires talking individuals out of the behavioral pattern they have selected or into another they have not, along with respecting that many forces other than will or choice govern behavioral patterns. Thus, effective dietary counseling begins with identification of what is feasible for a given patient and then leans heavily on the power of persuasion. A therapeutic alliance is essential, as are patience and accommodation.

An assessment of dietary pattern should be routinely incorporated into every history and physical examination. A brief overview of a health-promoting diet should be provided on such occasions as well (see Chapter 45). Dietary counseling should always be linked to advice about physical activity, as the

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health benefits of each support those of the other; there is evidence that physician counseling effectively promotes physical activity (37,38,58–60) (see Chapter 46). Difficulties involved in making dietary and other lifestyle changes should be acknowledged.

When more involved dietary counseling is indicated as part of weight loss or disease management efforts, referral to a physician or allied provider with dietary counseling expertise is generally advisable. In such circumstances, the referring physician's role is to reinforce the detailed counseling provided by the practitioner, situate diet in the overall clinical plan, and encourage the patient's efforts by applying realistic behavior modification principles that distinguish between responsibility and blame, the reasons, and the methods.

No matter how refined clinical counseling techniques may become, it is rather implausible that they would ever represent a sufficient counterforce to the obesogenic modern environment (34,35,61–67). For the health care setting to contribute meaningfully to weight management will likely thus require fundamental adjustments to the systems of care delivery as well as coordination with resource allocations in other settings will be necessary for the health care system to contribute meaningfully to weight management (32,68).

The evidence that dietary counseling in the context of clinical care can change behavior and/or outcomes is limited, but such evidence does exist and is increasing. The application of methods specifically tailored to the setting of clinical practice should lead to better outcomes than have been described to date. A concerted effort by clinicians to incorporate nonjudgmental dietary guidance into routine clinical care is clearly indicated by the importance, and universal relevance, of diet to health.

Though effective counseling and patient education is necessary to promote healthy lifestyles, it is not sufficient. In order to make effective lifestyle changes, in addition to knowing what choices to make, patients need to have the *means* and *abilities* to make those choices. For example, even if a patient of a low socioeconomic status wanted to increase her fruit and vegetable consumption, the price of fresh produce may be prohibitively expensive. Similarly, if she wanted to increase her physical activity, her neighborhood might not have a safe outdoor space for exercise. The very structure of the environment can make healthy eating a challenge and physical inactivity the norm (see Chapter 5). In order to curtail the obesity epidemic, lifestyle counseling needs to be coupled with broader changes to the environment that facilitate rather than hinder healthy living.

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Contemporary Topics in Nutrition

The tone of a good textbook is measured and restrained. The objective of a textbook is to present, to the extent possible, the truth, the whole truth, and nothing but the truth—that its readers may then form their own perspectives, in accord with the weight of established evidence. The job of a textbook editor, therefore, is to refine, not opine. The chore is to sift for established truth and valid argument and unencumber it of clutter that it may speak for itself. The preceding pages are duly rendered in service to that endeavor, however well or poorly met.

Not so the pages that follow.

In this collection of chapters on timely topics, I give you my own unfettered (more or less) voice—my perspective, off leash. That said, my single most unwavering opinion is that anyone's personal ideology, my own included, should be subordinate to epidemiology—that our opinions worth sharing must strive to align with the weight of evidence and adapt over time to remain current. So, you have my voice and my perspective here—but if I am true to my own cause, these chapters, and the weight of pertinent evidence, will point to much the same conclusions. The very value in perspective, however, is that it offers something pure data cannot.

To those who find merit here, my humble thanks—along with notice that there is much more of the same from whence these came. See "Additional Topics & Sources" for my quite vast online archive of essays and columns on topics in preventive medicine, public health, and, more often than not, nutrition. You might expedite topical retrieval by putting my name and the topic of interest into your favored search box; on any given topic in nutrition, there will likely be a sizable haul.

To those who find deficiencies here, the blame is, of course, solely and entirely mine. Please tell me about them, and I promise to amend my perspective, and the sharing of it, fully in accord with your persuasion. My thanks in advance, for you are among my teachers. Praise is lovely—but we learn far more when listening to those with opinions other than those we already own.

—David L. Katz

ADDITIONAL TOPICS AND SOURCES

Books

- Katz DL. The Truth about Food: Why Pandas Eat Bamboo and People Get Bamboozled. *True Health Initiative*; October 1, 2018
- Bittman M, Katz DL. How to Eat: All Your Food and Diet Questions Answered. *Houghton Mifflin Harcourt*. March 3, 2020.

David L. Katz Online Column Archives

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- US News & World Report: https://www.usnews.com/topics/author/david-l-katz
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- Huffington Post: https://www.huffpost.com/author/david-katz-md
- VeryWell: https://www.verywellhealth.com/
- LinkedIn*: https://www.linkedin.com/in/david-l-katz-md-mph-facpm-facp-faclm-4798667/detail/recent-activity/posts/

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Chapter 48

The Calorie

David L. Katz

INTRODUCTION

The refractory nature of the obesity epidemic has invited extensive reflection in the nutrition community, with almost all time-honored precepts subject to scrutiny and reconsideration. Included among these is the bedrock principle that weight regulation is ultimately a matter of energy balance, in turn a product of calories consumed versus calories expended. The question “is a calorie a calorie?” (1,2) has become a prominent refrain in both popular culture and the scientific literature.

The ostensible basis for the question is that a focus on calories has failed to produce an effective countermeasure to the obesigenic elements in modern society. An additional consideration is that a given incremental reduction in energy consumption or increase in energy expenditure does not translate into a standard change in weight or body composition. These and related observations have induced some writers to ask whether or not calories really matter (3), and others to go further and declare that they do not (4).

Fundamentally, the calorie is a standardized measure of stored energy, as is the joule, used routinely in Europe. The actual measure in common application to food in the United States is the kilocalorie. A kilocalorie is the energy required to raise the temperature of 1 L of water 1°C at sea level. From the perspective of a calorimeter, a calorie then is clearly a calorie, and exactly that.

But human beings are not calorimeters. Energy consumed as food is expended in support of basal metabolism; used for growth and repair; used to fuel physical exertion; wasted as heat; and/or converted into a storage reserve in the form of either glycogen (see Chapters 1 and 5) or fat (see Chapters 2 and 5). Energy demands for growth and repair vary with stage of the life cycle, and daily circumstance. The efficiency with which calories are utilized varies among people just as fuel efficiency varies among vehicles, with consequent variation in the degree to which calories are wasted as heat (i.e., thermogenesis). Resting energy expenditure and basal metabolic rate vary in accord with genetic factors and body composition. Body composition in turn varies with genetic factors, dietary factors, and physical activity. Physical activity influences energy requirements both directly and indirectly via effects on lean body mass.

Such factors readily account for variable responses, in terms of weight and body composition, of different people to the same load of calories. The variation to account for this need not be vested in calories, for it is readily accounted for by known variations in human metabolism. The analogy to other vehicles is again apt. If two cars travel different distances or perform variably in other ways on identical gallons of fuel, it does not require hidden enigmas in the definition of a gallon. Rather, it invokes the far more evident explanation that not all cars are created equal (5).

The clinician is certainly well advised to acknowledge that two patients may eat and exercise much the same, yet wind up with very different weights. This is not testimony to flaws in the laws of thermodynamics, but simply a reflection on the well-established and in some cases quite marked (6)

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variance in human metabolic efficiency. New insights in this area derive both from studies of the genome and of the microbiome (see Chapter 5). There are some cases of quite marked vulnerability to weight gain, and/or resistance to weight loss, that are frustrating to patient and clinician alike, and likely multifactorial in origin. In addition, there is evolving understanding of the implications of changing body mass and composition for caloric requirements, with models elucidating the dynamic nature of energy balance (7–11).

Explanations for the disappointing performance of a calorie-centric view of weight management are no more elusive at the level of epidemiology. Despite a long-standing emphasis on portion control in official dietary guidance, the modern era has seen a consistent, and even accelerating, proliferation of energy-dense processed foods literally engineered to be as nearly irresistible as possible (12). With a standardized definition of "ultraprocessed food" now in wide use (13), studies—including randomized controlled trials (RCTs)—are demonstrating the direct link between such willful adulterations and increased consumption (14).

Against this seemingly unstoppable force driven by profit motive, portion control has been an all too readily moveable object. Consequently, national nutrition surveys in the United States suggest that while there has been variation in the percentage of calories from specific macronutrient sources over recent decades, overall calorie intake has trended up, not down (see Chapter 5). The failure of the "calorie hypothesis" in public health is attributable not to flaws in the concept of the calorie, but egregious impairment in the execution of guidance due to the obesigenic influences of modern culture and modern environment.

Intervention studies of weight loss, reviewed extensively in Chapter 5, superficially imply differential effects of the macronutrient classes on weight. Reviewed thoroughly, however, the literature shows that diets achieve weight loss by restricting calories—some directly, and some indirectly by restricting choices—but all doing so. In addition, the weight-loss differences seen with competing diets tend to be nominal and devolve to insignificance over time, including any distinctions between intermittent fasting and comparable calorie deficits achieved by means of daily restraint (15,16). Any means to restricting calories, including a diet willfully comprised of "junk" foods, is conducive to weight loss in the short term (17), if not necessarily good health over time. Similarly, an intake of calories beyond requirement results in weight gain, regardless of the source of those calories (18).

There remains the contention that the same number of calories from different food sources will exert different effects on important aspects of metabolism, such as hormonal balance. Situated artfully in the context of argument, this point is leveraged to imply the inadequacy of the calorie concept and to justify ruminations on the utility of the measure.

But this contention, stripped of its pretensions, is merely the assertion that the quality of foods matters along with the quantity. This does not rise above the level of self-evident. Of course a given number of calories from a sugar-sweetened beverage bereft of nutrient value is utilized quite differently by the body than the same number of calories from walnuts, or avocado, or wild salmon. In essence, a specious straw man argument has been contrived so that it can be debunked: if calories count, then calories from diverse foods should all have the same effects. If all fixed quantities of food energy do not have the same effects, then calories must not count. Therefore, a calorie is "not" a calorie.

The argument is specious because the first clause is unfounded. The same amount of latent energy may be stored in foods of markedly varying nutritional quality. Nutritional quality, in turn, is a term defined on the basis of health effects: Foods vary in nutritional quality if they vary in their effects on health and metabolism. If, in fact, 100 kcal of apple, applesauce, apple cider, or apple strudel were metabolized identically, they would, ipso facto, be nutritionally identical. It is differential effects of food on

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measurable aspects of health and metabolic responses that justifies any relative ranking from less to more "nutritious" in the first place (19).

The effects of foods on endocrine responses vary, and this in turn has implications for the fate of calories. When insulin responses are brisk, the deposition of calories in fat may be facilitated (see Chapter 6), with preferential accumulation of fat centrally, including in the liver. Such visceral fat is an inciting element in the pathway leading to metabolic syndrome (see Chapter 6). That the quality of foods and their effects on metabolic responses matter was never in question. These factors can matter, and calories can matter, too. That both do matter is just what the weight of evidence suggests.

One final issue is of particular practical value. The quality of calories may provide the best means to controlling their quantity. As noted, portion control advice has tended to fail against the temptations of the modern food supply with RCTs now showing that ultraprocessing of food is a causal trigger of overconsumption and weight gain (14). Investigative journalists have revealed more than once the diligent and well-informed food industry efforts to maximize the number of calories it takes to achieve fullness (20,21). There is both reason to believe and evidence to suggest (see Chapter 5), that this process can be reverse engineered. Food formulations that raise energy density, increase glycemic load, and minimize satiety effects—all components of "ultraprocessing" (22)—will result in both the adverse effects of poor quality and those of increased quantity. Foods with opposing properties—high nutrient density, relatively lower energy density, low glycemic load, and a high satiety index—will tend to exert favorable effects on health directly, and indirectly will facilitate portion control by reducing the calories required to achieve a satisfying feeling of fullness.

A calorie is a calorie. But soda pop is not salmon, or spinach. Both the quality and quantity of calories count. The best way to control the latter may well be a focus on the former. An unending debate about the implications of a measure of latent energy is unlikely to be conducive to either.

For additional commentary on the topic of calories by the author, see:

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Chapter 49

The Pernicious Wag of Dietary Dogma

David L. Katz

The tail is famously said to “wag the dog” when the less important element subordinates the greater. This, alas, is business as usual where the incremental advances in nutrition as a science and clinical discipline encounter the pacing of pop culture fascination. The burden falls on the enlightened clinician to perceive the greater truths past the clutter of lesser pretenders; to renounce the often dogmatic assertions made in the service of fads, fashions, and rogue theories; and to disabuse patients of their beliefs in scapegoats, silver bullets, false promises, and magical formulas.

The modern era of nutrition guidance has propagated a focus on nutrient details to the relative exclusion of foods, and the overall dietary pattern. Michael Pollan has aptly characterized this preoccupation as “nutritionism” (1) and attributed much of what bedevils modern nutritional epidemiology to the tendency. To the extent that nutritionism does not fully account for prevailing dietary woes, the law of unintended consequences may explain the remainder (2). Nutrient-focused recommendations have created almost limitless opportunities for food industry elements to accentuate some particular positive part, with relative inattention to the whole.

We may thus hypothesize that the combination of nutritionism and opportunistic exploitation of it has done much to divert and forestall progress in public health nutrition (3). If that hypothesis is correct, many constituencies are complicit in the impasse, including clinicians.

Beginning with nutritional epidemiology, the modern era may be said to have begun with the work of Ancel Keys and the association of specific dietary patterns in developed and affluent countries, rich in animal foods, with cardiovascular disease (4). The era of nutritionism may be said to have begun then as well, as observations that were principally about overall dietary pattern and overall health pattern devolved into assertions about specific nutrients, specific chronic disease risk factors, and specific health outcomes—in this case, the implication of saturated fat and dietary cholesterol in dyslipidemia and the propagation of coronary atherosclerosis (see Chapter 7). The era of preoccupation with “low fat” eating ensued, though this was never the intent of Keys, nor the implication of his work (5,6).

The complexities, subtleties, validities, and fallacies of blaming atherosclerosis on saturated fat and/or dietary cholesterol are addressed at greater length in Chapter 7. Here, it suffices to note that dietary cholesterol appears to exert a generally weak influence on serum cholesterol levels and cardiovascular risk for those with typical, modern diets (the relative effect may be greater in those with more salutary diets at baseline); and saturated fat represents a whole class of nutrients with varying effects (see Chapters 2 and 7). Neglected in the initial focus on the daily dose of these nutrients was that they varied in accord with the overall dietary pattern. Of necessity, a diet deriving a greater proportion of its energy from foods rich in saturated fat and cholesterol—meat and processed meat, dairy and processed dairy in particular—was deriving less from plant foods intrinsically low in these constituents (7). The health effects of lowering saturated fat intake vary, as sense would anticipate, with the particulars of its replacement (8).

Even so, the advice that evolved (or devolved) from the work of Keys and others—to restrict dietary

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fat intake—may have led to improvements in health if it had been translated to mean: eat more foods naturally low in fat. That, in turn, could have led to higher intake of vegetables, fruits, beans, and lentils—prominent elements in many of the diets most decisively associated with good overall health (3) (see Chapter 45). Instead, the food industry took advantage of a "just cut fat" fixation by devising what is now a fixture in the food supply: low-fat processed (and ultra-processed) (9) foods, or as it is colloquially known: junk. Naturally, there was never any evidence that eating more low-fat cookies was going to promote health, nor did it do so.

The evolving historical perspective now tends toward an indictment of the "low fat" hypothesis, and era. But, in fact, naturally low-fat, plant-rich diets are among the contenders for best diet laurels (3) (see Chapter 45). The misstep was, as noted above, the conflation of a part of the diet (and, indeed, parts of foods) for the whole, and food industry opportunism translating dietary guidance into unanticipated products.

This action in which researchers, epidemiologists, clinicians, policy-makers, food manufacturers, and the public were all complicit induced (10,11), with Newtonian inevitability, a harsh reaction born of frustration and disgust as epidemics of obesity and chronic disease worsened rather than improved (see Chapters 5 and 6). If advice to reduce dietary fat had been so wrong, clearly the wrong nutrient class had been targeted. So it was society moved on to its next scapegoat: carbohydrate.

This topic, too, is addressed at considerable length elsewhere in these pages (see Chapters 1, 5, and 6) and need not be belabored here. Suffice to say that foods as diverse as lentils and lollipops are carbohydrate sources, and the notion that all such foods could constructively meet with summary judgment was nonsensical from the start. But as with the low-fat dogma, "low-carb" admonishments had some potential to do good if they directed people away from starchy, sugary foods to wholesome foods relatively richer in protein and/or fat. Such a diet might have replaced bread and pastries with fish, seafood, nuts, seeds, avocado, and so on.

Instead, the food industry once again saw the opportunity in societal preoccupation with a rubric and gave us low-carb pasta, low-carb bread, and low-carb brownies. As before with low-fat junk foods, there had never been a shred of evidence that consumption of more low-carb brownies would lead to health improvements. Whatever the flaws in the guidance, they were much compounded by misguided and unintended applications.

An adage famously asserts that failure to learn from the follies of history results in their repetition. This is ominously pertinent to modern public health nutrition, as is the Newtonian link between action and reaction. Combine the two, and a formula ensues for the cyclical repetition of follies—costly for the many, lucrative for the few (10)—in opposing directions.

Even as the effects of low-fat and low-carb preoccupation linger, inviting some degree of vitriol among competing factions, and some loss of faith in so-called nutrition "experts," the tendency to seek isolated dietary scapegoats or silver bullets persists. Among the recent entries in this category are fructose, gluten, and lectins.

Without question, an excess of added sugar is among the salient liabilities of the modern diet. But this is a case of the dose making the poison. Fructose, per se, is almost never a stand-alone ingredient in processed food. Alone, fructose is found almost exclusively in fruit, and fruit juices (see Chapter 1). Overall, the weight of evidence supports fruit (but not juice) consumption even for the control of weight and prevention of diabetes (12), the particular harms of which fructose is accused. Thus, advice to restrict fructose intake, per se, is immediately encumbered by the need to clarify that the principal source of pure fructose in the diet be excluded. Whatever the particular ill effects of fructose, under real-world conditions it is configured into a prevailing excess of overall added sugar consumption that is clearly

injurious (13).

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Even as the fructose hypothesis has maintained a large following (14), competing contentions have done the same. Whereas concerns about the rising prevalence of gluten enteropathy and lesser forms of gluten sensitivity (see Chapters 18 and 24) are entirely legitimate, claims that the entire population should avoid wheat (15) are not. Evidence suggests that haphazard efforts to avoid gluten, or wheat, can reduce overall diet quality (16). Even so, the idea that gluten and/or wheat is "the" thing wrong with modern diets has captured the public's imagination.

Going a step further, another best-selling book argued that all grains are essentially toxic (17) despite their prominence in traditional diets associated with both exceptional longevity and vitality (18). Advice to avoid wheat or grains competes with long-standing advice to avoid animal products (19), which in some cases ascribes virtually all of the ills of modern epidemiology to that cause. Noteworthy is that each of these arguments is built on a selective sampling of the relevant literature, with each ignoring the evidence on which the claims of the others depend. Consequently, equally compelling, evidence-based indictments are built against wheat and meat, gluten, and fructose—and most recently lectins (20). The systematic avoidance of lectins would banish from one's diet many of the foods most robustly associated with every kind of desirable outcome pertaining to health, as well as sustainability (21). The problem for each of these contentions, adamantly made by leading proponents, is that if any of the competing theories is right about "one cause" of dietary ills, all of the others are wrong, and thus millions of adherents have been perilously misled.

The almost inevitable truth is far more probable: The legitimate among such theories each tells a partial but incomplete and generally exaggerated truth, while the illegitimate tell lies, intentional or otherwise (10). The expanse and diversity of the nutrition literature are such that studies can almost invariably be found to substantiate an a priori hypothesis. The fact that such arguments readily substantiate mutually exclusive claims to truth, however, reveals their inherent inadequacies. A theory is robust not when carefully selected studies support it, but when the unselected weight of evidence tips in its favor.

Commenting on the challenges of natural selection and environmental adaptation, evolutionary biologist Richard Dawkins noted there are many more ways to be dead than alive (22). The statement indicates that most genetic mutations are useless or harmful, and only the rare among them confer a survival advantage (of timely relevance to the proliferation of novel strains during the COVID-19 pandemic) (23). Similar thinking may be extended to public health nutrition: There are many more ways to eat badly than well. A low-fat diet may be composed of highly nutritious plant foods, or exclusively of cotton candy. A low-carb diet may be rich in salmon and walnuts, or bologna and ultra-processed brownies.

The perpetuation of efforts to identify a single dietary scapegoat or silver bullet represents a form of collusion. A public, frustrated with failed attempts to lose weight and find health in a society that profits mightily from frustrating just such attempts (10,24), has subordinated common sense applied to other areas, such as money management or the education of children, to gullibility and the perennial hope for a magical quick fix.

Publishers and producers exploit this combination of hope and gullibility to profit from a seemingly endless parade of books and products (10). Clinicians have long contributed to the confusion, both as the expert sources behind competing claims and by offering dietary counseling subject to the "one nutrient at a time fallacy" (25,26). Dietary advice specific to medical specialty, health outcome, or organ system has long prevailed. Mainstream cardiologists have warned for years about the perils of atherogenic fats, even as diabetologists focused preferentially on sugar and glycemic load.

A view from no great altitude reveals the obvious fallacy of any such construct. People with diabetes are at particular risk for cardiovascular disease; should they then adhere to dietary guidance related to

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their diabetes or competing guidance to safeguard their coronaries? Similarly, cardiac patients generally have a constellation of risk factors, including inflammation, conducive to insulin resistance and type 2 diabetes; should they protect their hearts with a heart-healthy diet or by defending themselves against the advent of diabetes?

Equal clarity ensues from viewing the situation in reverse. Dietary patterns associated with low rates of one chronic disease at the population level are almost invariably associated with low rates of all major chronic diseases (see Chapter 45). Adhering to the basic theme of healthful eating (3) is supportive of good health in general, and consequently protective against all chronic diseases by suppressing the common pathogenic elements: inflammation, oxidation, glycation, etc. (3).

As for discord among "experts," it too is fomented by many confluent forces. A demand for silver bullets and scapegoats predictably engenders a supply. The ambitions of individuals and industry align (10) to propagate an unending parade of mutually exclusive propositions, conveying a degree of dissent that is illusory. In reality, when sensible questions are posed, a remarkable diversity of experts agree about the best science-based answers regarding the fundamentals of feeding *Homo sapiens* sustainably and well (27–29).

There is one final consideration with regard to dietary scapegoats and silver bullets. An isolated focus on the addition or exclusion of any given nutrient, nutrient category, or food is apt to be inattentive to a question the approach requires: If people exclude (or add) food "A," what food "B" will they add (or exclude) to compensate? A popular ad campaign suggests that the American population is fueled by the products of a national chain of donut shops (30); surely this was not the intended effect of advice to limit intake of eggs for breakfast. The "instead of what" question has always been integral to nutritional epidemiology done right, and as of late, has at last been getting some of the attention it warrants (31–33).

One might argue that literal decades of opportunity in public health nutrition have been squandered in a repetition of the seminal folly of modern nutritional epidemiology: facile, but ultimately fatuous, attempts to blame all of the challenges of eating well in the modern world on a single scapegoat. A focus on the overall nutritional quality of foods and the dietary pattern was, and remains, far more consistent with the weight of evidence, and far more conducive to public health objectives (34).

Readers of this text are encouraged to renounce the hunt for salvation or doom in any given nutrient or food, to adopt a more holistic view of nutrition, and to counsel patients accordingly. The general dietary theme conducive to human health—balanced, plant-predominant assemblies of wholesome, minimally processed foods—will not change with fads, fashions, or the preoccupations of a given news cycle. When alternative answers are proposed, it is advisable to question not the established weight of evidence, but the question—along with the motivations attached to it.

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Chapter 50

Should Obesity Be Considered a “Disease”?

David L. Katz

When the prior edition of this book was published in 2014, the American Medical Association (AMA) had only recently declared obesity a “disease” in 2013 (1). That step was ostensibly intended to lend the condition medical legitimacy and encourage greater attention to it by clinicians, physicians in particular. While the designation facilitated new reimbursement mechanisms (2), attention to obesity remains much neglected in clinical practice, for many reasons. Among these, no doubt, is a sense of clinical futility while striving to “fix” what modern culture is devoted to “breaking” for profit (3,4).

Novel at the time, that concept has settled into the conventions of modern medicine since. Now as then, however, there are reasons to explore the implications of that designation and consider its liabilities, as well as intended benefits (5).

The basis for an effort directed at the legitimatization of obesity as a medical condition much like diabetes, hypertension, or dyslipidemia is clear and compelling. There have long been significant barriers to weight management counseling by physicians (6). The historical approach to obesity by physicians (and perhaps other clinicians, albeit to a lesser extent) has been either to ignore the problem entirely for want of comfort addressing it or to wag an admonishing finger. The latter approach has the distinct disadvantage of assaulting a patient’s potentially fragile self-esteem and, to borrow an expression from the vernacular, making them feel “about an inch tall” (see Chapters 46 and 47). If clinical counseling reduces height (albeit figuratively) but not weight, the effect on body mass index is counter-productive, to say the least.

Compounding such challenges to counseling that is both constructive and compassionate is the problem of obesity bias, long noted to be prevalent in society at large and identified as a tendency among health professionals as well (7,8), including even those specializing in obesity treatment (9). While in some cases the admonishing wag of a finger may merely imply lack of competency, in other cases it may truly indicate the harsh judgment of a clinician “blaming” the victim based on preconceived notions about the causes of obesity (10).

To the extent that the AMA position was directed at rectifying such past transgressions, and encouraging both more attention to obesity by clinicians and the acquisition of competencies to confront obesity compassionately and effectively, the measure was a welcome advance. Obesity as disease is preferable to obesity as character flaw.

However, obesity as disease carries enormous potential liabilities (11). First among these is that with the great power to assert by fiat that obesity resides in the medical domain comes the great responsibility to fix it. Clinicians are obligated to shoulder a far greater share of the burden if obesity is medicalized than is implied by the call for multidisciplinary action by such sources as the Institute of Medicine (12). Obesity was rare before culture chose to propagate it for profit (4). There is no evidence from anywhere at any time that high-quality clinical counseling is a sufficient countermeasure to alter obesity trends at the population level when the prevailing winds of culture blow the other way.

Second is the implied course of therapeutic action. If obesity is a disease, the standard approaches to

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disease presumably constitute the remedy, namely drugs and procedures. While there are U.S. Food and Drug Administration (FDA)-approved drugs for obesity treatment (see Chapter 5), and some recent advances in that area (13), they have been controversial with regard to both safety and efficacy. The history of pharmacotherapy for weight control has been singularly unencouraging to date. Bariatric surgery is effective but comes with the human and monetary costs of operations, and with uncertainty about long-term effectiveness in the absence of robust, ancillary lifestyle coaching (see Chapter 5). Given the prevalence of obesity, if either drugs or surgery are the principal response, the capacity of our society to bear the economic burden of it is questionable at best.

Third, and most important, is the fact that the widespread acceptance of obesity as a disease may invite nonclinical entities to renounce their role in combating it. A medical problem with clinical solutions absolves the food industry, advertising, schools, businesses, and policy makers of any substantive commitment to remedial action (4). The AMA position invites our society, at least tacitly, to wait for the disease of obesity to manifest and then let clinicians treat it as clinicians are wont to do.

The AMA position may thus derive partly from medical hubris (i.e., physicians can fix this), partly from the proverbial tendency to see nails when you hold a hammer, and partly from a failure to consider the breadth of medically legitimate conditions. Not all medically legitimate conditions are diseases. There are, of course, injuries and toxic exposures, and, perhaps most relevant of all, there is drowning.

Obesity as disease implies that the human body that gets fat is malfunctioning somehow; maladaptive responses are intrinsic to the definition of “disease.” But, in fact, a human body that converts a surplus of food energy into a storage depot is functioning normally. The abnormality derives from an unending surplus of food energy so that the storage depot, once made, is only grown rather than being metabolized and replenished intermittently. The fault, to paraphrase the Bard (14), lies not in our selves, but on our shelves, perennially stocked with hyperpalatable junk (3,15).

Without question, diseases can result from obesity; indeed, obesity is on the causal pathway to all prevalent chronic diseases that plague modern societies (see Chapter 5). But equally clear is that “fatness” can occur in the absence of significant metabolic derangement or overt morbidity. If obesity is a disease, then everyone with a body mass index above 30, however well they may feel, and however normal their metabolic profile, is accordingly “diseased” (16).

Drowning is a medically legitimate condition. Clinicians who deal in medical emergencies and intensive care must know how to treat it, and insurers are obligated to cover the costs of related care. However, drowning is not misconstrued for disease because it is self-evident that even the healthiest of human bodies is subject to drowning if under water for too long. Drowning denotes the harms of an interaction between a normal human body and an environment to which it lacks adequate adaptations.

The case might be made that the description exactly suits epidemic obesity. Normal human bodies gain weight as body fat in the context of constant food energy surplus. The obesigenic modern environment provides exactly that. Obesity may result from “drowning” in a constant surplus of willfully irresistible calories (see Chapters 5 and 49) and labor-saving technology because *Homo sapiens* has no native defenses against caloric excess or the lure of the couch. If the analogy is apt and extended to its limits, it suggests that the hunt for effective pharmacotherapy for weight control may be as likely to succeed as the effort to devise a pill to prevent drowning.

This, in turn, leads to considerations of how our culture does address the peril of drowning. The emphasis is overwhelmingly societal and preventive, rather than medical and therapeutic. Doctors treat drowning when it occurs, but other elements in our society take steps to ensure that drowning occurs as rarely as possible.

There are laws regarding drinking and boating; public beaches provide lifeguards; pools are invariably

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fenced; parents all know to be vigilant when their children are near water; and swimming lessons are encouraged and widely available. There are analogies to each of these in the realm of obesity control, from regulating food marketing, to ensuring access to wholesome foods and opportunities for physical activity, to imparting routinely the requisite skill set for selecting nutritious foods and fitting fitness into daily routines (5,17,18). The gravest danger in the AMA declaration was, and remains, that it might dissuade our society from such comprehensive approaches to obesity prevention.

Obesity need not be a disease to be medically legitimate. Weight management counseling should be well informed, compassionate, and constructive (see Chapters 46 and 47). However, the problem of obesity is culture wide (19); modern society is drowning in it. Clinicians are a part of the solution or—either by admonishing or abdicating—a part of the problem. However, an effort by the medical community to claim the whole problem and provide the whole solution misconstrues obesity as a by-product of pathophysiology. Obesity ensues from normal human physiology in an obesigenic environment for which it lacks adaptations. Culture-wide remedies directed at that interface undoubtedly constitute the most promising and cost-effective approach to this, as to any, form of drowning.

RECOMMENDED READINGS

For more real-time commentary by the author on topics in nutrition and preventive medicine, see LinkedIn: https://www.linkedin.com/in/david-l-katz-md-mph-facpm-facp-faclm-4798667/detail/recent-activity

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Chapter 51

Nutrition: What We Know, and How We Know It

David L. Katz

Consider this: every wild species on the planet knows what to feed itself. There is, so far as we know, no debate, doubt, diatribe, or confusion in the mix. When it is time to eat, all wild creatures know what food to seek.

Certainly, along with times of plenty, many animals experience times of want—but this is never for want of clarity. No wild creature is lost and confused about what or how to eat—they may simply, episodically lack the opportunity.

What is the basis for this widespread knowledge? Partly, it is a matter of instinct and adaptation, the endowments of evolution. Partly it is a lack of vending machine access and the lure of hyper-palatable Frankenfoods (1). Largely, it is rearing, experience, and habituation—the quintessential model of the venerable "see one, eat one, teach one" method.

Somehow, all creatures, great and small, have perfect clarity about what and how to eat, with no recourse to randomized controlled trial (RCT) and meta-analyses. One presumes that our own species once had a place at this same table of understanding. Does it make sense that we knew how to feed ourselves before inventing randomization, contriving double-blinding, or conceiving of placebos, but can no longer figure it out now that these are at our disposal? Does it make any sense that we knew perfectly well how to eat before we had science, and are bogged down in doubt and dissent now that we do?

No, it makes no sense—and sense is of the essence. Sense is every bit as crucial to what humans know, and how we know it, as is science (2).

To be clear, this is no disparagement of science. This text—the hundreds of pages preceding these—is a veritable monument to the aggregation of scientific insights across a vigorous expanse of hybrid methods. Science is the greatest means ever devised to probe the abstruse, find the elusive, reach the distant, reveal the hidden, and validate or refute our intuitive trust.

But if science drives toward hidden answers with the force of a freight train, it does so on the tracks laid by sense. Science is the train that leads to answers; sense is the track that guides toward meaningful questions. They are, ineluctably, symbiotic.

Most of what we know that matters most to our routine function owes nothing to science, let alone some particular method in its service. We need science to know *why* objects fall when tossed in the air, but we need only observation to know *that* they do. At some level of unfailing consistency, correlation is, in fact, causation (3). We know that water is better than gasoline for dousing campfires, never having read the definitive systematic review on the topic. We know it is ill-advised for our children to run with scissors and prudent to look both ways before crossing a busy street.

Much of what we know about feeding ourselves well is of just such pedigree. The job of science here is to append to what sense had already taught us reliably. The job of science is to answer new and more difficult questions, not cause us to question the clear, reliable answers that we already had; the answers that guide the sustenance, survival, and successes of every species on the planet—including our own.

There is a potential tyranny in science, a despotism that denies the rightful role of sense. In medicine

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generally, and nutrition specifically (4), that despotism narrows its focus to champion specific methods of inquiry as the "one true way" to know. Valuable as they are, however, the RCT and meta-analysis are not a universal remedy for the plight of ignorance, any more than a hammer is the universal tool of construction. A hammer makes an excellent hammer, a very poor saw, and a dreadful lathe. The tool must suit the job, and so too the tools of inquiry (5). Sometimes, sense alone will suffice—just as unaided hands can manage some types of construction. Sometimes, the tools of science are required, but there are many, and all have their contributions to make (5).

We do not know exactly what some specific amount at a particular frequency of a particular food, nutrient, or ingredient will unfailingly do to health—because such effects will vary with the baseline diet, other aspects of health, variations in metabolism, and more. We can nonetheless know reliably that foods, ingredients, and nutrients that amplify existing imbalances will be prone to harm, while those that remediate such imbalances will tend to confer benefit (6).

We do not know that some specific, prescriptive, proprietary diet is better than any other for human health or weight control, and cannot hope to know that either. The studies to prove that any given dietary pattern is superior to others for the outcomes that matter most—longevity and overall vitality—would require massive samples and a timeline in numerous decades—essentially, a human lifetime. Such trials are implausible for many reasons.

Despite this lack of knowledge about every particular, we can still know the fundamentals of feeding *Homo sapiens* well, predicated on a bounty of both science and experiential sense (7). Again, the preceding pages are the only testimony required to defend that contention.

There is, however, one more crucial consideration: the reverberations of our dietary choices beyond the bounds of our own skin. This book concludes in the next chapter with commentary on that topic, arguably the signature issue of our time (see Chapter 52).

The gravest nutritional threat to human health is not a given variety of added sugar; not animal protein; not some particular source of saturated fat. The gravest threat is misinformation in the place of reliable information; confusion where confidence ought to prevail.

If obesity may be likened to drowning (see Chapter 50), then the effects of perennial misinformation may be likened to treading water—a tremendous expenditure in time and effort to remain in much the same place (8). Diet quality has been poor for decades in the United States, with nearly negligible improvement despite all that has been learned over that interval (9). There is more than one way to eat badly, and the net effect of copious misinformation is that Americans seem doomed to buy, and try, them all (7).

Acknowledging what we know about feeding our own species well, how we know it, and how reliably, by means of sense, science, and global expert consensus (10,11) is not commensurate with getting there from here (12)—but it is prerequisite. Our progress begins by embracing the contention that we do, indeed, know where "there" is. Progress toward it cannot begin too soon.

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Chapter 52

The Planet Is Your Patient

David L. Katz

In 2021, as I write this, in any subsequent year that finds you reading it, and for that matter, for some number of years before this, too, one can no longer legitimately claim to be a "health" professional if not advocating frequently, and fiercely, for the health of the planet. Stated simply, there are no healthy people on a blighted planet no longer hospitable to the human animal. The planet is your patient; you should practice accordingly.

There is a specific motivation for this concluding exhortation beyond the obvious, the obvious being that our planet is desperately imperiled by our collective actions, our prevailing dietary patterns among them (1). That motivation is an amalgam of license, and relief.

On some number of occasions, before the COVID pandemic put actual podiums out of reach, I was privileged to address a sizable audience of fellow clinicians, and then meet many of them afterward, one on one, at a book signing or reception.

Those brief meetings routinely followed a talk in which I made the very assertion above, accompanied by some flourish of impassioned gesticulations: "*You cannot truly be a 'health' professional anymore if you do not promote and protect by every means at your disposal the health of the planet! Yes, you are indeed authorized to address it with your patients; we are duty bound to do so*." Or something along those lines.

That is the "license" piece of the amalgam. I took it upon myself, presumptuously perhaps, to authorize my fellow clinicians to consider planetary health a clinical obligation because I deemed, and deem, it so. I exhorted them to take on the great public health imperative of nutrition in clinical practice in that crucial context.

And they lined up to thank me; therein lies the "relief." More times than I can recall, colleagues in that queue or gathering shook my hand (another bit of pre-pandemic nostalgia!) and thanked me for providing them the "license" to address what (1) mattered enormously to them and kept them up at night worrying and (2) always felt to them like something outside their professional purview. By contending otherwise, I inadvertently took down a wall between personal exasperation and professional expression, and the relief rendered was something like the release of a pressure valve. Clinicians—educated, informed, aware, and alarmed—could, at last, do something other than stew in anxious insomnia over the fate of our shared home. They could raise the same awareness among their patients and offer guidance in the one area where we individuals might make a meaningful difference independent of government and industry: our daily food choices.

And so can you, and so you should. In this brief culmination, I presume to offer you what I offered those prior audiences: the opportunity, and the obligation, to advise your patients to eat as if the world depends on it. Quite simply, it does (2)—and that is the signature health issue of our time.

For the most part, this is a relatively easy task for readers of this text. You are presumably, by self-selection, in a group more inclined than your recent predecessors to acknowledge and address the salience of nutrition in human health. The exhortation to factor the planet into those exchanges would

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complicate matters were the exigencies of human and planetary health discordant. Fortuitously, as detailed by the seminal EAT-Lancet Commission on Food, Planet, Health (2)—among others—the needs of people and planet for a shared vitality are highly if not entirely confluent. Both are massively favored by…food, not too much, mostly plants (3).

This need not have been so. The planet, the climate, and biodiversity might all benefit from less energy-intensive and resource-intensive processing of food and from less reliance on animal foods (4)—while humans did not. However, we humans benefit as well and mightily from drinking water rather than soda, and thus avoiding enormous costs in water waste (5); from eating more beans and vastly less beef (6); from eating foods direct from nature, rather than foods whose nature is psychedelically inscrutable through many layers of ultraprocessing (7,8).

Dietary patterns for human and planetary benefit are gratifyingly confluent (9). That is true even when examining the independent influences of dietary intake on key aspects of human health, notably longevity and lasting vitality, and on the planet in terms of soil integrity, water purity, air quality, climate stability, the security of biodiversity, the preservation of wild places and diverse ecosystems, and the sustainable capacity of planetary resources to feed us all. However, this independence is an illusion, and lifting the veil that shrouds it should suffice to persuade any reticent among you that your opportunity to address planetary health in clinical practice is an obligation as well.

Much has been written on the ineluctable, direct links between planetary and human health (10). The COVID pandemic will no doubt inspire much more on the topic, given the associations among trade in wildlife, ecosystem incursions, and emerging infections (11). Virtually all great plagues in human history, SARS-CoV-2 ostensibly among them, are zoonotic in origin. The ramifications extend well beyond infectious disease, however, to respiratory disease, cardiometabolic disease, and mental illness. Planetary health is not just important to human health because we need a place to live; degradations of planetary health are direct assaults on human health on a massive scale even as the Earth still sustains us. This case is made expertly and thoroughly by Myers and Frumkin in *Planetary Health: Protecting Nature to Protect Ourselves*, and I commend it to you accordingly (12).

The congruent requirements of human and planetary health reverberate through the topic of nutrition and find expression throughout the preceding chapters. While the direct human health effects of highly processed “meat alternatives” remain subject to debate (13), the planetary benefits are clear (14), and thus such products are boon not bane, and all the more so if they serve as “gateway foods” to actual plants in their more native state. The diverse, prevailing arguments for animal-food-centric diets, from Paleo to keto, are egregiously ill-timed and rather a non-sequitur at the scale of 8 billion hungry Homo sapiens. Any dietary pattern that conspires against planetary health conspires against human health. For the current human population to eat remotely as our Stone Age ancestors are thought to have done would require more than 15 times the surface area of Earth (15).

I won’t belabor more particulars here, as they abundantly populate the prior pages of this text. I will simply reiterate: If you are any kind of “health” professional, then the health of the planet is part of your professional purview, just as it is your personal business. Your devotion to nutrition in clinical practice should be bounded accordingly.

So I implore you, and in the most personal of terms. For I am among those lying awake at night, worrying over our abuses of this beautiful Earth. I am among those wondering what we will bequeath our children and grandchildren, as deserving of the wonders of a vital planet and the treasures of biodiversity and natural grandeur as ever we were. I am among those anxious that our every effort to advance the health of patients is futile if we do not fight to preserve and restore the health of our one, shared home.

Collectively, we are a great force for change. There is a basic confluence of dietary practices

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conducive to the health of people and planet alike, variations on a clear theme (16): real food, mostly plants. Pick one; do one; teach one; repeat—as if the world depends on it.

It does (17).

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Appendices and Resource Materials

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Nutrition Formulas of Clinical Interest

BIOLOGICAL VALUE OF PROTEIN

Biological value = Food N − (Fecal N + Urinary N)/(Food N − Fecal N), *where biological value of egg albumin is set at 100 as the reference standard.*[**]

PROTEIN CHEMICAL SCORE (TO MEASURE QUALITY)

Chemical score = (mg of limiting amino acid in 1 g of test protein/mg of amino acid in 1 g of reference protein) × 100, *where lysine, sulfur-containing amino acids, or tryptophan are generally the limiting amino acids.*

CREATININE HEIGHT INDEX AS A MEASURE OF SOMATIC PROTEIN STATUS

(mg urinary creatinine in 24 h in the study subject/mg urinary creatinine in 24 h by normal subject of same height and sex) × 100

ENERGY UNITS

1 kcal = 4.18 kJ

HAMWI EQUATION FOR IDEAL BODY WEIGHT

Men: 106 lb/5 ft + 6 lb/additional inch ± 10%

Women: 100 lb/5 ft + 5 lb/additional inch ± 10%

HARRIS –BENEDICT EQUATION FOR BASAL ENERGY EXPENDITURE

Men: BEE = [66 + (13.8 × W) + (5 × H) − (6.8 × A)] × SF

Women: BEE = [655 + (9.6 × W) + (1.8 × H) − (4.7 × A)] × SF

General: W × 30 kcal/kg/day × SF

BEE, basal energy expenditure; W, weight in kg; H, height in cm; A, age in years; SF = stress factor.

For weight gain of approximately 1 kg/week, an additional 100 kcal/day should be provided.

REPRESENTATIVE STRESS FACTORS

Alcoholism	0.9
Burn (<40%)	2.0–2.5
Cancer	1.10–1.45
Head trauma	1.35
Long-bone fracture	1.25–1.30
Mild starvation	0.85–1.0
Multiple trauma	1.30–1.55
Peritonitis	1.05–1.25
Severe infection	1.30–1.55
Uncomplicated postoperative recovery	1.00–1.05

NITROGEN BALANCE

B = I − (U + F + S)

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B, balance; I, intake; U, urine; F, feces; S, skin (desquamation)

Alternatively, nitrogen balance = (Ni/6.25) − Ne + 4

Ni = dietary protein intake in g/24 h, Ne = urinary urea nitrogen in g/24 h, 4 estimates nonurea nitrogen losses

PERCENT IDEAL BODY WEIGHT

Percent ideal body weight = (actual BW/ideal BW) × 100 BW, body weight

PERCENT USUAL BODY WEIGHT

Percent usual body weight = (actual BW/usual BW) × 100 BW, body weight

PROTEIN REQUIREMENT IN LACTATION

Additional protein required = [(750 mL × 0.011 g protein/mL)/0.70 efficiency] × 1.25 variance = 14.7 g/day

RESTING ENERGY EXPENDITURE BY OXIMETRY

Metabolic rate (kcal/h) = 3.9 × VO_2(L/h) + 1.1 × VCO_2(L/h), VO_2 = oxygen consumption, VCO_2 = carbon dioxide generation

UNITS OF MEASURE

1 oz = 28.4 g

1 lb = 454 g

1 kg = 2.2 lb

1 pint (16 oz) = 568 mL

1 liter = 1.76 pints = 0.88 quarts

mg = mmol/atomic weight

**A modernized definition of protein quality has been proposed that accounts for the health and environmental impacts of dietary protein sources.

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Growth and Body Weight Assessment Tables (Pages 752–760)

WHO GROWTH STANDARDS ARE RECOMMENDED FOR USE IN THE UNITED STATES FOR INFANTS AND CHILDREN 0 TO 2 YEARS OF AGE

The World Health Organization (WHO) released a new international growth standard statistical distribution in 2006, which describes the growth of children aged 0 to 59 months living in environments believed to support what WHO researchers view as optimal growth of children in six countries throughout the world, including the United States. The distribution shows how infants and young children grow under these conditions, rather than how they grow in environments that may not support optimal growth.

The CDC recommends that health care providers use the WHO growth charts to monitor growth for infants and children aged 0 to 2 years of age in the United States and use the CDC growth charts to monitor growth of children aged 2 years and older in the United States.

The CDC growth charts can be used continuously from ages 2 to 19. In contrast, the WHO growth charts only provide information on children up to 5 years of age. For children aged 2–5 years, the methods used to create the CDC growth charts and the WHO growth charts are similar (http://www.cdc.gov/growthcharts/who_charts.htm; accessed on 12/06/2020).

APPENDIX B1 BIRTH TO 24 MONTHS: BOYS WEIGHT-FOR-LENGTH PERCENTILES AND HEAD CIRCUMFERENCE-FOR-AGE PERCENTILES

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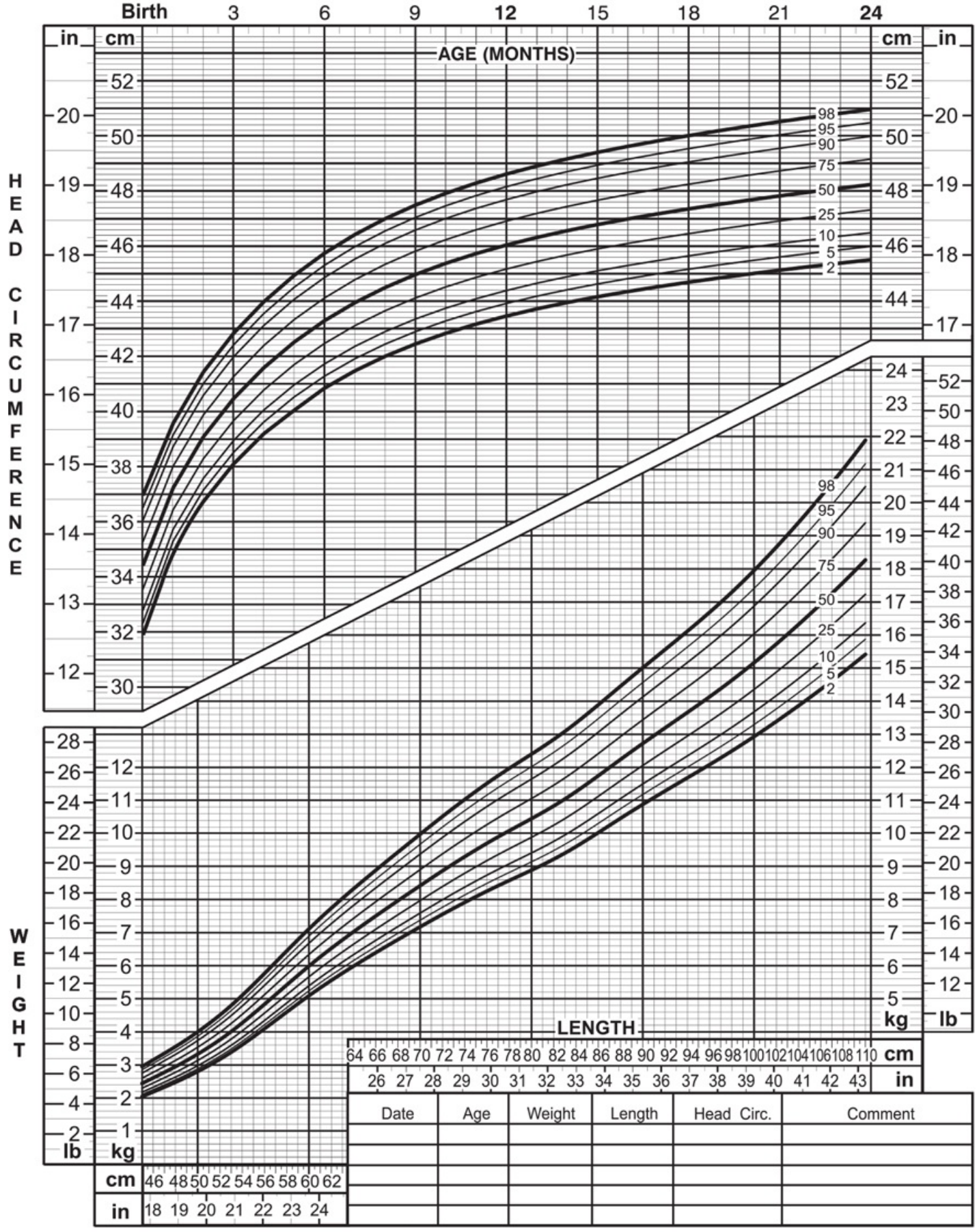
Birth to 24 months: Boys
Head circumference-for-age and Weight-for-length percentiles

NAME _____

RECORD # _____



Date	Age	Weight	Length	Head Circ.	Comment

Published by the Centers for Disease Control and Prevention, November 1, 2009
SOURCE: WHO Child Growth Standards (http://www.who.int/childgrowth/en)

https://nhathuocngocanh.com
Reprinted from https://www.cdc.gov/growthcharts/data/who/GrChrt_Boys_24HdCirc-L4W_rev90910.pdf

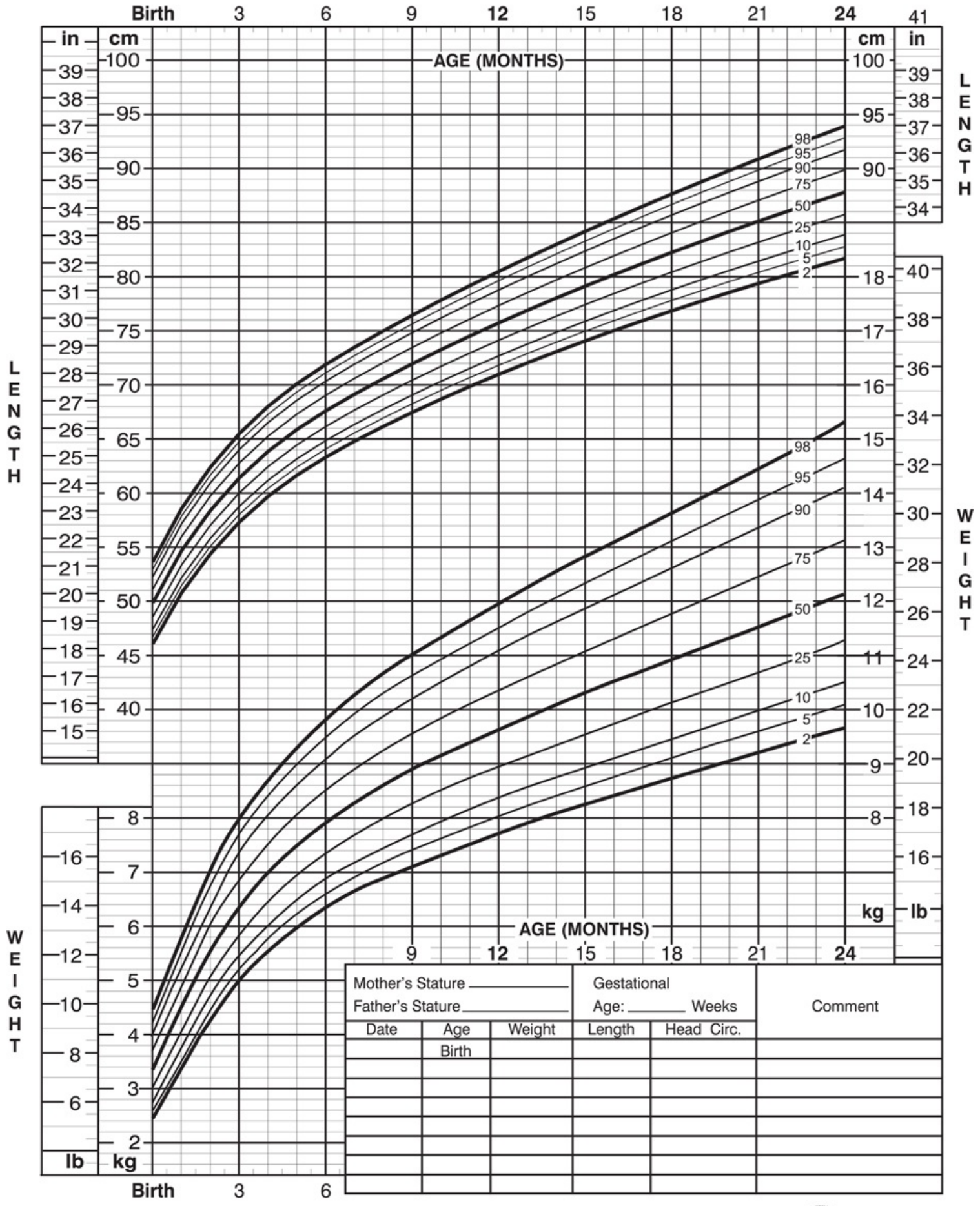
APPENDIX B2 BIRTH TO 24 MONTHS: BOYS LENGTH-FOR-AGE PERCENTILES AND WEIGHT-FOR-AGE PERCENTILES

https://nhathuocngocanh.com

Birth to 24 months: Boys
Length-for-age and Weight-for-age percentiles

NAME _____

RECORD # _____



Mother's Stature _____
Father's Stature _____

Gestational Age: _____ Weeks

Date	Age	Weight	Length	Head Circ.	Comment
	Birth				

Published by the Centers for Disease Control and Prevention, November 1, 2009
SOURCE: WHO Child Growth Standards (http://www.who.int/childgrowth/en)

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Reprinted from https://www.cdc.gov/growthcharts/data/who/GrChrt_Boys_24LW_100611.pdf

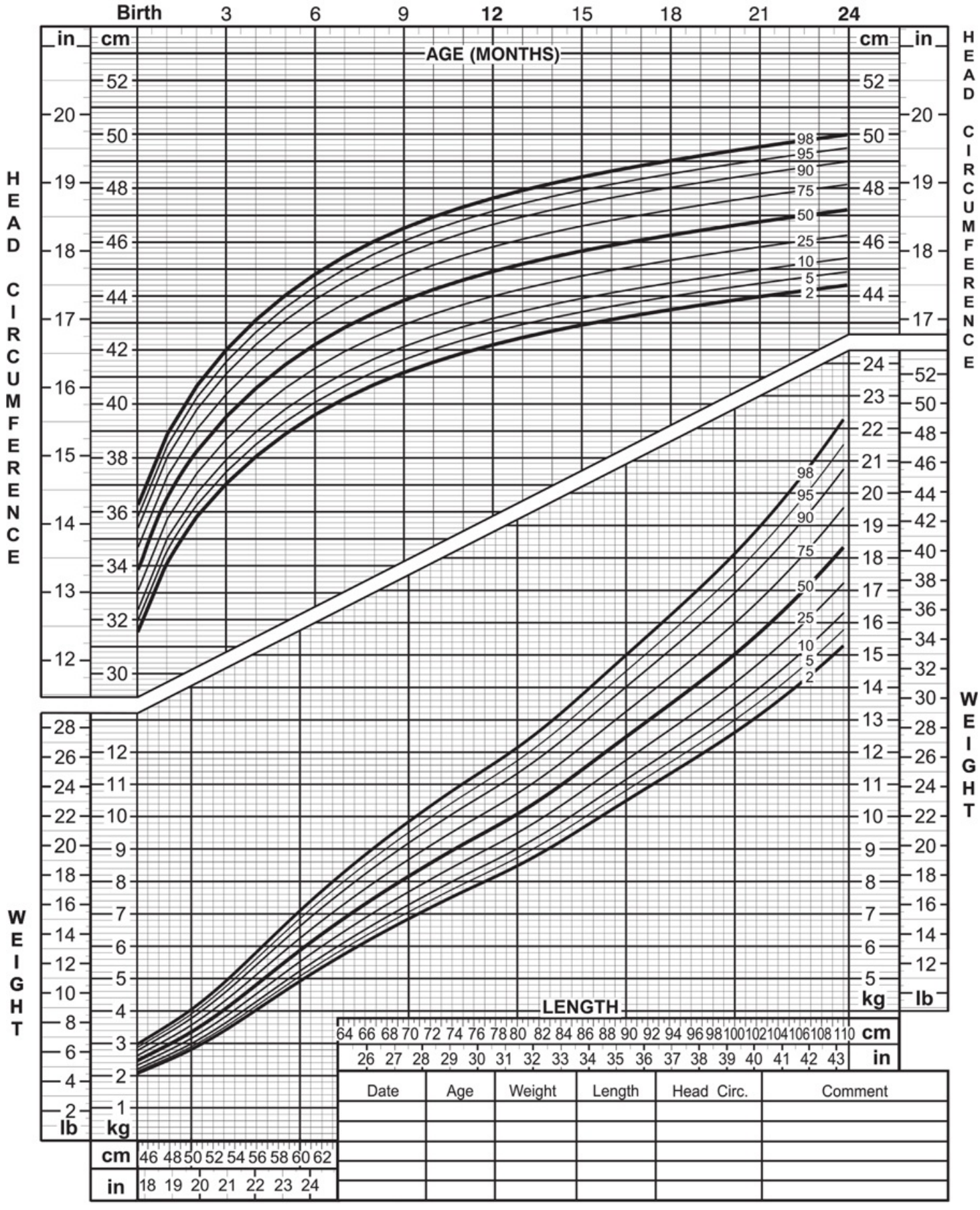
APPENDIX B3 BIRTH TO 24 MONTHS: GIRLS WEIGHT-FOR-LENGTH PERCENTILES AND HEAD CIRCUMFERENCE-FOR-AGE PERCENTILES

https://nhathuocngocanh.com

Birth to 24 months: Girls
Head circumference-for-age and Weight-for-length percentiles

NAME _____

RECORD # _____



Date	Age	Weight	Length	Head Circ.	Comment

Published by the Centers for Disease Control and Prevention, November 1, 2009
SOURCE: WHO Child Growth Standards (http://www.who.int/childgrowth/en)

https://nhathuocngocanh.com
Reprinted from https://www.cdc.gov/growthcharts/data/who/GrChrt_Girls_24HdCirc-L4W_9210.pdf

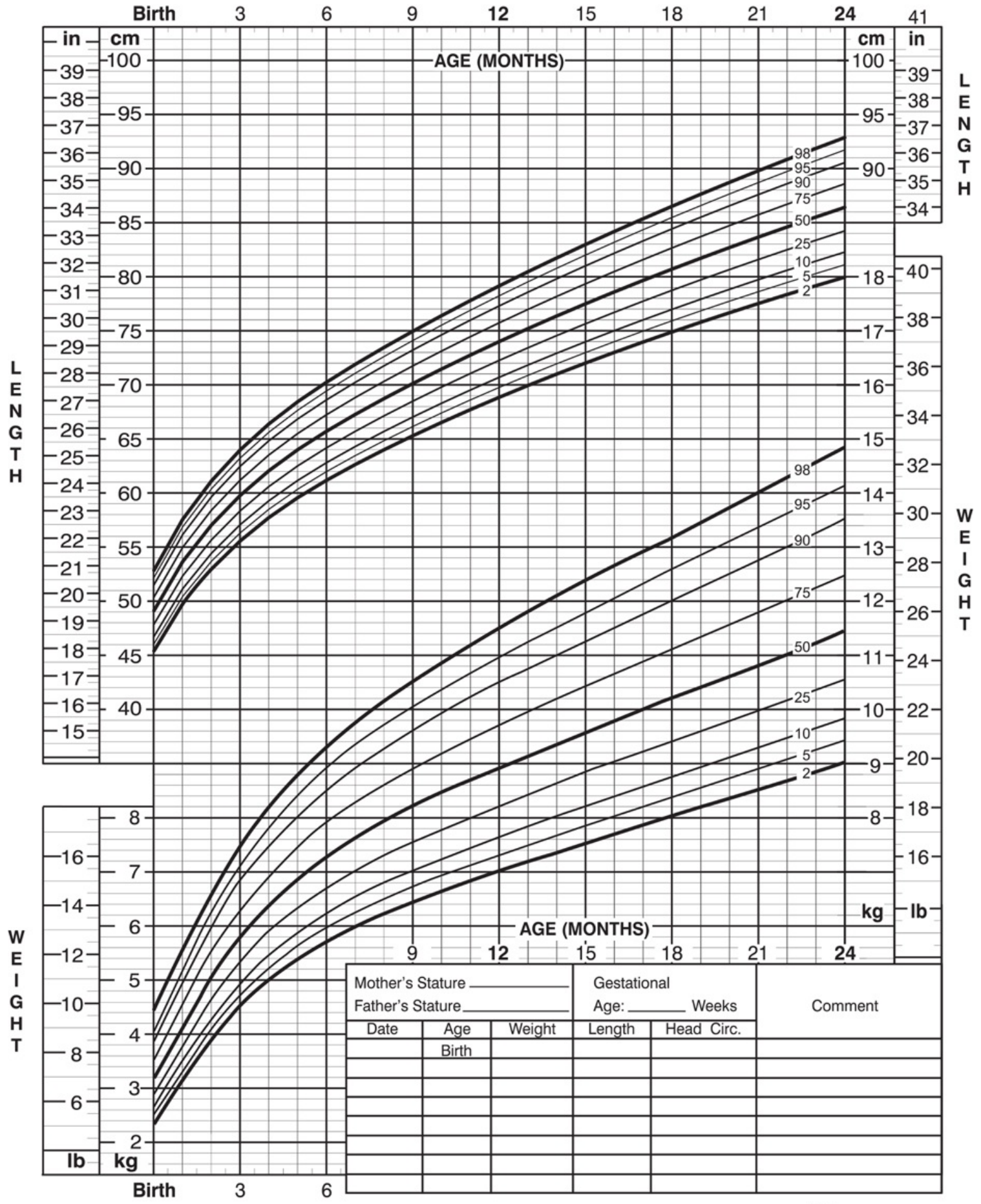
APPENDIX B4 BIRTH TO 24 MONTHS: GIRLS LENGTH-FOR-AGE PERCENTILES AND WEIGHT-FOR-AGE PERCENTILES

https://nhathuocngocanh.com

Birth to 24 months: Girls
Length-for-age and Weight-for-age percentiles

NAME _____

RECORD # _____



Mother's Stature _____ Father's Stature _____			Gestational Age: _____ Weeks		Comment
Date	Age	Weight	Length	Head Circ.	
	Birth				

Published by the Centers for Disease Control and Prevention, November 1, 2009
SOURCE: WHO Child Growth Standards (http://www.who.int/childgrowth/en)

https://nhathuocngocanh.com
Reprinted from https://www.cdc.gov/growthcharts/data/who/GrChrt_Girls_24LW_9210.pdf
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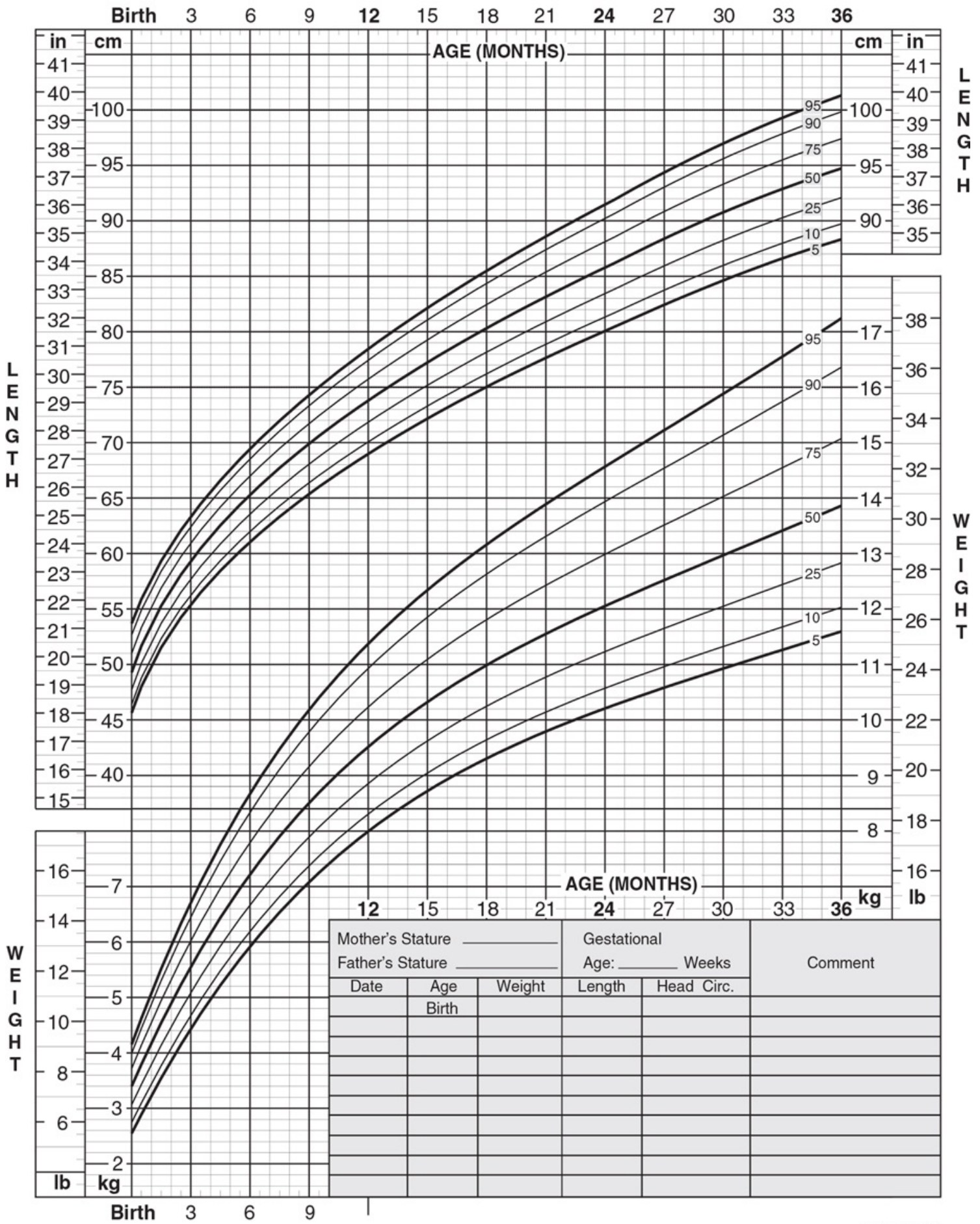
APPENDIX B5 GROWTH CHART, BIRTH TO 36 MONTHS, GIRLS

https://nhathuocngocanh.com

Birth to 36 months: Girls
Length-for-age and Weight-for-age percentiles

NAME _____

RECORD # _____



Published on May 30, 2000 (modified on April 20, 2001).

SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).

http://www.cdc.gov/growthcharts

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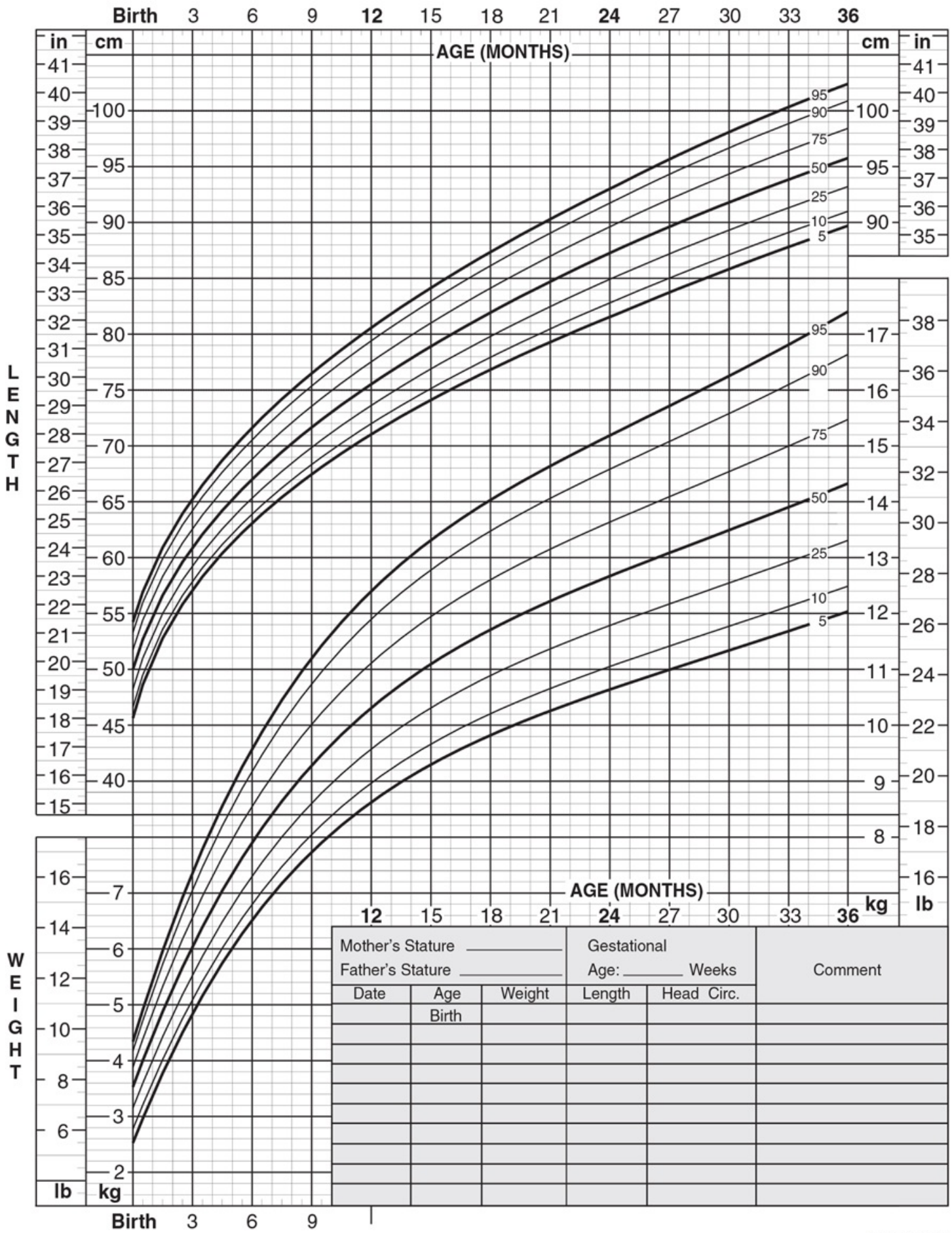
APPENDIX B6 GROWTH CHART, BIRTH TO 36 MONTHS, BOYS

https://nhathuocngocanh.com

Birth to 36 months: Girls
Length-for-age and Weight-for-age percentiles

NAME _____

RECORD # _____



Published on May 30, 2000 (modified on April 20, 2001).
SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
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APPENDIX B7 GROWTH CHART, 2 TO 20 YEARS, GIRLS

https://nhathuocngocanh.com

2 to 20 years: Girls
Stature-for-age and Weight-for-age percentiles

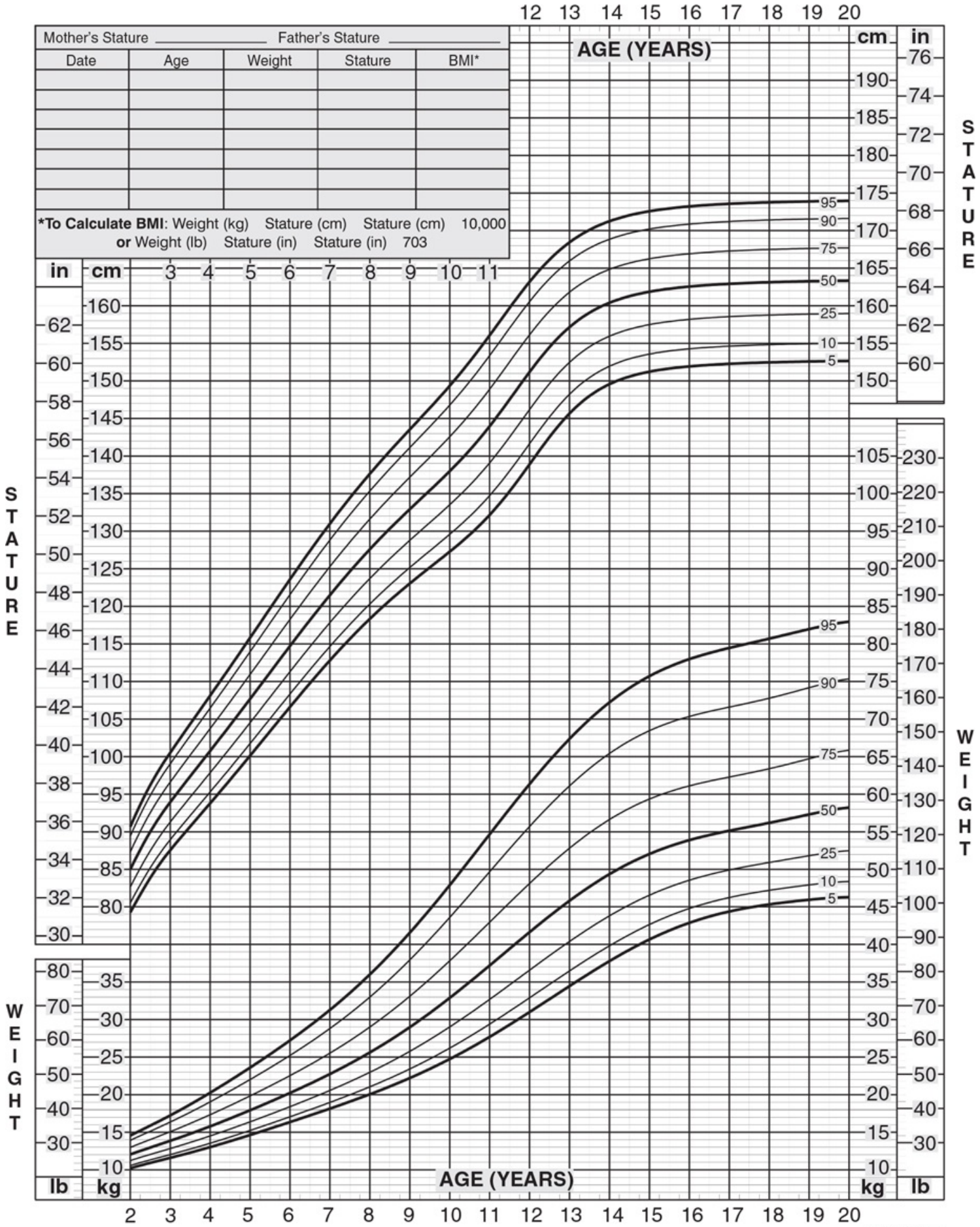
NAME _____

RECORD # _____

Mother's Stature _____ Father's Stature _____

Date	Age	Weight	Stature	BMI*

*To Calculate BMI: Weight (kg) / Stature (cm) / Stature (cm) × 10,000
or Weight (lb) / Stature (in) / Stature (in) × 703



Published on May 30, 2000 (modified on November 21, 2000).
SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
http://www.cdc.gov/growthcharts

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https://nhathuocngocanh.com
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APPENDIX B8 GROWTH CHART, 2 TO 20 YEARS, BOYS

https://nhathuocngocanh.com

2 to 20 years: Boys
Stature-for-age and Weight-for-age percentiles

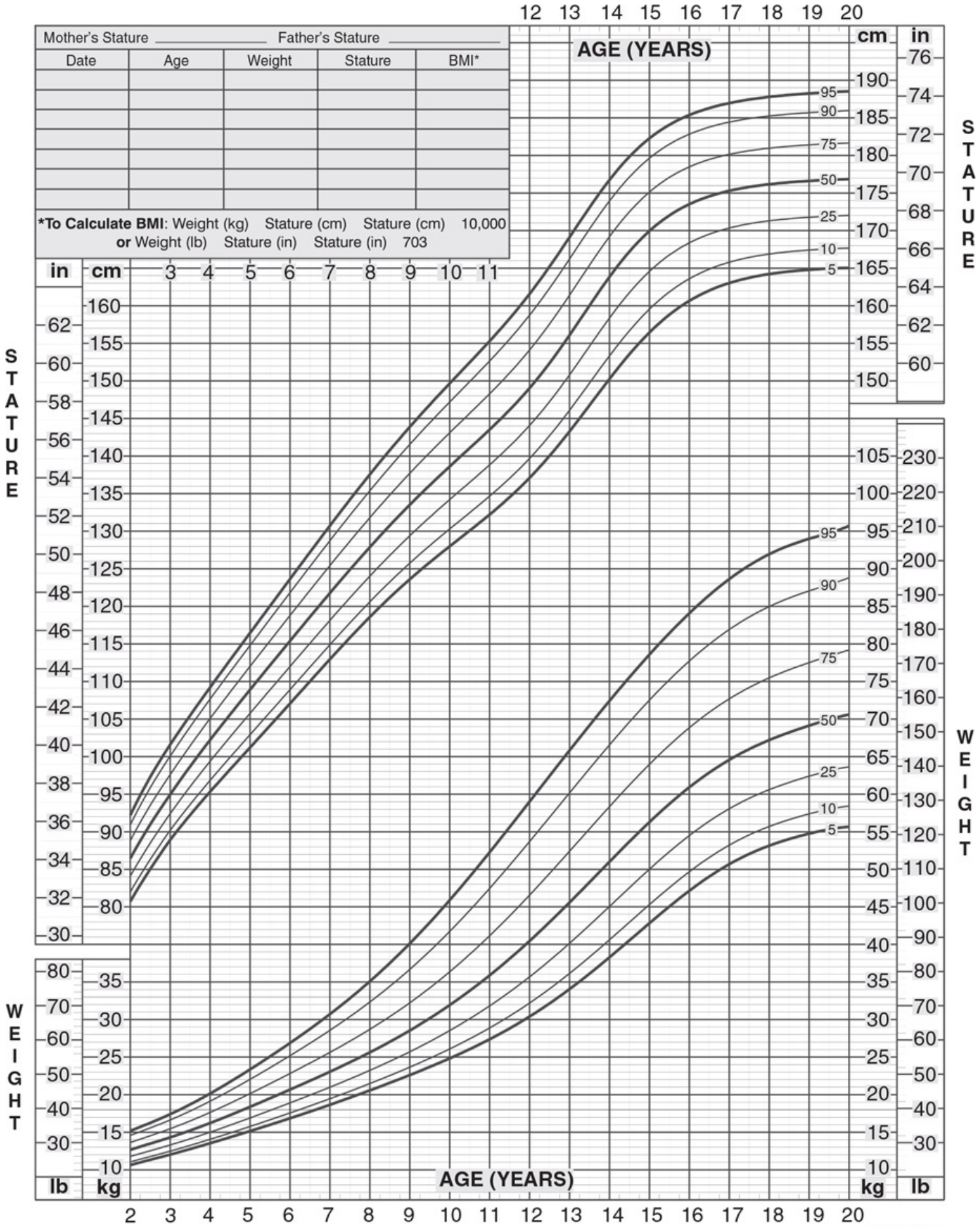
NAME _____

RECORD # _____

Mother's Stature _____ Father's Stature _____

Date	Age	Weight	Stature	BMI*

*To Calculate BMI: Weight (kg) / Stature (cm) / Stature (cm) × 10,000
or Weight (lb) / Stature (in) / Stature (in) × 703



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APPENDIX B9 BODY MASS INDEX NOMOGRAM: ADULTS

Weight in Pounds	HEIGHT IN FEET AND INCHES[a]									
	4′10″	5′	5′ 2	5′ 4″	5′ 6″	5′ 8″	5′ 10″	6′	6′ 2″	6′ 4″
	2	20	18	<18	<18	<18	<18	<18	<18	<18
110	23	21.5	20	19	<18	<18	<18	<18	<18	<18
120	**25**	23.5	22	21	19	18	<18	<18	<18	<18
130	27	25	24	22	21	20	19	<18	<18	<18
140	29	27	**26**	24	23	21	20	19	18	<18
150	**31**	29	27.5	**26**	24	23	22	20	19	18
160	33.5	31	29	27.5	**26**	24	23	22	20.5	19.5
170	**36**	33	**31**	29	27.5	**26**	24	23	22	21
180	38	35	33	**31**	29	27	**26**	24.5	23	22
190	**40**	37	**35**	33	**31**	29	27	**26**	24.5	23
200	>40	39	37	34	32	**30**	29	27	**26**	24
210	>40	41	38	**36**	34	32	**30**	28.5	27	**26**
220	>40	>40	**40**	38	**36**	33	32	**30**	28	27
230	>40	>40	>40	**40**	37	**35**	33	31	**30**	28
240	>40	>40	>40	>40	39	37	34.5	33	31	29
250	>40	>40	>40	>40	**40**	38	**36**	34	32	**30.5**
260	>40	>40	>40	>40	>40	**40**	37	**35**	33	32
270	>40	>40	>40	>40	>40	>40	39	37	**35**	33
280	>40	>40	>40	>40	>40	>40	**40**	38	36	34
290	>40	>40	>40	>40	>40	>40	>40	39	37	**35**
300	>40	>40	>40	>40	>40	>40	>40	41	39	37

Evidence suggests the implications of body mass index (BMI) vary by race/ethnicity with South Asian, Chinese, and Black subjects developing diabetes at a higher rate, at an earlier age, and at lower ranges of BMI than their White counterparts (1).
As such, more specific BMI cut-offs have been considered (2) and calculators have been developed for specific geographic populations: e.g., Asians and Asian Americans (*Asian American Diabetes Initiative—Joslin Diabetes Center*. Available at http://aadi.joslin.org/content/bmi-calculator; accessed on September 23, 2013) and South Asians (*South Asian BMI calculator*. Available at https://sites.google.com/site/southasianbmicalculator/; accessed on September 23, 2013).

[a]Height in feet and inches is shown across the top, and weight in pounds is shown in the left-hand column. Each entry in the table represents the body mass index (BMI) for a particular

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combination of height and weight. BMIs that represent the transition points from lean to overweight, from overweight to obese, and from one stage of obesity to the next are shown in bold. BMI values are close approximations due to rounding. BMI values in the recommended, or “healthiest,” range are shaded in gray. Note that if a patient is very slight, or very muscular, that person’s BMI might fall above or below the shaded area and still be consistent with excellent health.

REFERENCES

1. Chiu M, Austin PC, Manuel DG, Shah BR, Tu JV. Deriving ethnic-specific BMI cutoff points for assessing diabetes risk. *Diabetes Care*. 2011 Aug;34(8):1741–8.
2. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet*. 2004 Jan 10;363(9403):157–63.

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APPENDIX C

Dietary Intake Assessment in the US Population

Dietary intake patterns in the United States have been tracked with several surveys of nationally representative samples:

NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEYS (NHANES)

These surveys are conducted by the National Center for Health Statistics of the Centers for Disease Control and Prevention (CDC). Probability samples of the US population are surveyed, using 24-h recall and food-frequency questionnaire.

NHANES I:	1971–1974	*N* = 28,000
NHANES II:	1976–1980	*N* = 25,000
Hispanic HANES:	1982–1984	*N* = 14,000
NHANES III:	1988–1994	*N* = 35,000
Continuous NHANES:	1999–present	*N* = 5,000 per year*

* In 1999, the survey became a continuous program that examines a nationally representative sample of about 5,000 persons each year. These persons are located in counties across the country, 15 are visited annually. (National Health and Nutrition Examination Survey. Available at http://www.cdc.gov/nchs/nhanes/about_nhanes.htm; accessed on December 6, 2020.)

CONTINUING SURVEY OF FOOD INTAKES BY INDIVIDUALS (CFSII)

These surveys are conducted by the US Department of Agriculture (USDA) at 3-year intervals. Probability samples of the US population are surveyed, using one or more 24-h recall surveys and a 2-day food record.

CFSII:	1985–1986	*N* = 9,000
	1989–1991	*N* = 15,000
	1994–1996, 1998	*N* = 20,000

BEHAVIORAL RISK FACTOR SURVEILLANCE SYSTEM

This annual telephone survey is conducted by the CDC and US States on a sample of >400,000 households in the 50 states and 3 US territories.*a* Limited information is provided on dietary intake.

[a]Available at http://www.cdc.gov/brfss/about/index.htm; accessed on December 6, 2020 and https://www.cdc.gov/brfss/annual_data/annual_2019.html; accessed on December 6, 2020.

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APPENDIX D

Dietary Intake Assessment Instruments

Various instruments are available for the assessment of individual dietary intake, each with particular advantages and disadvantages. Standard methods include 24-h recall; food diaries of varying length (typically 2 to 7 days), semiquantitative food-frequency questionnaires, and most recently, diet quality photo navigation (DQPN). Useful resource materials for identifying and understanding the strengths and limitations of dietary-intake assessment instruments include the following:

- Katz DL, Rhee LQ, Katz CS, Aronson DL, Frank GC, Gardner CD, Willett WC, Dansinger ML. Dietary assessment can be based on pattern recognition rather than recall. *Med Hypotheses*. 2020 Feb 26;140:109644.
- Bonilla, C., Brauer, P., Royall, D. *et al*. Use of electronic dietary assessment tools in primary care: an interdisciplinary perspective. *BMC Med Inform Decis Mak*. 15**,**14(2015).
- Thompson FE, Byers T. Dietary assessment resource manual. *J Nutr*. 1994;124:2245s–2317s.
- Olendzki B, Hurley TG, Hebert JR, et al. Comparing food intake using the Dietary Risk Assessment with multiple 24-h dietary recalls and the 7-day dietary recall. *J Am Diet Assoc*. 1999;99:1433–1439.
- Bingham SA, Gill C, Welch A. Comparison of dietary assessment methods in nutritional epidemiology: weighed records v. 24-h recalls, food-frequency questionnaires and estimated-diet records. *Br J Nutr*. 1994;72(4):619–643. http://www.ncbi.nlm.nih.gov/pubmed/7986792.
- Willett, W. *Nutritional epidemiology*, 3rd ed. 2012.
- USDA Food and nutrition service. Healthy Eating Index. Information available at: https://www.fns.usda.gov/resource/healthy-eating-index-hei; accessed on 01/2021.
- USDA National Agriculture Library. Dietary assessment instruments for research. https://www.nal.usda.gov/fnic/dietary-assessment-instruments-research; accessed on 01/2021There are also several instruments and methodologies for measuring food environments to which individuals are exposed. Standard methods include geographic analysis, menu analysis, nutrient analysis, sales analysis, and food supply analysis with instruments to measure food stores, public facilities, restaurants, schools, worksites, and homes.

- Lytle LA, Sokol RL. Measures of the food environment: A systematic review of the field, 2007–2015. *Health Place*. 2017 Mar;44:18–34. doi: 10.1016/j.healthplace.2016.12.007. Epub 2017 Jan 27. PMID: 28135633.
- Robert Wood Johnson Foundation, Healthy Eating Research: https://healthyeatingresearch.org/ accessed on 01/2021On the following page is a form patients can use for compiling a diet diary. The form is supportive of the counseling goals provided in Chapter 47. The patient should be given one copy of the form for each day of intake assessment.

DIETARY INTAKE QUESTIONNAIRES

- National Cancer Institute: Diet History Questionnaire (DHQ) for use by clinicians, Educators and

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researchers to assess food and dietary supplement intakes. https://epi.grants.cancer.gov/dhq3/index.html

- DietID: An online dietary assessment tool that uses visual pattern recognition to assess dietary patterns rather than tracking intake of individual foods. www.dietid.com

DIETARY INTAKE FORM

To the patient: Use the following table to record your dietary intake *during a single day* (indicate the date and day of the week at the top of the table). Make an effort to eat as you usually do and to record everything in detail. Provide information on what you ate, an estimate of the portion size, when you ate (time), where you ate or the source of the food (e.g., home, car, restaurant, office, vending machine), and why (e.g., for hunger, boredom, stress relief, or some other reason). You will be able to review this diary with your doctor, dietitian, or other professional nutrition counselor to identify both what you should change to improve your diet and how you can implement recommended changes successfully.

MEAL/SNACK	DESCRIPTORS	DAY OF THE WEEK DATE WORK DAY? Y/N
Prebreakfast	What	
	How much	
	When	
	Where	
	Why	
Breakfast	What	
	How much	
	When	
	Where	
	Why	
A.M. snack(s)	What	
	How much	
	When	
	Where	
	Why	
Lunch	What	
	How much	
	When	
	Where	
	Why	
P.M. snack(s)	What	
	How much	
	When	
	Where	
	Why	
Dinner	What	

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	How much	
	When	
	Where	
	Why	
Evening	What	
	Snack(s)	
	How much	
	When	
	Where	
	Why	
Other		

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Nutrient/Nutriceutical Reference Tables: Intake Range and Dietary Sources

The following tables provide detailed information for a representative sample of micronutrients for which there are both current interest in supplementation beyond the traditionally recommended range and a body of pertinent and controversial research evidence in the literature.

ARGININE

BIOLOGICAL FUNCTION(s) IN HUMANS/KEY PROPERTIES: Amino acid is essential in infants but not in healthy adults who can synthesize it endogenously; may become essential in stress conditions when demand increases; and plays an important role in cell division, wound healing, and immune function. Immediate precursor of nitric oxide (NO), necessary for synthesis of creatine and other vital proteins. Synthesized primarily in the kidney.

ABSORPTION/SOLUBILITY/STORAGE/PHARMACOKINETICS: Water soluble. Intestinal absorption is active. Arginine is rapidly transported into enterocytes and then transported to the liver for metabolism before distribution to the systemic circulation.

Rationale for Supplementation: Enhanced vascular function; hypotensive effect; potential contributions to immune function, wound healing, and preservation of lean body mass.*a*

Evidence in Support of Supplementation to and Above the Dietary Reference Intake (DRI): No Recommended Dietary Allowance (RDA) or AI (adequate intake) set for arginine.

Recommended Intake Ranges (US RDA): None established.

Average Intake, US Adults	3.5–5.0 g
Estimated Mean Paleolithic Intake (Adult)	Not available
Common Dose Range for use as Supplement	2–30 g
DO DIETARY PATTERNS MEETING GUIDELINES PERMIT INTAKE IN THE SUPPLEMENT RANGE?	Yes
INCLUDED IN TYPICAL MULTIVITAMIN/MULTIMINERAL TABLET?	No
Deficiency	
Intake Level	Variable.
Syndromes	Impaired insulin production, muscle weakness, possible hair loss. Decreased sperm function in men.
Toxicity	
Intake Level	The maximum dose considered to be safe is 400–6,000 mg, although

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	doses as high a 24 g have been given daily for 8 weeks in the treatment of peripheral vascular disease and claudication, for example, without apparent adverse effect.*b* There are no known signs of toxicity in doses up to 30 g/day. Adverse symptoms may occur at higher doses (>30 g) or if administered rapidly.
Syndromes	Nausea, abdominal cramps, diarrhea, skin thickening, weakness may increase activity of some viruses (e.g., herpes).

Dietary Sources*c*: Whole wheat, chocolate, nuts, dairy products, meat, peanuts, brown rice, corn/popcorn, soy products, raisins, sesame and sunflower seeds, coconut, gelatin, buckwheat, barley, chicken, meats, oats.*d*

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[a]May PE, Barber A, D'Olimpio JT, et al. Reversal of cancer-related wasting using oral supplementation with a combination of beta-hydroxy-beta-methylbutyrate, arginine, and glutamine. *Am J Surg*. 2002;183:471–479.

[b]Available at https://doi.org/10.1016/j.ahj.2011.09.012; accessed December 6, 2020.

[c]The nutrient composition of most foods can be checked by accessing the U.S. Department of Agriculture nutrient database, at http://www.nal.usda.gov/fnic/foodcomp/search.

[d]Additional information available at https://www.mayoclinic.org/drugs-supplements-l-arginine/art-20364681; accessed December 6, 2020.

Additional details, evidence, and references for dosing and safety for many nutrients and substances individuals might choose to ingest can be found at http://www.mayoclinic.com/health/search/search, http://ods.od.nih.gov/, and http://www.nlm.nih.gov/medlineplus/

BIOTIN/Vitamin B_7

BIOLOGICAL FUNCTION(S) IN HUMANS/KEY PROPERTIES: Functions in the transport of carboxyl grou Essential in carbohydrate and lipid metabolism and is a cofactor in the metabolic pathways of certain amir acids. Exists in both protein-bound and free forms in diet; free form is functional.

ABSORPTION/SOLUBILITY/STORAGE/PHARMACOKINETICS: Water soluble. Absorption is thought to c primarily in the jejunum. Produced by intestinal flora. There is some egestion of biotin in feces; excretion i rises with dietary intake. Avidin, a protein found in uncooked egg albumin, binds biotin and prevents abso

Rationale for Supplementation: Advocated to improve insulin sensitivity in diabetes mellitus, to strengthen and hair, and for treatment of seborrheic dermatitis.

EVIDENCE IN SUPPORT OF SUPPLEMENTATION TO AND ABOVE THE DRI: Studies of biotin supplementation in humans are limited; animal literature is far more extensive.

Recommended Intake Range (US RDA): Intake in the range of 30–35 μg/day is considered safe and adequate.

BIOTIN RECOMMENDED INTAKE RANGE (US AI)*a*:

Infancy (age 0–6 mo)	Infancy (age 7–12 mo)	Childhood (age 1–3 y)	Childhood (age 4–8 y)	Adolescence (age 9–13 y)	Adolescence (age 14–18 y)	Adult (age ≥19 y)	Pregnancy	La

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Male	7 µg	7 µg	8 µg	12 µg	20 µg	25 µg	30 µg	—
Female	7 µg	7 µg	8 µg	12 µg	20 µg	25 µg	30 µg	30 µg

AVERAGE INTAKE, US ADULTS:	30–70 µg/day
ESTIMATED MEAN PALEOLITHIC INTAKE (ADULT)*b*:	Not available
COMMON DOSE RANGE FOR USE AS SUPPLEMENT:	1,000–10,000 µg/day
DO DIETARY PATTERNS MEETING GUIDELINES PERMIT ADEQUATE INTAKE?	No
INCLUDED IN TYPICAL MULTIVITAMIN/MULTIMINERAL TABLET?	Yes (dose: 45 µg)

Deficiency

Intake Level Intake threshold for deficiency not established in healthy individuals. Deficiency may be induced after intestinal resection or with ingestion of large amounts of raw egg whites. R white contains a substance (avidin) that binds biotin in the intestine and keeps it from be absorbed. Eating two or more uncooked egg whites daily for several months has caused deficiency that is serious enough to produce symptoms.*a* Deficiency may also be induce

protracted antibiotic use and eradication of normal intestinal flora. Long-term anticonvuls drug use affects absorption and may result in a deficiency.

Syndromes Anorexia, nausea, vomiting, glossitis, seborrheic dermatitis, depression, lethargy, alopec

TOXICITY

Intake Level Not established; no toxicity demonstrated at doses up to 10 mg/day.
Note: Biotin can interfere with laboratory assays for thyroid function at doses commonly supplements. Patients should discontinue biotin supplementation for at least 3 days prio bloodwork assess to thyroid function. https://www.fda.gov/medical-devices/safety-communications/update-fda-warns-biotin-may-interfere-lab-tests-fda-safety-communicati

Syndromes None known.

Dietary Sources*c*: Cereal grains contain biotin in amounts in the range 3–30 µg/100 g but with varying bioavailability: Most of the biotin in wheat, for example, is bound and not bioavailable. Fruits and meats co negligible amounts of biotin. Peanut butter and mushrooms are sources.

Food	Serving Size (g)	Energy (kcal)	Biotin (µg)	Food	Serving Size (g)	Energy (kcal)	Biotin (µg)
Liver	100	161	100–200	Yeast	100	295	100–200
Soy flour	100	436	60–70	Egg yolk	100	358	16

Effects of Food Preparation and Storage: Not reported to be a generally important determinant of dieta intake levels.

Additional details, evidence, and references for dosing and safety for many nutrients and substances individuals might choose to ingest can be found at http://www.mayoclinic.com/health/search/search, http://ods.od.nih.gov/, and http://www.nlm.nih.gov/medlineplus/

[a]Biotin MedlinePlus. Available at http://www.nlm.nih.gov/medlineplus/druginfo/natural/313.html; accessed December 6, 2020.

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[b]Eaton SB, Eaton SB III, Konner MJ. Paleolithic nutrition revisited: a twelve-year retrospective on its nature and implications. *Eur J Clin Nutr*. 1997;51:207–216; Eaton SB, Eaton SB. Paleolithic vs. modern diets–selected pathophysiological implications. *Eur J Nutr*. 2000;39:67–70.

[c]The nutrient composition of most foods can be checked by accessing the US Department of Agriculture nutrient database, at http://www.nal.usda.gov/fnic/foodcomp/search.

Sources: Ensminger AH, Ensminger ME, Konlande JE, et al. The concise encyclopedia of foods and nutrition. Boca Raton, FL: CRC Press, Inc., 1995.

Margen S. The wellness nutrition counter. New York, NY: Health Letter Associates, 1997.

Murray MT. Encyclopedia of nutritional supplements. Rocklin, CA: Prima Publishing, 1996.

National Research Council. Recommended dietary allowances, 10th ed. Washington, DC: National Academy Press, 1989.

Otten JJ, Hellwig JP, Meyers LD, eds. Dietary reference intakes. The essential guide to nutrient requirements. Washington, DC: National Academies Press, 2006.

Pizzorno JE, Murray MT. Textbook of natural medicine, 3rd ed. St. Louis, MO: Church Livingstone Elsevier, 2006.

Shils ME, Shike M, Ross AC, et al., eds. Modern nutrition in health and disease, 10th ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2005.

US Department of Agriculture. USDA nutrient database for standard reference. Release 19. 2006. Resources for Nutrient Composition of Foods.

Ziegler EE, Filer LJ Jr. eds. Present knowledge in nutrition, 7th ed. Washington, DC: ILSI Press, 1996.

BORON

BIOLOGICAL FUNCTION(S) IN HUMANS/KEY PROPERTIES: May play a role in the metabolism of calci phosphorous, magnesium, steroid hormones, and vitamin D. May play a role in the regulation of cell mem function. Boron may enhance the effects of estrogen on bone density.

ABSORPTION/SOLUBILITY/Storage/Pharmacokinetics: Boron in food is rapidly absorbed and excreted predominantly in urine. Boron is distributed throughout the body compartments but most concentrated in b teeth hair, nails, spleen, and thyroid tissue.

Rationale for Supplementation: Prevention and treatment of osteoporosis and arthritis. Possibly preventio urolithiasis and prostate cancer. May lower cardiovascular risks as a result of increasing endogenous estrogen.

EVIDENCE IN SUPPORT OF SUPPLEMENTATION TO AND ABOVE THE DRI: No RDA or AI establishe The study of therapeutic effects of supplemental boron is in its infancy. Small human studies, including fe randomized, double-blind pilot studies, show beneficial effects on bone metabolism and symptoms of osteoarthritis (see Chapter 14).

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Recommended Intake Range (US RDA): No RDA has been established; no essential biological role fo has been identified. Approximately 0.25 and 3.25 mg of boron daily per 2,000 kcal are considered high an intake, respectively.[a]

AVERAGE INTAKE, US ADULTS	0.33–2.74 mg/da
ESTIMATED MEAN PALEOLITHIC INTAKE (ADULT)[b]	Not available
COMMON DOSE RANGE FOR USE AS SUPPLEMENT	3 mg/day
DO DIETARY PATTERNS MEETING GUIDELINES PERMIT INTAKE IN THE SUPPLEMENT RANGE?	Yes
INCLUDED IN TYPICAL MULTIVITAMIN/MULTIMINERAL TABLET?	No
DEFICIENCY	
Intake Level	Below 0.3 mg/da possibly, below 1 mg/day.
Syndromes	Uncertain; may contribute to osteoporosis and depress both mu and cognitive fun
TOXICITY	
Intake Level[a]	Boron Tolerable Intake Levels (UL

	Infancy (age 0–6 mo)	Infancy (age 7–12 mo)	Childhood (age 1–3 y)	Childhood (age 4–8 y)	Adolescence (age 9–13 y)	Adolescence (age 14–18 y)	Adult (age ≥A;19 y)	Pregnancy (age 19–50 y)*	Lact (age 50 y
Male	—	—	3 mg	6 mg	11 mg	17 mg	20 mg	—	-
Female	—	—	3 mg	6 mg	11 mg	17 mg	20 mg	20 mg	20

Syndromes: Nausea, vomiting, diarrhea, dermatitis, lethargy.

Dietary Sources[c]: The boron content of foods is not included in the US Department of Agriculture datab and is not readily available from other published sources. Boron is abundant in non-citrus fruits, green lea vegetables, nuts, legumes, beer, wine, and cider. Meat, fish, and dairy products are poor sources.

Effects of Food Preparation and Storage: Not available.

* Pregnant or breastfeeding women 14–18 years of age, the UL is 17 mg/day.

Additional details, evidence, and references for dosing and safety for many nutrients and substances individuals might choose to ingest can be found at http://www.mayoclinic.com/health/search/search, http://ods.od.nih.gov/, and

http://www.nlm.nih.gov/medlineplus/

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[a] Boron MedlinePlus. Available at http://www.nlm.nih.gov/medlineplus/druginfo/natural/894.html; accessed 12/06/2020.

[b]Eaton SB, Eaton SB. Paleolithic vs. modern diets—selected pathophysiological implications. *Eur J Nutr*. 2000;39:67–70.

[c]The nutrient composition of most foods can be checked by accessing the U.S. Department of Agriculture nutrient database, at https://fdc.nal.usda.gov/

Sources: Ensminger AH, Ensminger ME, Konlande JE, et al. The concise encyclopedia of foods and nutrition. Boca Raton, FL: CRC Press, Inc., 1995.

Margen S. The wellness nutrition counter. New York, NY: Health Letter Associates, 1997.

Murray MT. Encyclopedia of nutritional supplements. Rocklin, CA: Prima Publishing, 1996

National Research Council. Recommended dietary allowances, 10th ed. Washington, DC: National Academy Press, 1989.

Otten JJ, Hellwig JP, Meyers LD, eds. Dietary reference intakes. The essential guide to nutrient requirements. Washington, DC: National Academies Press, 2006.

Pizzorno JE, Murray MT. Textbook of natural medicine, 3rd ed. St. Louis, MO: Church Livingstone Elsevier, 2006.

Shils ME, Shike M, Ross AC, et al., eds. Modern nutrition in health and disease, 10th ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2005.

US Department of Agriculture. USDA nutrient database for standard reference. Release 19. 2006. US Department of Agriculture. USDA nutrient intake from NHANES 2001–2002 data.

Ziegler EE, Filer LJ Jr, eds. Present knowledge in nutrition, 7th ed. Washington, DC: ILSI Press, 1996.

CAFFEINE

BIOLOGICAL FUNCTION(S) IN HUMANS/KEY PROPERTIES: Stimulates central nervous system through antagonism of adenosine receptors, enhancing dopamine activity and leading to increased alertness. Can also acutely raise serotonin levels, leading to enhanced mood. Caffeine is a xanthine alkaloid compound, and while not necessary for health, it constitutes the world's most commonly used psychoactive substance and may have health benefits when used in moderation (see Chapter 41).

ABSORPTION/SOLUBILITY/STORAGE/PHARMACOKINETICS: Slightly water soluble. Stomach and intestinal absorption is rapid following ingestion. Caffeine is metabolized by the liver by the cytochrome P450 oxidase enzyme system, generating three active metabolites: paraxanthine (84%), theobromine (12%), and theophylline (4%). Crosses the blood–brain barrier.

Rationale for Supplementation: Enhanced cognitive or physical performance; combating drowsiness.

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EVIDENCE IN SUPPORT OF SUPPLEMENTATION TO AND ABOVE THE DRI: No RDA or DRI established for caffeine. Caffeine supplementation has been shown to improve speed in cycling and rowing events, (Kovacs EM, Stegen JH, Brouns F. Effect of caffeinated drinks on substrate metabolism, caffeine excretion, and performance. *J Appl Physiol*. 1998;85(2):709–715. Bruce CR, Anderson ME, Fraser SF, et al. Enhancement of 2000-m rowing performance after caffeine ingestion. *Med Sci Sports Exerc*. 2000;32(11):1958–1963), reduce perceived exertion during exercise (Scand J Med Sci Sports. 2005 Apr;15(2):69–78. Effects of caffeine ingestion on rating of perceived exertion during and after exercise: a meta-analysis. Doherty M, Smith PM.), and enhance endurance in sports activities at doses of 2–5 mg/kg (J Sports Sci. 2006 Jul;24(7):749–61. Dietary supplements for football. Hespel P, Maughan RJ, Greenhaff PL.) Caffeine has also demonstrated efficacy as an adjuvant treatment for acute pain (Cochrane Database Syst Rev. 2012 Mar 14;3:CD009281. doi: 10.1002/14651858.CD009281.pub2. Caffeine as an analgesic adjuvant for acute pain in adults. Derry CJ, Derry S, Moore RA.) and may be useful in enhancing performance in shift workers (Cochrane Database Syst Rev. 2010 May 12; (5):CD008508. doi: 10.1002/14651858.CD008508. Caffeine for the prevention of injuries and errors in shift workers. Ker K, Edwards PJ, Felix LM, Blackhall K, Roberts I.) In people with asthma, caffeine may modestly improve airway function (Cochrane Database Syst Rev. 2010 Jan 20;(1):CD001112. doi: 10.1002/14651858.CD001112.pub2. Caffeine for asthma. Welsh EJ, Bara A, Barley E, Cates CJ).

Recommended Intake Range (US RDA): None established. Two to four 8-oz cups of coffee (about 200–300 mg of caffeine) per day and five servings of caffeinated soft drinks or tea are considered an average or moderate amount of caffeine.*a*

AVERAGE INTAKE, US ADULTS*b*	200–300 mg/day
ESTIMATED MEAN PALEOLITHIC INTAKE (ADULT)	Not available
COMMON DOSE RANGE FOR USE AS SUPPLEMENT	100–200 mg
DO DIETARY PATTERNS MEETING GUIDELINES PROVIDE ADEQUATE INTAKE?	N/A
INCLUDED IN TYPICAL MULTIVITAMIN/MULTIMINERAL TABLET?	No

Deficiency

Intake Level	Not required for health; therefore, no deficiency syndrome exists. However, regular usage may induce tolerance and produce a withdrawal syndrome if intake is stopped abruptly.
Syndromes	Withdrawal symptoms include headache, nausea, fatigue, drowsiness, inability to concentrate, irritability, depression.

Toxicity

Intake Level	Caffeine intake in excess of 500–600 mg may cause unpleasant symptoms,*c* and hospitalization from toxicity may be required at 2 g of ingestion. Lethal doses are possible, but very rare, usually only from overdose of caffeine pills.
Syndromes	Restlessness, insomnia, facial flushing, polyuria, gastrointestinal disturbance, tremors, irritability, irregular or rapid heartbeat, psychomotor agitation.

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Dietary Sources: Coffee, tea, chocolate, and cola (unless they are labeled “caffeine-free”) are the main sources in the diet.

Additional details, evidence, and references for dosing and safety for many nutrients and substances individuals might choose to ingest can be found at http://www.mayoclinic.com/health/search/search, http://ods.od.nih.gov/, and http://www.nlm.nih.gov/medlineplus/

[a] MedlinePlus. Caffeine in the diet. Available at https://medlineplus.gov/ency/article/002445.htm; accessed 12/06/2020 and Mayo Clinic. Nutrition and healthy eating: Caffeine. Available at https://www.mayoclinic.org/healthy-lifestyle/nutrition-and-healthy-eating/in-depth/caffeine/art-20045678; accessed December 6, 2020.

[b] https://emedicine.medscape.com/article/1182710-overview#a2; accessed December 6, 2020.

[c] FDA. Spilling the beans: how much caffeine is too much? https://www.fda.gov/consumers/consumer-updates/spilling-beans-how-much-caffeine-too-much; accessed December 6, 2020.

CALCIUM

BIOLOGICAL FUNCTION(S) IN HUMANS/KEY PROPERTIES: Calcium is the most abundant mineral in the body. It is the principal mineral of bone and teeth. Extraskeletal calcium functions in nerve conduction muscle, contraction, coagulation and hemostasis, and cell membrane permeability.

ABSORPTION/SOLUBILITY/Storage/Pharmacokinetics: When daily calcium intake is at or near the mean for adults in the United States (750 mg), approximately 25%–50% is absorbed. Calcium absorption is enhanced when it is ingested with food; gastric acid appears to be a factor. Absorption in the duodenum and proximal jejunum is saturable and vitamin D dependent. Passive nonsaturable absorption occurs throughout the small bowel especially in the ileum. Approximately 4% of ingested calcium is absorbed in the large bowel. Calcium in serum is about 8%–10% ionized and 40%–45% protein bound; 45%–50% is found as free ions disassociated. Ionized calcium is the metabolically active moiety. Serum levels are maintained at or near 10 mg/dL by the actions of parathyroid hormone calcitonin and vitamin D. Body stores are 99% skeletal and 1% exchangeable pool. Calcium regulation is influenced by the actions of glucocorticoids, thyroid hormone, growth hormone, insulin, and estrogen. Renal filtration in the adult is approximately 8.6 g/day of which all but 100–200 mg is reabsorbed. Daily fecal losses include approximately 150 mg of calcium in intestinal secretions as well as unabsorbed dietary calcium; losses therefore vary with intake and approximate 300–600 mg. Small losses in sweat (i.e., 15 mg/day) occur as well. Dietary protein potentiates loss of calcium in urine: for every 50 g increment in daily protein ingestion, an additional 60 mg of calcium is excreted. Increased sodium and caffeine intake also increases urinary calcium excretion. Absorption is enhanced by lactose mainly in infants, pregnancy, and calcium deficiency. Plants with oxalates (e.g., spinach, rhubarb, beets) interfere with calcium absorption by forming indigestible salts with calcium, and calcium absorption is likewise reduced when foods contain high amounts of phytates (e.g., soy).*a* Calcium competes for absorption with certain other mineral cations (e.g., magnesium).*b* Vitamin D helps promote calcium absorption.*c*

Rationale for Supplementation: Women in the United States consistently ingest less calcium than the RDA. Intake in males generally approximates recommended levels. Supplementation is particularly advocated for the prevention of osteoporosis in women. Supplemental calcium may lower blood pressure and may confer some protection against colon cancer. Oyster shell calcium, dolomite calcium, and bone meal calcium supplements should generally be avoided due to the possibility of lead contamination.

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Preferred supplements include chelated calcium citrate, gluconate, lactate, and fumarate. Calcium carbonate may be slightly less well absorbed although this appears to be insignificant if ingested with food.

EVIDENCE IN SUPPORT OF SUPPLEMENTATION TO AND ABOVE THE DRI: The literature on both dietary and supplemental calcium is extensive. There is strong evidence that supplemental calcium contributes to bone density, but not bone fracture risk. Evidence of a modest beneficial effect on blood pressure, particularly systolic blood pressure, as well as on blood pressure in pregnancy is well substantiated. There is supportive evidence for preventive efficacy against colon cancer. Evidence for other benefits is preliminary.

Recommended Intake Range (US RDA): An intake of 1,000–1,300 g/day of calcium is recommended for adults.

CALCIUM RECOMMENDED INTAKE RANGE (US AI)*d*

	Infancy (age 0–6 mo)	**Infancy (age 7–12 mo)**	**Childhood (age 1–3 y)**	**Childhood (age 4–8 y)**
Male	200 mg	260 mg	700 mg	1,000 mg
Female	200 mg	260 mg	700 mg	1,000 mg
	Adolescence (age 9–13 y)	**Adolescence (age 14–18 y)**	**Adult (age 19–50 y)**	**Adult (age 51 y)**
Male	1,300 mg	1,300 mg	1,000 mg	1,000 mg
Female	1,300 mg	1,300 mg	1,000 mg	1,000 mg
	Pregnancy (age ≤18 y)	**Pregnancy (age 19–50 y)**	**Lactation (age ≥18 y)**	**Lactation (age 19–50 y)**
Male	—	—	—	—
Female	1,300 mg	1,000 mg	1,300 mg	1,000 mg

Recommended Intake Range (National Institutes of Health [NIH] Consensus Statement*e*):

	Infancy (age 0–6 mo)	**Infancy (age 6 m–1 y)**	**Childhood (age 1–5 y)**	**Childhood (age 6–10 y)**	**Puberty/Adolescence/Early Adulthood (age 11–24 y)**
Male	400 mg	600 mg	800 mg	800–1,200 mg	1,200–1,500 mg
Female	400 mg	600 mg	800 mg	800–1,200 mg	1,200–1,500 mg
	Adulthood (age 25–50 y)	**Postmenopause**	**Senescence**	**Pregnancy**	**Lactation**
Male	1,000 mg	—	1,500 mg	—	—
Female	1,000 mg	On estrogen: 1,000 mg; Not on estrogen: 1,500 mg	1,500 mg	1,200–1,500 mg	1,200–1,500 mg
AVERAGE INTAKE, US ADULTS				746–982 mg/day 1,622 mg/day	

Estimated Mean Paleolithic Intake (Adult)[f]

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COMMON DOSE RANGE FOR USE AS SUPPLEMENT	Up to 1,200 mg/day
DO DIETARY PATTERNS MEETING GUIDELINES PROVIDE THE RDA?	Yes
Included in typical multivitamin/multimineral tablet?	Yes (dose: 175 mg)

Deficiency

Intake Level	Approximately 550 mg/day
Syndromes	Accelerated osteoporosis, hypocalcemia

TOXICITY

Intake Level	**Safe Upper Limits**[d]
Life Stage	**Upper Safe Limit**
Birth to 6 mo	1,000 mg
Infants 7–12 mo	1,500 mg
Children 1–8 y	2,500 mg
Children 9–18 y	3,000 mg
Adults 19–50 y	2,500 mg
Adults 51 y and older	2,000 mg
Pregnant and breastfeeding teens	3,000 mg
Pregnant and breastfeeding adults	2,500 mg

Syndromes Hypercalcemia; constipation; impaired absorption of iron, zinc, and other micronutrients. While foods rich in calcium appear to decrease risk for symptomatic kidney stones, supplemental calcium may increase risk.[g] Similarly, there is evidence that calcium supplementation, but not dietary intake, particularly in excess of 500 mg daily, may increase the risk of cardiovascular events (myocardial infarction, coronary revascularization, death from coronary heart disease, and stroke).[h] The most recent meta-analysis did not find that increased cardiovascular disease (CVD) risk was statistically significant[i]; however, randomized controlled trials (RCTs) of 800–1,600 mg of supplemental calcium daily do suggest a statistically significant increased risk of hip fracture with calcium supplementation.[j]

Dietary Sources[k] Abundant in dairy products, tofu, sardines, and green leafy vegetables. However, for calcium, as for other nutrients, the nutrient content of specific foods may overestimate the amount of nutrient available to consumer (due to various interactions and absorption issues like those noted earlier).

Food	Serving Size	Energy (kcal)	Calcium (mg)	Food	Serving Size	Energy (kcal)	Calcium (mg)
Sardines	1 can (370	770	1,413	Sesame seeds, roasted	1 oz	158	277

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	g)		
Yogurt, nonfat, plain	1 cup	137	488
Ricotta cheese	1 cup	339	669
Skim milk	1 cup	86	301
Whole milk	1 cup	146	276
Buttermilk, low fat	1 cup	98	284
Collard greens, boiled	1 cup (190 g)	49	266
Amaranth	100 g	374	153
Soybeans	1 cup (172 g)	253	339
Almonds	1 oz	164	70
Onions	1 medium (110 g)	44	25
and toasted			
Swiss cheese	1 slice (1 oz)	106	221
Oatmeal with water	100 g	55	56
Provolone cheese	1 slice (1 oz)	98	212
Cheddar cheese	1 slice (1 oz)	114	300
Tofu, fried	1/4 block (81 g)	220	301
Peas, frozen	1/2 cup		
	(72 g)	55	16
Figs, dried	1 fig	21	14
Celery	1 stalk (40 g)	6	16

Effects of Food Preparation and Storage: Generally unimportant.

Additional details, evidence, and references for dosing and safety for many nutrients and substances individuals might choose to ingest can be found at http://www.mayoclinic.com/health/search/search, http://ods.od.nih.gov/, and http://www.nlm.nih.gov/medlineplus/

[a]Heaney RP, Weaver CM, Fitzsimmons ML. Soybean phytate content: effect on calcium absorption. *AJCN*. 1991;53(3):745–747. Available at http://ajcn.nutrition.org/content/53/3/745.short; accessed January 7, 2021.

[b]Hendrix JZ, Alcock NW, Archibald RM. Competition between calcium, strontium, and magnesium for absorption in the isolated rat intestine. *Clin Chem*. 1963;9(6):734–744. Available at http://www.clinchem.org/content/9/6/734.short; accessed January 7, 2021.

[c]MedlinePlus. Calcium in the diet. Available at http://www.nlm.nih.gov/medlineplus/ency/article/002412.htm; accessed January 7, 2021.

[d]Office of Dietary Supplements. Calcium. Available at http://ods.od.nih.gov/factsheets/Calcium-QuickFacts/; accessed January 7, 2021.

[e]Optimal calcium intake. *NIH Consensus Statement* 1994;12:1–31.

[f]Eaton SB, Eaton SB. Paleolithic vs. modern diets—selected pathophysiological implications. *Eur J Nutr*. 2000;39:67–70.

[g]Curhan GC, Willett WC, Speizer FE, et al. Comparison of dietary calcium with supplemental

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calcium and other nutrients as factors affecting the risk for kidney stones in women. *Ann Intern Med*. 1997;126(7):497–504. http://annals.org/article.aspx?articleid=710409.

[h]Bolland M, Avenell A, Baron JA, et al. Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. *BMJ*. 2010;341:c3691. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2912459/; and Bolland M, Grey A, Avenell A, et al. Calcium supplements with or without vitamin D and risk of cardiovascular events: reanalysis of the Women's Health Initiative limited access dataset and meta-analysis. *BMJ*. 2011;342:d2040. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3079822/

[i]Mao PJ, Zhang C, Tang L, et al. Effect of calcium or vitamin D supplementation on vascular outcomes: a meta-analysis of randomized controlled trials. *Int J Cardiol*. 2013;169(2):106–111. doi:10.1016/j.ijcard.2013.08.055. http://www.ncbi.nlm.nih.gov/pubmed/24035175.

[j]Bischoff-Ferrari HA, Dawson-Hughes B, Baron JA et al. Calcium intake and hip fracture risk in men and women: a meta-analysis of prospective cohort studies and randomized controlled trials. *Am J Clin Nutr*. 2007;86(6):1780–1790. http://ajcn.nutrition.org/content/86/6/1780.short.

[k]The nutrient composition of most foods can be checked by accessing the U.S. *Department of Agriculture nutrient database, at* http://www.nal.usda.gov/fnic/foodcomp/search. *A more extensive list of food sources of calcium is available in Margen S. The wellness nutrition counter*. New York, NY: Health Letter Associates, 1997.

Sources: Ensminger AH, Ensminger ME, Konlande JE, et al. The concise encyclopedia of foods and nutrition. Boca Raton, FL: CRC Press, Inc., 1995.

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Press, 1996.

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CARNITINE/LEVOCARNITINE

BIOLOGICAL FUNCTION(S) IN HUMANS/KEY PROPERTIES: Transports long-chain fatty acids into mitochondria. Carnitine may function in fatty acid synthesis and ketone body metabolism. Carnitine is synthesized in the liver and kidney from lysine and methionine; vitamins C, B_6, and niacin are cofactors in carnitine biosynthesis. Carnitine may be an essential nutrient for newborns, who have limited ability to synthesize carnitine. It is present in breast milk at a concentration of 28–95 μmol/L.

ABSORPTION/SOLUBILITY/STORAGE/PHARMACOKINETICS: Water soluble. Intestinal absorption is both active and passive. Carnitine is rapidly transported into cells, and intracellular stores greatly exceed levels in circulation. Approximately 97% of body stores are in skeletal muscle. Carnitine is filtered in the kidney, and approximately 95% is reabsorbed. With elevated serum levels, reabsorption declines.

Rationale for Supplementation: Enhancement of exercise tolerance in healthy individuals and performance athletes. Improvement in oxidation metabolism with reduced symptoms in angina and peripheral vascular disease. Improved cardiac function in congestive heart failure (CHF). Improved cognitive function in Alzheimer's and other forms of senile dementia. Anemia management in end-stage renal disease. Relief of diabetic neuropathy. May slow the death of lymphocytes/HIV progression, reduce neuropathy, and favorably affect blood lipid levels in HIV-infected individuals.*a*

EVIDENCE IN SUPPORT OF SUPPLEMENTATION TO AND ABOVE THE DRI: No established RDA or AI. But an extensive literature on carnitine dates back to the 1970s. Evidence of some benefit in cardiac ischemia, hemodialysis, cardiomyopathy, dementia, and male infertility is supported by randomized, placebo-controlled trials. There is also trial evidence for improved walking distance and perceived quality of life in those with peripheral vascular disease, reduced nerve pain and improved vibration perception in those with diabetic neuropathy,*a* and reduced all-cause mortality in those with established cardiovascular disease.*b*

Recommended Intake Range (US RDA): None established. Carnitine is considered a conditionally essential nutrient; dietary deficiency may cause adverse effects under predisposing conditions. The liver and kidneys produce sufficient amounts of carnitine from the amino acids lysine and methionine to meet daily needs.*a*

AVERAGE INTAKE, US ADULTS	100–300 mg/day
ESTIMATED MEAN PALEOLITHIC INTAKE (A_{DULT})*c*	Not available; likely higher than current levels due to importance of red meat in the Paleolithic diet.
COMMON DOSE RANGE FOR USE AS SUPPLEMENT	1,500–4,000 mg/day
DO DIETARY PATTERNS MEETING GUIDELINES permit intake in the supplement range?	No
INCLUDED IN TYPICAL MULTIVITAMIN/MULTIMINERAL TABLET?	No

Deficiency

Intake Level	No intake level has been specified for healthy adults; deficiency generally results from a genetic defect. Deficiency may occur in

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	newborns, especially premature, on formula not containing carnitine. May be induced by hemodialysis, total parenteral nutrition, or use of valproic acid. Strict vegetarian diets are likely to be low in carnitine but have not been decisively linked to relevant carnitine deficiencies.
Syndromes	Progressive muscle weakness, impaired ketogenesis, and cardiomyopathy.

Toxicity

Intake Level	Supplementation with the naturally occurring L-stereoisomer is apparently safe; use of the D isomer should be avoided as it can lead to functional carnitine deficiency. At doses of approximately 3 g/day, carnitine supplements can cause symptoms.*a*
Syndromes	Nausea, vomiting, abdominal cramps, diarrhea, and a “fishy” body odor. Rarer side effects include muscle weakness in uremic patients and seizures in those with seizure disorders. Supplementation with the D isomer may result in deficiency symptoms, particularly muscle pain and reduced exercise tolerance.a Emerging evidence suggests intestinal bacteria metabolize carnitine to TMAO (trimethylamine-*N*-oxide), a substance that might increase the risk of CVD. This effect appears to be less pronounced in vegetarians than in those who consume meat, who seem to have different gut flora*d*,*e*,*f*,*g*

Dietary Sources[*h*]**:** Red meat, dairy to a lesser extent.

Food	Serving Size (g)	Energy (kcal)	Carnitine (mg)
Beef steak	100	321	95
Ground beef	100	282	94
Pork	100	226	28
Bacon	100	576	23
Cod fish	100	82	5.6
Chicken breast	100	172	3.9
American cheese	100	331	3.7
Ice cream	100	201	3.7
Whole milk	100	60	3.3

Effects of Food Preparation and Storage: Not reported to be a generally important determinant of dietary intake levels.

Additional details, evidence, and references for dosing and safety for many nutrients and substances individuals might choose to ingest can be found at http://www.mayoclinic.com/health/search/search, http://ods.od.nih.gov/, and http://www.nlm.nih.gov/medlineplus/

[*a*]Office of Dietary Supplements. Carnitine. Available at http://ods.od.nih.gov/factsheets/Carnitine-HealthProfessional/;accessed 01/08/2021.

[*b*]DiNicolantonio JJ, Lavie JC, Fares H, et al. L-carnitine in the secondary prevention of

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[c]Eaton SB, Eaton SB. Paleolithic vs. modern diets—selected pathophysiological implications. *Eur J Nutr*. 2000;39:67–70.

[d]Tang WHW, Wang Z, Levison BS, et al. Intestinal microbial metabolism of phosphatidylcholine and cardiovascular risk. *N Engl J Med*. 2013;368:1575. http://dx.doi.org/10.1056/NEJMoa1109400; Loscalzo J. Gut microbiota, the genome, and diet in atherogenesis. *N Engl J Med*. 2013;368:1647. http://dx.doi.org/10.1056/NEJMe1300954; Koeth RA, Wang Z, Bruse S, et al. Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. *Nat Med*. 2013;19:576. http://dx.doi.org/10.1038/nm.3145; Bäckhed F. Meat-metabolizing bacteria in atherosclerosis. *Nat Med*. 2013;19:533. http://dx.doi.org/10.1038/nm.3178; Koeth RA, Wang Z, Levison BS, et al. Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. *Nat Med*. 2013;19:576–585. doi:10.1038/nm.3145. http://www.nature.com/nm/journal/v19/n5/full/nm.3145.html.

[e]Loscalzo J. Gut microbiota, the genome, and diet in atherogenesis. *N Engl J Med*. 2013 Apr 25; 368:1647. (http://dx.doi.org/10.1056/NEJMe1300954)

[f]Koeth RA. et al. Intestinal microbiota metabolism of l-carnitine, a nutrient in red meat, promotes atherosclerosis. *Nat Med*. 2013 May; 19:576. (http://dx.doi.org/10.1038/nm.3145)

[g]Bäckhed F. Meat-metabolizing bacteria in atherosclerosis. *Nat Med*. 2013 May; 19:533. (http://dx.doi.org/10.1038/nm.3178)

[h]The carnitine content of foods is not currently included in the USDA nutrient database. As a general rule, carnitine is abundant in meat and more abundant the redder the meat. Carnitine is present in dairy products; levels in plant foods are negligible. The table is adapted from Broquist HP. *Carnitine*. In: Shils ME, Shike M, Ross AC, et al., eds. *Modern nutrition in health and disease*, 10th ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2005:540. Energy content of foods listed is from the USDA nutrient database, at http://www.nal.usda.gov/fnic/foodcomp/search.

Sources: Ensminger AH, Ensminger ME, Konlande JE, et al. The concise encyclopedia of foods and nutrition. Boca Raton, FL: CRC Press, Inc., 1995.

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CAROTENOIDS/VITAMIN A

BIOLOGICAL FUNCTION(S) IN HUMANS/KEY PROPERTIES: The essential role of carotenoids in human health as precursors of vitamin A has long been recognized; potential health effects of their antioxidant properties have come under investigation more recently. Vitamin A is essential in cell proliferation and growth, immune function, and vision. There are more than 600 carotenoids known, of which approximately 50 are known to serve as precursors of retinol, the biologically active form of vitamin A. These carotenoid precursors of retinol are said to have provitamin A activity. Of the many, only a few are considered important sources of vitamin A: *α*-carotene, *β*-carotene, and *β*-cryptoxanthin. Of these, all-trans-*β*-carotene is the most active. Carotenoids are responsible for the bright pigments in many plants and are essential to photosynthesis. They apparently act as antioxidants in both plants and animals. The functions of carotenoids other than as antioxidants and vitamin A precursors remain to be elucidated.

ABSORPTION/SOLUBILITY/STORAGE/PHARMACOKINETICS: Carotenoids are fat soluble. Retinol is 70%–90% absorbed in the small intestine, while carotenoids are generally 9%–22% absorbed. Carotenoid absorption is downregulated by high intake. Absorption is dependent on the activity of pancreatic enzymes and bile acids and is enhanced by dietary fat, protein, and vitamin E. Ingested provitamin A carotenoids and preformed vitamin A (retinyl esters) are directly absorbed from the intestine. Carotenoids are widely distributed in tissues, while *β*-carotene and ingested retinol are stored in the liver as retinyl esters in subject with adequate vitamin A stores. Inactive metabolites of retinol are 70% egested in stool, 30% excreted in urine. Retinol is slowly released from liver stores to meet metabolic requirements and it circulates in conjunction with a binding protein. Due to hepatic storage capacity, large, intermittent doses of vitamin A or its precursors can prevent deficiency as effectively as consistent dietary intake.

Rationale for Supplementation: There is no specific RDA for carotenoids, other than as vitamin A precursors. Carotenoid intake from dietary sources will be high if the diet is rich in dark green and other brightly colored vegetables and fruits (see “Dietary Sources”). For individuals with limited intake of vegetables and individuals with limited intake of dietary vitamin A, provitamin A carotenoid supplementation may be indicated to assure adequate vitamin A status. The use of carotenoid supplements has been recommended to enhance immune function and to treat photosensitivity. Other carotenoids, such as lutein, are recommended to prevent age-related eye diseases. In those who are deficient, supplementation may be helpful for preventing CVD and cancer, but the evidence is thus far inconclusive.

EVIDENCE IN SUPPORT OF SUPPLEMENTATION TO AND ABOVE THE DRI: Epidemiologic evidence

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is consistent that high dietary intake and high serum levels of carotenoids are associated with reduced risk of certain cancers[a] and mortality.[b] However, only β-carotene has been studied as a supplement in randomized trials, with consistently negative results. In such trials, β-carotene has been associated with lack of effect on angina or cardiovascular events[c,d] and either no effect[e] or an adverse effect[c] on cancer incidence in smokers. Proponents of carotenoid supplementation argue that antioxidant effects require combination supplements, but evidence of benefit is lacking to data. Preliminary studies of other carotenoids, including lycopene and lutein, are promising.

Recommended Intake Range (US RDA[f])

VITAMIN A RECOMMENDED INTAKE RANGE (US RDA)[g]
RAE = retinol activity equivalents, IU = International Units

- 1 IU RETINOL = 0.3 µg RAE
- 1 IU β-CAROTENE FROM DIETARY SUPPLEMENTS = 0.15 µg RAE
- 1 IU β-CAROTENE FROM FOOD = 0.05 µg RAE
- 1 IU α-CAROTENE or β-cryptoxanthin = 0.025 µg RAE
- 1 µg RAE RETINOL = 3.33 IU
- 1 µg RAE β-CAROTENE FROM DIETARY SUPPLEMENTS = 6.67 IU
- 1 µg RAE β-CAROTENE FROM FOOD = 20 IU
- 1 µg RAE α-CAROTENE ORβ-CRYPTOXANTHIN = 40 IU

	Infancy (age 0–6 mo)	Infancy (age 7–12 mo)	Childhood (age 1–3 y)	Childhood (age 4–8 y)
Male	400 µg RAE	500 µg RAE	300 µg RAE	400 µg RAE
Female	400 µg RAE	500 µg RAE	300 µg RAE	400 µg RAE
	Adolescence (age 9–13 y)	**Adolescence (age 14–18 y)**	**Adult (age ≥19 y)**	**Pregnancy (age ≤18 y)**
Male	600 µg RAE	900 µg RAE	900 µg RAE	—
Female	600 µg RAE	700 µg RAE	700 µg RAE	750 µg RAE
	Pregnancy (age 19–50 y)	**Lactation (age ≤18 y)**	**Lactation (age 19–50 y)**	
Male	—	—	—	
Female	770 µg RAE	1,200 µg RAE	1,300 µg RAE	

AVERAGE INTAKE, US ADULTS:	570–661 µg RAE
ESTIMATED MEAN PALEOLITHIC INTAKE (ADULT)[h]	2,870 µg RE
COMMON DOSE RANGE FOR USE AS SUPPLEMENT	A daily dose of 900 µg RAE for men and 700 µg RAE for women; acute doses up to 50,000 µg RAE are proposed for use during acute viral illness.
DO DIETARY PATTERNS MEETING GUIDELINES PERMIT ADEQUATE INTAKE?	Yes
INCLUDED IN TYPICAL MULTIVITAMIN/MULTIMINERAL TABLET?	Yes (dose: 1,375 µg RAE)

Deficiency(CAROTENOIDS/VITAMIN A)

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Intake Level	Below 390 µg RAE (when vitamin A blood levels dip below 0.7 *µ*mol/L).
Syndromes	Xerophthalmia, anorexia, hyperkeratosis, immunosuppression, increased risk of morbidity and mortality through symptoms such as diarrhea.

Toxicity (CAROTENOIDS)

Intake Level	None for carotenoids; 3,000 µg/day vitamin A.

VITAMIN A TOLERABLE UPPER INTAKE LEVEL (UL): Safe upper limits for *β*-carotene and other forms of provitamin A have not been established. The safe upper limits for preformed vitamin A in IU.*g*

	Infancy (age 0–6 mo)	**Infancy (age 7–12 mo)**	**Childhood (age 1–3 y)**	**Childhood (age 4–8 y)**
Male	2,000 IU	2,000 IU	2,000 IU	3,000 IU
Female	2,000 IU	2,000 IU	2,000 IU	3,000 IU
	Adolescence (age 9–13 y)	**Adolescence (age 14–18 y)**	**Adult (age ≥19 y)**	**Pregnancy (age 14–18 y)**
Male	5,667 IU	9,333 IU	10,000 IU	—
Female	5,667 IU	9,333 IU	10,000 IU	—
	Pregnancy (age 19–50 y)	**Lactation (age 14–18 y)**	**Lactation (age 19–50 y)**	
Male	—	—	—	
Female	—	—	—	

Syndromes	**Carotenoids:** None; with extreme doses, harmless and reversible skin discoloration may occur; in smokers, high doses of *β*-carotene—with or without vitamin A—may increase the risk of lung and other cancers, and the combination of *β*-carotene and vitamin A may be associated with greater risk of cardiovascular events.*i*
Vitamin A	Hepatotoxicity; bone abnormalities; in pregnancy, birth defects.

Dietary Sources: Vitamin A is found abundantly in animal-based foods, such as liver, dairy products, and fish liver oils. Dietary carotenoids are found primarily in specific oils, dark green and other brightly colored vegetables, and fruits. The following chart uses RAE units to equate carotenoids and vitamin A.*g*

Food	**Serving Size**	**Energy (kcal)**	**Carotenoid (*µ*g RAE)**	**Food**	**Serving Size**	**Energy (kcal)**	**Carotenoid (*µ*g RAE)**
Apricot, dried	1 cup (130 g)	309	941	Peppers, red	1 medium (119 g)	32	678
Sweet potato,	1 medium (114 g)	117	2,487	Collard greens,	1 cup (190 g)	49	595

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cooked			
Tomato juice	1 cup (243 g)	41	136
Carrots	1 medium (61 g)	26	1,716
Kale, raw	1 cup (67 g)	33.5	596
Pumpkin, cooked	1 cup (245 g)	49	265
Peppers, yellow	1 large (186 g)	50	45
Parsley, raw	1 cup (60 g)	22	312
Tomato paste	1 can (170 g)	139	415
Romaine lettuce	1/2 cup (28 g)	4	73
Broccoli, cooked	1 medium stalk (180 g)	50	250
Cantaloupe	1 medium wedge (69 g)	24	222

cooked			
Saffron	1 table spoon (2.1 g)	6.5	1.1
Paprika	1 table spoon (6.9 g)	20	418
Apricots, fresh	1 medium (35 g)	17	91
Swiss chard, cooked	1 cup (175 g)	35	550
Spinach, raw	10 oz (284 g)	62	1,908
Corn, cooked	1 ear (77 g)	83	17
Tangerines	1 medium (84 g)	37	77
Orange	1 medium (131 g)	62	28
Watermelon	1 wedge (286 g)	92	106
Tomato, fresh	1 medium (123 g)	26	76

Distribution of Carotenoids of Potential Clinical Importance in the Food Supply (Leading Sources):

β-carotene	Apricots, carrots, sweet potato, collard greens, spinach, kale
Lycopene	Tomato juice, tomato paste, guava, watermelon, grapefruit (pink)
Lutein	Kale, collard greens, spinach, endive, watercress, Swiss chard, romaine lettuce
α-Carotene	Pumpkin, carrots, squash, corn, apples, peaches
α-Cryptoxanthin	Tangerine, papaya, lemons, oranges, persimmons, corn, green peppers
Zeaxanthin	Spinach, paprika, corn

Effects of Food Preparation and Storage: The bioavailability tends to increase somewhat with lower-temperature cooking (e.g., steaming or sautéing in oil), whereas bioavailability decreases with higher-temperature methods, such as boiling. The addition of dietary fiber, inadequate dietary fat, and use of nondigestible fat substitutes can decrease carotenoid bioavailability. Some carotenoid tends to be lost with freezing.

Additional details, evidence, and references for dosing and safety for many nutrients and substances individuals might choose to ingest can be found at http://www.mayoclinic.com/health/search/search, http://ods.od.nih.gov/, and http://www.nlm.nih.gov/medlineplus/

[a]Sun SY, Lotan R. Retinoids and their receptors in cancer development and chemoprevention. *Crit Rev Oncol Hematol*. 2002;41:41–55.

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[b]Darlow BA, Grahm PJ. Vitamin A supplementation for preventing morbidity and mortality in very low birthweight infants. *Cochrane Database Syst Rev*. 2002;4:CD000501.

[c]Rappola JM, Virtamo J, Haukka JK, et al. Effect of vitamin E and beta carotene on the incidence of angina pectoris. *JAMA*. 1996;275:693–698. Alpha-tocopherol, Beta Carotene Cancer Prevention Study Group. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. *N Engl J Med*. 1994;330:1029–1035. Omenn GS, Goodman G, Thornquist M, et al. The carotene and Retinol Efficacy Trial (CARET) for chemoprevention of lung cancer in high risk populations: smokers and asbestos-exposed workers. *Cancer Res*. 1994;54:2038s–2043s.

[d] Hennekens CH, Buring JE, Manson JE, et al. Lack of effect of long-term supplementation with beta carotene on the incidence of malignant neoplasms and cardiovascular disease. *N Engl J Med*. 1996;334:1145–1149.

[e]Greenberg ER, Baron JA, Tosteson TD, et al. A clinical trial of antioxidant vitamins to prevent colorectal adenoma. *N Engl J Med*. 1994:331:141–147.

[f]There is no RDA for carotenoids per se, other than as vitamin A precursors. Recommended intake is therefore expressed as *μ*g RAE. One *μ*g RAE is equal to 1 μg all-trans-retinol, 12 μg *β*-carotene, and 24 μg *α*-carotene or *β*-cryptoxanthin. An intake of 700–1,300 μg RAE/day of vitamin A is recommended for adults.

[g]Office of Dietary Supplements. *Vitamin A*. Available at http://ods.od.nih.gov/factsheets/VitaminA-QuickFacts/; accessed January 7, 2021.

[h]Eaton SB, Eaton SB. Paleolithic vs. modern diets—selected pathophysiological implications. *Eur J Nutr*. 2000;39:67–70.

N.B: Vitamin A supplementation should be avoided during pregnancy; see vitamin A table.

[i]Blomhoff R. Vitamin A and carotenoid toxicity. *Food Nutr Bull*. 2001;22(3):320–334. http://www.ingentaconnect.com/content/nsinf/fnb/2001/00000022/00000003/art00009.

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CHROMIUM

BIOLOGICAL FUNCTION(S) IN HUMANS/kEY PROPERTIES: The principal role of chromium is as an insulin cofactor, improving glucose tolerance.

ABSORPTION/SOLUBILITY/STORAGE/PHARMACOKINETICS: Chromium absorption is limited and varies with intake level from a low of 0.4% to a high of 2.5% of the portion ingested. Chromium is stored in bone, spleen, kidney, and liver. Chromium accumulates in the lungs with advancing age, while levels in other tissues decline; the significance of this is unclear. Ingested chromium that remains unabsorbed is excreted in the feces; absorbed chromium is excreted in urine. Evidence suggests a correlation between the ingestion of certain substances and an effect on chromium bioavailability. Vitamin C has been shown to increase absorption of chromium, while phytate and some antacid drugs have been shown to decrease chromium absorption. A diet excessive in simple sugars has been shown to increase urinary excretion of chromium.

RATIONALE FOR SUPPLEMENTATION: Usual intake in the United States is below the recommended intake range of 50–200 µg/day. Chromium deficiency may contribute to insulin resistance. Doses higher than the RDA show promise for ameliorating insulin resistance or impairments of glucose metabolism.*a* Up to 1,000 µg/day is recommended by some practitioners for treatment of insulin resistance or diabetes and as an aid in weight loss.

EVIDENCE IN SUPPORT OF SUPPLEMENTATION TO AND ABOVE THE DRI: The literature on chromium supplementation is fairly extensive, but evidence of therapeutic effect in any condition is not definitive. There is evidence of benefit in some groups of diabetics and in the preferential loss of fat during weight reduction efforts.*b* Arguments against routine supplementation for primary prevention have been raised.*c* Trow et al.*d* found no evidence of benefit from chromium supplementation in a small group of type 2 diabetics. Chromium also failed to enhance the beneficial effects of exercise on glucose tolerance in overweight adults.*e* However, corticosteroid-induced diabetes mellitus has been reported to respond to chromium supplementation.*f* High-dose supplementation apparently has some potential toxicity,*g* although this is generally considered to be limited. Overall, chromium supplementation is considered promising in diabetes and insulin resistance,*h*,*i* less so for weight management.*j* A meta-analysis of 15 trials of chromium supplementation on markers of diabetes failed to show an effect on glucose or insulin concentrations in nondiabetic subjects or in those with diabetes, except in one trial in China in which study subjects were likely chromium deficient.*k* Thus far, chromium does not appear to be effective at reducing body fat or building lean muscle mass to a degree that is clinically

meaningful.[l,m]

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Recommended Intake Range (US RDA): Estimated safe and adequate daily dietary intake is provided rather than RDA. An intake of 25–45 μg/day of chromium is recommended for adults.

CHROMIUM RECOMMENDED INTAKE RANGE (US AI):

	Infancy (age 0–6 mo)	Infancy (age 7–12 mo)	Childhood (age 1–3 y)	Childhood (age 4–8 y)
Male	0.2 μg	5.5 μg	11 μg	15 μg
Female	0.2 μg	5.5 μg	11 μg	15 μg
	Adolescence (age 9–13 y)	**Adolescence (age 14–18 y)**	**Adult (age 19–50 y)**	**Adult (age ≥51 y)**
Male	25 μg	35 μg	35 μg	30 μg
Female	21 μg	24 μg	25 μg	20 μg
	Pregnancy (age ≤18 y)	**Pregnancy (age 19–50 y)**	**Lactation (age ≤18 y)**	**Lactation age 19–50 y)**
Male	—	—	—	—
Female	29 μg	30 μg	44 μg	45 μg

AVERAGE INTAKE, US ADULTS	30–80 μg
ESTIMATED MEAN PALEOLITHIC INTAKE (ADULT))[n]	Not available
COMMON DOSE RANGE FOR USE AS SUPPLEMENT	50–1,000 μg/day
DO DIETARY PATTERNS MEETING GUIDELINES PERMIT ADEQUATE INTAKE?	Yes
INCLUDED IN TYPICAL MULTIVITAMIN/MULTIMINERAL TABLET?	Yes (25 μg)

DEFICIENCY	
Intake Level	Below 50 μg/day
Syndromes	Insulin resistance, glucose intolerance
TOXICITY	
Intake Level	Uncertain
Syndromes	None known

Dietary Sources[o]: Chromium is found abundantly in whole foods like meats, liver, eggs, whole-grain products, brewer's yeast, seafood, nuts, and some fruits, vegetables, and spices.

Effects of Food Preparation and Storage: Processing of food may directly affect the chromium content. Processing of refined sugars, grains, and flours tends to reduce the chromium content, while acidic foods have been shown to increase chromium content if processing involves stainless steel.

Additional details, evidence, and references for dosing and safety for many nutrients and substances individuals might choose to ingest can be found at http://www.mayoclinic.com/health/search/search, http://ods.od.nih.gov/, and http://www.nlm.nih.gov/medlineplus/

[a]Martin J, Wang ZQ, Zhang XH, et al. Chromium picolinate supplementation attenuates body weight gain and increases insulin sensitivity in subjects with type 2 diabetes. *Diabetes Care*.

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2006;29:1826–1832; Wang ZQ, Zhang XH, Russell JC, et al. Chromium picolinate enhances skeletal muscle cellular insulin signaling in vivo in obese, insulin-resistant JCR:LA-cp rats. *J Nutr*. 2006;136:415–420; Cefalu WT, Hu FB. Role of chromium in human health and in diabetes. *Diabetes Care*. 2004;27:2741–2751; Cefalu WT, Wang ZQ, Zhang XH, et al. Oral chromium picolinate improves carbohydrate and lipid metabolism and enhances skeletal muscle Glut-4 translocation in obese, hyperinsulinemic (JCR-LA corpulent) rats. *J Nutr*. 2002;132:1107–1114.

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[c]Porter DJ, Raymond LW, Anastasio GD. Chromium: friend or foe? *Ann Fam Med*. 1999;8:386–390.

[d]Trow LG, Lewis J, Greenwood RH, et al. Lack of effect of dietary chromium supplementation on glucose tolerance, plasma insulin and lipoprotein levels in patients with type 2 diabetes. *Int J Vitam Nutr Res*. 2000;70:14–18.

[e]Joseph LJ, Farrell PA, Davey SL, et al. Effect of resistance training with or without chromium picolinate supplementation on glucose metabolism in older men and women. *Metabolism*. 1999;48:546–553.

[f]Ravina A, Slezak L, Mirsky N, et al. Reversal of corticosteroid-induced diabetes mellitus with supplemental chromium. *Diabet Med*. 1999;16:164–167.

[g]Young PC, Turiansky GW, Bonner MW, et al. Acute generalized exanthematous pustulosis induced by chromium picolinate. *J Am Acad Dermatol*. 1999;41:820–823.

[h]Lukaski HC. Chromium as a supplement. *Annu Rev Nutr*. 1999;19:279–302.

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[j]Vincent JB. The potential value and toxicity of chromium picolinate as a nutritional supplement, weight loss agent and muscle development agent. *Sports Med*. 2003;33:213–230.

[k]Althuis MD, Jordan NE, Ludington EA, et al. Glucose and insulin responses to dietary chromium supplements: a meta-analysis. *Am J Clin Nutr*. 2002;76:148–155.

[l]Clarkson PM, Rawson ES. Nutritional supplements to increase muscle mass. *Crit Rev Food Sci Nutr.* 1999;39:317–328.

[m]Vincent JB. The potential value and toxicity of chromium picolinate as a nutritional supplement, weight loss agent and muscle development agent. *Sports Med*. 2003;33:213–230; Pittler MH, Stevinson C, Ernst E. Chromium picolinate for reducing body weight: meta-analysis of randomized trials. *Int J Obes Relat Metab Disord*. 2003;27:522–529.

[n]Eaton SB, Eaton SB. Paleolithic vs. modern diets—selected pathophysiological implications.

Eur J Nutr. 2000;39:67–70.
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[o]Chromium content is not routinely listed in the USDA nutrient database (http://www.nal.usda.gov/fnic/foodcomp/search).

COENZYME Q_{10}/UBIQUINONE

BIOLOGICAL FUNCTION(S) IN HUMANS/KEY PROPERTIES: Functions in electron transport and as an antioxidant, quenching free radicals. Involved in the generation of adenosine triphosphate (ATP) in mitochondria. May contribute to exercise capacity. Can be synthesized endogenously.

ABSORPTION/SOLUBILITY/STORAGE/PHARMACOKINETICS: Coenzyme Q_{10} absorption is limited in the small intestine because of its lipid-soluble nature. Higher absorption is therefore observed when coenzyme Q_{10} is taken with meals in combination with a higher lipid load. Upon absorption, coenzyme Q_{10} is packaged inside chylomicrons for transport to the liver. The nutrient is later released into circulation in a combination of lipoproteins to reach its target tissues. Coenzyme Q_{10} is a benzoquinone, also known as ubiquinone because of its remarkably widespread distribution in nature and in virtually every cell in the human body. Metabolically active tissues and cells (e.g., heart, liver, kidney, muscle) have the highest coenzyme Q_{10} requirements and concentrations. The major excretory pathway is through biliary and fecal passing, with smaller amounts seen in urine excretion.*a*

RATIONALE FOR SUPPLEMENTATION: Generation of ATP in myocardium; antioxidant effects. Recommended for CHF and coronary disease. Because coenzyme Q_{10} shares a common metabolic pathway with the production of cholesterol, HMG-CoA reductase inhibitors (statins) are shown to cause a depletion of coenzyme Q_{10}.*b* May be beneficial in a wide range of disease states associated with oxidative injury. Preserves vitamin E and vitamin C levels.

EVIDENCE IN SUPPORT OF SUPPLEMENTATION TO AND ABOVE THE DRI: No RDA or AI established. There have been numerous animal and observational studies. There are positive results from double-blind, placebo-controlled studies in humans, in particular for use in CHF (see Chapter 7); a meta-analysis suggests improved ejection fraction with coenzyme Q10 supplementation in CHF.*c* Coenzyme Q_{10} may also improve endothelial function*d* and ameliorate myalgia associated with use of statins according to an updated meta-analysis of RCTs.*e* Solubilized forms of coenzyme Q_{10} tend to show the most benefit. Coenzyme Q10 helps protect the heart from the damaging side effects of the cancer drug, doxorubicin.*f* More widespread use of coenzyme Q_{10} in cardiology and primary care practice appears to warrant consideration, although definitive evidence of benefit is for the most part lacking. RCTs have shown no evidence of benefit for fatigue, arterial stiffness, metabolic parameters, inflammatory markers, or blood pressure.*g* The usual doses in trials range from 100–300 mg/day (1–2 mg/kg/day). Such doses appear safe, with virtually no reports of significant toxicity.*h*

Recommended Intake Range (US RDA): None established.

AVERAGE INTAKE, US ADULTS:	Unknown
ESTIMATED MEAN PALEOLITHIC INTAKE (ADULT))*i*	Unknown
COMMON DOSE RANGE FOR USE AS SUPPLEMENT	30–1,200 mg/day; 1–2 mg/kg/day

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DO DIETARY PATTERNS MEETING GUIDELINES PERMIT INTAKE IN THE SUPPLEMENT RANGE?	No
INCLUDED IN TYPICAL MULTIVITAMIN/MULTIMINERAL TABLET?	No
DEFICIENCY	
Intake Level	Unknown
Syndromes	Unknown
TOXICITY	
Intake Level	Unknown
Syndromes	Unknown

Dietary Sources[j]: Coenzyme Q_{10} is known as ubiquinone due to its ubiquitous distribution in nature. While widely distributed in both plant and animal foods, however, dietary sources do not allow for intake in the supplement range. The concentration of ubiquinone in various foods has been studied, but not systematically reported. Foods such as meats, fish, vegetables, and fruits appear to contain decent sources for replenishment of coenzyme Q_{10}.[k]

Effects of Food Preparation and Storage: Not reported to be a generally important determinant of dietary intake levels.

Additional details, evidence, and references for dosing and safety for many nutrients and substances individuals might choose to ingest can be found at http://www.mayoclinic.com/health/search/search, http://ods.od.nih.gov/, and http://www.nlm.nih.gov/medlineplus/

[a]Bhagavan HN, Chopra RK. Coenzyme Q_{10}: absorption, tissue uptake, metabolism and pharmacokinetics. *Free Radic Res*. 2006;40:445–453.

[b]Nawarskas JJ. HMG-CoA reductase inhibitors and coenzyme Q_{10}. *Cardiol Rev*. 2005;13:76–79.

[c]Fotino AD, Thompson-Paul AM, Bazzano LA. Effect of coenzyme Q_{10} supplementation on heart failure: a meta-analysis. *Am J Clin Nutr*. 2013;97(2):268–275. doi:10.3945/ajcn.112.040741.

[d]Gao L, Mao Q, Cao J, et al. Effects of coenzyme Q_{10} on vascular endothelial function in humans: a meta-analysis of randomized controlled trials. *Atherosclerosis*. 2012;221(2):311–316. doi:10.1016/j.atherosclerosis.2011.10.027.

[e]Qu H, Guo M, Chai H, Wang WT, Gao ZY, Shi DZ. Effects of coenzyme Q10 on statin-induced myopathy: an updated meta-analysis of randomized controlled trials. *J Am Heart Assoc*. 2018;7(19):e009835. doi:10.1161/JAHA.118.009835.

[f]NCI—Coenzyme Q10. Available at http://www.cancer.gov/cancertopics/pdq/cam/coenzymeQ10/patient; accessed 01/08/2021.

[g]Lee YJ, Cho WJ, Kim JK, et al. Effects of coenzyme Q_{10} on arterial stiffness, metabolic

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[h]Hathcock JN, Shao A. Risk assessment for coenzyme Q_{10} (ubiquinone). *Regul Toxicol Pharmacol*. 2006;45:282–288.

[i]Eaton SB, Eaton SB. Paleolithic vs. modern diets—selected pathophysiological implications. *Eur J Nutr*. 2000;39:67–70.

[j]The USDA nutrient database does not currently report ubiquinone content.

[k]Weant KA, Smith KM. The role of coenzyme Q_{10} in heart failure. *Ann Pharmacother*. 2005;39:1522–1526.

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CREATINE

BIOLOGICAL FUNCTION(S) IN HUMANS/KEY PROPERTIES: Creatine is synthesized endogenously from the amino acids glycine and arginine and available methyl groups. Concentrated in skeletal muscle and brain, creatine functions in energy metabolism, supplying energy to muscle cells and neurons.

ABSORPTION/SOLUBILITY/STORAGE/PHARMACOKINETICS: Creatine is a water-soluble molecule

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synthesized from amino acids in the kidney and liver and transported for use to skeletal muscles.*a* Its absorptions, storage, and pharmacokinetics are largely unknown. Muscle creatine rises with supplementation, apparently to a maximum level of approximately 20% above baseline with supplementation in the range of 3 g/day.*b* Urinary excretion of creatinine rises with creatine loading.

Ingesting carbohydrates with creatine can increase muscle creatine levels more than ingesting creatine alone.*c*

RATIONALE FOR SUPPLEMENTATION: Enhanced athletic performance. Possible improved endurance in patients with heart failure and improved muscle strength in people with muscular dystrophies.

EVIDENCE IN SUPPORT OF SUPPLEMENTATION TO AND ABOVE THE DRI: No RDA or AI established. Numerous double-blind, randomized, and crossover studies showing improved work output with creatine supplementation. Most studies have been small and of short duration.*d* Evidence of benefit for sustained activity appears less convincing than evidence for an effect on short-burst activity. The available literature includes both positive and negative studies (see Chapter 32). Creatinine appears to enhance select athletic performance, lean muscle mass, and peak muscle strength but provides no statistically significant improvements in swimming, running, peak torque, or acceleration times.*e* Meta-analyses support the benefits of creatine supplementation in people with muscular dystrophies and neuromuscular disorders.*f*

Recommended Intake Range (US RDA): Unknown.

AVERAGE INTAKE, US ADULTS	Unknown; daily turnover in an adult male is estimated at 2 g/day*g*
ESTIMATED MEAN PALEOLITHIC INTAKE (A_{DULT}))*h*	Unknown; Paleolithic dietary patterns likely resulted in higher intake than do current patterns.
COMMON DOSE RANGE FOR USE AS SUPPLEMENT	Approximately 2–10 g/day.
DO DIETARY PATTERNS MEETING GUIDELINES PERMIT INTAKE IN THE SUPPLEMENT RANGE?	No
INCLUDED IN TYPICAL MULTIVITAMIN/MULTIMINERAL TABLET?	No
DEFICIENCY	
Intake Level	None; creatine can be synthesized endogenously. Genetic deficiencies in synthesizing creatine lead to severe neurological defects.
Syndromes	None known
TOXICITY	
Intake Level	Unknown

TOLERABLE UPPER INTAKE LEVEL (UL): Creatine has been used in doses as high as 20 g/day in heart failure and as loading doses for athletic performance with apparently no adverse effects.*c*

Syndromes	Unknown; side effects with common dosing are limited largely to gastrointestinal cramping and weight gain.

Dietary Sources: Dietary sources of creatine are not systematically reported. Creatine is abundant in red meat and fish.

Effects of Food Preparation and Storage: Not available.

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Additional details, evidence, and references for dosing and safety for many nutrients and substances individuals might choose to ingest can be found at http://www.mayoclinic.com/health/search/search, http://ods.od.nih.gov/, and http://www.nlm.nih.gov/medlineplus/

[a]MayoClinic. Creatinine. Available at https://www.mayoclinic.org/drugs-supplements-creatine/art-20347591; accessed January 8, 2021.

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ESSENTIAL FATTY ACIDS

BIOLOGICAL FUNCTION(S) IN HUMANS/KEY PROPERTIES: Essential fatty acids (EFAs) are those polyunsaturated fatty acids (PUFAs) required in metabolism that cannot be synthesized endogenously. The two classes of EFAs are n-6 and n-3. Linoleic acid is an essential n-6 fatty acid (C_{18}; i.e., 18 carbons in its chain) that is a precursor to arachidonic acid (C_{20}); when linoleic acid intake is deficient, arachidonic acid becomes an essential nutrient as well. The other EFA is *α*-linolenic (ALA) acid, a n-3 with 18 carbons. Linolenic acid is a precursor to eicosapentaenoic acid (EPA; C_{20}) and docosahexaenoic acid (DHA; C_{22}). However, the efficiency of EPA, and particularly DHA, synthesis from linolenic acid is in question. Animal evidence suggests that supplementation with DHA more effectively raises tissue levels of DHA than does supplementation with ALA.*a*,*b* EFAs in phospholipids are key structural components of cellular and subcellular membranes. They are metabolic precursors of eicosanoids with a wide range of effects, from inflammatory reactions and immunity to platelet aggregation. DHA is concentrated in the brain and retina.

ABSORPTION/SOLUBILITY/STORAGE/PHARMACOKINETICS: The absorption of ingested fatty acids is highly efficient, ranging from 95% to nearly 100%. Ingested fat releases fatty acids (see Chapter 2) that can be utilized immediately as a fuel source, stored as triglyceride in adipose tissue, or used in anabolism. Changes in dietary intake of EFAs are reflected in tissue stores over a period of days to weeks. Animal data suggest that PUFAs, including EFAs, may be preferentially released from adipose tissue in response to catabolic stimuli.*c* A predominance of n-6 over n-3 fatty acids in the diet fosters preferential synthesis of the products of n-6 FA metabolism, as EFAs of both classes utilize the same enzyme systems. With the exception of *g*-linolenic acid (GLA), the products of n-6 fatty acid metabolism tend to be proinflammatory leukotrienes and prostaglandins that promote platelet aggregation, while the products of n-3 fatty acid metabolism generally have opposite effects. Thus, an imbalance in EFA intake in favor of the n-6 class may contribute to inflammation and a prothrombotic tendency. GLA, although of the n-6 class, uniquely bypasses the rate-limiting enzyme (Δ6 desaturase) in EFA metabolism and, as a result, preferentially leads to the synthesis of prostaglandins in the 1 series, which have anti-inflammatory and antiplatelet effects, as well as the suppression of proinflammatory cytokine synthesis.*d*–*g*

RATIONALE FOR SUPPLEMENTATION: There is no RDA per se for EFAs, and overt deficiency syndromes are exceedingly rare when dietary intake is basically adequate; EFA deficiency is generally associated with abnormal nutriture (e.g., parenteral nutrition, starvation). However, n-6 fatty acid intake in the United States is considerably greater than n-3 fatty acid intake due to the wide distribution of linoleic acid in commonly used vegetable oils. Approximately 7% of the energy in a typical diet in the

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United States is derived from linoleic acid. In contrast, the distribution of linolenic acid is narrow, and intake levels are low. Unlike most other nutrients with nutriceutical applications, fatty acids are ingested at a macro level, contributing appreciably to energy intake. Therefore, there is no rationale per se for megadosing of any fatty acid, and such a practice would carry with it the risk of excess energy intake or displacement of other vital nutrients from the diet. The underlying rationale for supplementation of either n-3 fatty acids or GLA is to reduce the synthesis of inflammatory cytokines and platelet-stimulating prostaglandins and preferentially support the synthesis of anti-inflammatory cytokines by shifting the distribution of fatty acids in the diet.

EVIDENCE IN SUPPORT OF SUPPLEMENTATION TO AND ABOVE THE DRI: There is no RDA for EFAs per se, but the adequate intake level established by the Institute of Medicine in 2002 is 1.1 g/day and 1.6 g/day of ALA for adult women and men, respectively. There is no reference intake for the other EFAs. There is suggestive evidence for the therapeutic use of supplemental EFAs in a wide range of inflammatory conditions and convincing evidence in the aggregate for shifting the distribution of EFAs from the now prevailing pattern in the United States to a more balanced distribution of n-3s and n-6s to promote health. The typical diet in the United States provides n-6 to n-3 fatty acids in a ratio of at least 10:1, with roughly 7% of calories derived from EFAs. An intake ratio of n-6 to n-3 of between 4:1 and 1:1 is thought to be preferable and health promoting, although conclusive evidence is not available. There is no clear evidence that total EFA intake should be increased, and there is at least suggestive evidence that substituting dietary linoleic acid for saturated fats increases the rates of death from CVD and all causes.*h* Total PUFA intake in the range of 10%–15% of calories is consistent with recommendations for diet and general health promotion (see Chapter 45). Relatively greater intake of n-3 fatty acids is supported by studies of cognitive development and visual acuity in infants (see Chapters 27 and 29); by studies of chronic inflammatory conditions (see Chapters 11, 20, 22–24); by studies of CVD (see Chapter 7); and, to a lesser extent, by the cancer prevention literature (see Chapter 12). Studies of prostate cancer specifically have produced inconsistent results, with some studies suggesting an increased risk of prostate cancer with ALA.*i* Convincing evidence is available of benefit from n-3 fatty acid supplementation at a daily dose of 3 g of EPA and DHA in combination in rheumatoid arthritis.*j* A similar benefit has been suggested in inflammatory bowel disease, but the evidence is less consistent and therefore must be considered preliminary.*k* Supplementation of the maternal diet with DHA during pregnancy has theoretical support and is unlikely to be harmful but is as yet not supported by conclusive outcome studies.*l*,*m* Evidence of benefit of DHA in infant nutrition is convincing with regard to visual acuity*n* and suggestive in the area of cognitive development.*o*,*p* In the aggregate, evidence of cardiovascular benefit from fish oil supplementation is convincing*q* (see Chapter 7). The immunologic effects of n-3 fatty acids are convincingly favorable in inflammatory states but may be disadvantageous in relatively immunocompromised individuals; concurrent vitamin E supplementation may prevent attendant immunosuppression.*r* A potential beneficial role in inflammatory diseases of the lung (e.g., asthma, bronchitis) has been suggested*s* (see Chapter 15).

There is some evidence that n-6 fatty acids may act as promoters in carcinogenesis, while n-3 fatty acids have the opposite effect. Therapeutic applications of GLA are supported by diverse sources of evidence as well. A 2000 study demonstrated an accelerated clinical response in patients with endocrine receptor-positive breast cancer treated with GLA (2.8 g/day) in addition to tamoxifen as compared to tamoxifen alone.*t* Inhibition of atherogenesis with GLA has been demonstrated *in vitro* and in animal studies.*u* A therapeutic role for GLA in atopic eczema is convincingly supported by available evidence.*v* A benefit of GLA in rheumatologic conditions*w* and diabetic neuropathy*x* is suggested.

Recommended Intake Range (US RDA): There is much uncertainty about the optimal percentage of daily calories that should come from fat, the percentage of this total that should derive from PUFAs, and

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the percentage of PUFAs that should be ALA, EPA, or DHA. The Food and Agriculture Organization of the United Nations and World Health Organization (FAO/WHO), based on varying levels of imperfect evidence, recommend that for adults, 15%–35% of total daily energy comes from dietary fat and 6%–11% of total daily energy comes from PUFAs. Somewhere between 2.5% and 9% of total daily energy should be from n-6 PUFAs and 0.5%–2% of total daily energy from n-3 PUFAs, with >0.5% of total daily energy form ALA and 0.25%–2% of total daily energy from DHA + EPA specifically. Recommended percentages for fat and PUFAs are higher for children and adolescents[y].

ESSENTIAL FATTY ACIDS RECOMMENDED INTAKE RANGE (US AI): N-6, LINOLEIC ACID/AI

	Infancy (age 0–6 mo)	**Infancy (age 7–12 mo)**	**Childhood (age 1–3 y)**	**Childhood (age 4–8 y)**
Male	4.4 g	4.6 g	7 g	10 g
Female	4.4 g	4.6 g	7 g	10 g
	Adolescence (age 9–13 y)	**Adolescence (age 14–18 y)**	**Adult (age 19–50 y)**	**Adult (age ≥51 y)**
Male	12 g	16 g	17 g	14 g
Female	10 g	11 g	12 g	11 g
	Pregnancy (all ages)	**Lactation (all ages)**		
Male	—	—		
Female	13 g	13 g		

N-3, *α*-LINOLENIC ACID/AI

	Infancy (age 0–6 mo)	**Infancy (age 7–12 mo)**	**Childhood (age 1–3 y)**	**Childhood (age 4–8 y)**
Male	0.5 g	0.5 g	0.7 g	0.9 g
Female	0.5 g	0.5 g	0.7 g	0.9 g
	Adolescence (age 9–13 y)	**Adolescence (age 14–18 y)**	**Adult (age 19–50 y)**	**Adult (age ≥51 y)**
Male	1.2 g	1.6 g	1.6 g	1.6 g
Female	1.0 g	1.6 g	1.1 g	1.1 g
Male	—	—		
Female	1.4 g	1.3 g		

AVERAGE INTAKE, US ADULTS	Total EFA: approximately 7%–10% of calories; n-6 to n-3 ratio: between 10:1 and 20:1
ESTIMATED MEAN PALEOLITHIC I_{NTAKE} (A_{DULT}))[z]	Total EFA: approximately 7%–10% of calories; n-6 to n-3 ratio: between 4:1 and 1:1

Paleolithic intake of n-3 fatty acids is thought to have been considerably greater than that in most industrialized countries in part because the meat of wild ungulates is rich in n-3 fatty acids. Thus, the Paleolithic diet is thought to have provided n-3 fatty acids from sources other than marine animals.

COMMON DOSE RANGE FOR USE AS SUPPLEMENT	Fish oil: 5–15 g/day (generally a combination of EPA and DHA)
	ALA: approximately 10 g/day

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GLA: approximately 1.5–3 g/day

DO DIETARY PATTERNS MEETING GUIDELINES PERMIT INTAKE IN THE SUPPLEMENT RANGE? Generally no; possibly, if intake of certain fish (e.g., salmon, mackerel), other marine animals, or wild game is unusually high. Of note, the n-3 fatty acid content of fish is derived from the algae and phytoplankton the fish ingest. Fish raised commercially tend to have a much reduced n-3 fatty acid content in their diet and therefore a much lower n-3 content in their flesh (much like what has occurred with the domestication of cattle). While the efficiency of conversion of ALA to EPA and especially DHA is questionable, dietary supplementation with ALA appears to provide most of the health benefit of directly ingesting the longer-chain n-3s. Given the potential importance of EFAs in health promotion, and the disproportionate representation of n-6 PUFAs in the Western diet, a general recommendation for increasing ALA in the diet is reasonable. The recommended dose of approximately 10 g/day can be obtained by using 1–2 tablespoons of flaxseed (flax) oil daily. Flaxseed oil is available in health food stores. It can be used on salads and in cold dishes but is not suitable for cooking (which changes the oil and its chemical and health properties). Vitamin E requirements rise with intake of PUFAs, and therefore vitamin E supplementation in conjunction with regular EFA ingestion is not unreasonable (see “Vitamin E”). Flaxseed oil might be used to displace other less-healthy or less-needed fats from the diet (particularly trans fats, and n-6 PUFAs).

INCLUDED IN TYPICAL MULTIVITAMIN/MULTIMINERAL TABLET? NO

DEFICIENCY

Intake Level	EFAs <1% of calories
Syndromes	Dry skin; hair loss; immunosuppression

TOXICITY

Intake Level	Variable; dependent in part on the ratio of n-6 to n-3
Syndromes	Prooxidant effects; cancer promotion; bleeding diathesis/platelet dysfunction

ALA Dietary Sources[b]

Food	Serving Size	Energy (kcal)	ALA (g)
Canola oil	1 tablespoon (14 g)	124	1.3
Flax (flaxseed) oil	1 tablespoon (13.6 g)	110	7.2
Kale	1 cup (67 g)	3	0.1
Soybean oil	1 tablespoon (13.6 g)	120	0.9
Spinach	2 cups (30 g)	14	0.1

DHA Dietary Sources

Food	Serving Size	Energy (kcal)	DHA (g)
Mackerel (Atlantic)	1 fillet (112 g)	230	1.6
Oysters (cooked)	6 medium (150 g)	244	0.8
Salmon (Atlantic)	1/2 fillet (198 g)	281	2.2
Sardines (canned in oil)	1 can (92 g)	191	0.5
Scallops (raw)	3 oz (85 g)	75	0.1

EPA Dietary Sources

Food	Serving Size	Energy (kcal)	EPA (g)

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Mackerel (Atlantic)	1 fillet (112 g)	230	1.0
Oysters (cooked)	6 medium (150 g)	244	1.3
Salmon (Atlantic)	1/2 fillet (198 g)	281	0.6
Sardines (canned in oil)	1 can (92 g)	191	0.4
Scallops (raw)	3 oz (85 g)	75	0.08

GLA (Medicinal Oils)

Food	Dose	Energy (kcal)	GLA (g)
Black currant seed oil	1 tablespoon (13.6 g)	120	2.3
Borage seed oil	1 tablespoon (13.6 g)	102	3.0
Evening primrose oil	1 tablespoon (13.6 g)	120	1.2

Linoleic Acid Dietary Sources[a1]

Food	Serving Size	Energy (kcal)	Linoleic Acid (g)
Corn oil	1 tablespoon (13.6 g)	120	7.2
Flax (flaxseed) oil	1 tablespoon (13.6 g)	120	1.7
Safflower oil	1 tablespoon (13.6 g)	120	10.1
Sunflower oil	1 tablespoon (13.6 g)	120	8.9

Effects of Food Preparation and Storage: Expeller pressing is the preferred extraction method for oil. Hydrogenation enhances the commercial properties of PUFAs at the expense of their health effects; “partial hydrogenation” produces trans stereoisomers (i.e., trans fats). PUFAs are susceptible to degradation when exposed to light and/or heat; opaque, plastic packaging is preferred. Oils rich in n-3 fatty acids are particularly heat intolerant and generally cannot be used for cooking.

Additional details, evidence, and references for dosing and safety for many nutrients and substances individuals might choose to ingest can be found at http://www.mayoclinic.com/health/search/search, http://ods.od.nih.gov/, and http://www.nlm.nih.gov/medlineplus/

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FIBER

BIOLOGICAL FUNCTION(S) IN Humans/Key Properties: Fiber is, by definition, indigestible plant material, generally categorized along with carbohydrate. Soluble fiber dissolves in water. Dissolution of soluble fiber in the gastrointestinal tract causes delayed absorption of glucose and fatty acids, blunting postprandial rises. Soluble fiber has lipid-lowering properties and attenuates postprandial insulin release. Soluble fibers of relative importance include guar gum, psyllium, pectin, and *β*-glucan. Insoluble fibers, such as lignins, celluloses, and hemicelluloses, reduce GI transit time and increase fecal bulk. Both categories of fiber may increase the satiating capacity of food. Certain fibers differentially support the growth of various gut bacteria, alternating the intestinal microbiome,*a* which is emerging as a key consideration for overall health promotion and disease prevention in humans. Some of the beneficial effects of fiber through gut bacteria and their metabolites may be mediated through systemic and local anti-inflammatory activites.*a* Still, some fibers may promote gastrointestinal sensitivity. Fibers like fructans and galactans are part of a heterogeneous group of compounds collectively knows as FODMAPs (Fermentable, Oligo-, Di-, Monosaccharides, and Polyols), which may produce symptoms similar to those of gluten-sensitivity/celiac disease, irrespective of gluten intake or actual bowel inflammation. Because many gluten-containing foods also are high in FODMAPs, improved symptoms with gluten-free diets in individuals reporting gluten sensitivity might actually reflect simultaneous reduction in FODMAP intake.*b*

ABSORPTION/SOLUBILITY/STORAGE/PHARMACOKINETICS: By definition, fiber is not digested and therefore neither absorbed nor stored. However, various species of bacteria in the human colon do ferment certain dietary fibers, producing short-chain fatty acids, which are absorbed. The exact role of these fatty acids in human energy balance remains uncertain, but it is clear that fibers contribute some calories to diets in man.*c*

RATIONALE FOR SUPPLEMENTATION: There is no RDA for dietary fiber.

Intake of soluble fiber at levels above the prevailing average in the United States is associated with reductions in lipid and insulin levels. Intake of insoluble fiber at levels above the prevailing average in the United States is generally associated with reduced risk of diverticular disease and colon cancer. However, gastrointestinal intolerance tends to be dose limiting so that megadosing of fiber is not practical.

EVIDENCE IN SUPPORT OF SUPPLEMENTATION TO AND ABOVE THE DRI: No RDA or AI established. Soluble fiber supplementation is effective in lowering serum lipids even when the diet is already fat restricted.*d* Soluble fiber can also improve glycemic control in diabetes.*e* Increased intake of insoluble fiber is effective in the management of constipation, and relatively high intake of insoluble fiber is associated with reduced risk of diseases of the large bowel, from diverticulosis to cancer (see Chapters 12 and 18).

Recommended Intake Range (US RDA): There is no RDA for either total or soluble fiber.*f*

FIBER RECOMMENDED INTAKE RANGE (US AI): g/1,000 kcal (g/day)

Infancy (age 0–6 mo)	Infancy (age 7–12 mo)	Childhood (age 1–3 y)	Childhood (age 4–8 y)

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Male	—	—	14 (19)	14 (25)
Female	—	—	14 (19)	14 (25)

	Adolescence (age 9–13 y)	Adolescence (age 14–18 y)	Adult (age 19–50 y)	Adult (age 51 y)
Male	14 (31)	14 (38)	14 (38)	14 (30)
Female	14 (26)	14 (26)	14 (25)	14 (21)

	Pregnancy (all ages)	Lactation (all ages)
Male	—	—
Female	14 (28)	14 (29)

AVERAGE INTAKE, US ADULTS	12 g/day total fiber
ESTIMATED MEAN PALEOLITHIC INTAKE (ADULT)[g]	104 g/day total fiber
COMMON DOSE RANGE FOR USE AS SUPPLEMENT	3–20 g/day soluble fiber
DO DIETARY PATTERNS MEETING GUIDELINES PERMIT INTAKE IN THE SUPPLEMENT RANGE?	Yes
INCLUDED IN TYPICAL MULTIVITAMIN/MULTIMINERAL TABLET?	No
DEFICIENCY	
Intake Level	Variable
Syndromes	Constipation
TOXICITY	
Intake Level	Variable
Syndromes	Gastrointestinal intolerance; micronutrient malabsorption

Dietary Sources[h]: Insoluble fiber is abundant in whole grains, especially wheat, nuts, beans, vegetables; soluble fiber is abundant in fruits, oats, lentils, peas, and beans, carrots, barley, and psyllium.

Food[i]	Serving Size	Energy (kcal)	Fiber (g)	Food[j]	Serving Size	Energy (kcal)	Fiber (g)
Wheat bran (raw)	1 cup (58 g)	125	25	Raspberries Lentils	1 cup (123 g)	64	8
Bulgur wheat (cooked)	1 cup (182 g)	151	8.2	Lentils (cooked)	1 cup (198 g)	230	15.6
Barley, pearled (cooked)	1 cup (157 g)	193	6	Chick peas	1 cup (164 g)	269	12.5
Bread, whole wheat	1 slice (28 g)	69	2	Apples	1 medium (138 g)	72	3.3
Brown rice (cooked)	1 cup (195 g)	218	3.5	Carrots	1 medium (61 g)	25	1.7
Pasta (fiber content not listed)	1 cup (140 g)	197	2.4				

Oat bran (raw)	1 cup (94 g)	231	14.5

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Effects of Food Preparation and Storage: Health effects of fiber are generally unaffected by food preparation and storage under normal conditions.

Additional details, evidence, and references for dosing and safety for many nutrients and substances individuals might choose to ingest can be found at http://www.mayoclinic.com/health/search/search, http://ods.od.nih.gov/, and http://www.nlm.nih.gov/medlineplus/

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FLAVONOIDS

BIOLOGICAL FUNCTION(S) IN HUMANS/KEY PROPERTIES: Flavonoids are brightly colored phenolic compounds in plants. While the class contains more than 4,000 known compounds, interest to date has focused on proanthocyanidins (procyanidolic oligomers [PCOs]), quercetin, a group of bioflavonoids in citrus (hydroxyethylrutosides [HER]), polyphenolic compounds in tea, and isoflavones in soy (see Chapter 33). Some proprietary products, such as Pycnogenol, are patented combinations of purified bioflavonoids. Flavonoids are not known as essential nutrients in humans; however, their deficiency may contribute to the manifestations of scurvy; some consider them semi-essential. Flavonoids play an important role as antioxidants. They chelate divalent cations and by doing so may preserve levels of ascorbate (vitamin C). An effect on capillary permeability under experimental conditions may be direct, or may be mediated via ascorbate.

ABSORPTION/SOLUBILITY/STORAGE/PHARMACOKINETICS: Flavonoids are water soluble; their metabolism is similar to that of ascorbate. In general, they are efficiently absorbed in the upper small bowel; however, absorption may vary between food sources and supplements. Excretion is in the urine, and storage is limited. The typical American diet provides 0.15–1 g of mixed flavonoids daily.

RATIONALE FOR SUPPLEMENTATION: Supplements of various flavonoids in varying doses are used by naturopathic practitioners for health promotion and for the treatment of venous insufficiency, vascular disease, respiratory, and inflammatory conditions. PCO is advocated for its antioxidant effects at a dose of approximately 50 mg/day and for therapy of venous insufficiency or retinopathy at a dose of up to 300 mg/day. A dose of 100 mg quercetin daily is advocated for chronic inflammatory conditions such as asthma, rheumatoid arthritis, or atopy. HER is recommended at a dose in the range of 1 g/day for conditions of venous insufficiency. Up to 400 mg/day of green tea polyphenols is recommended for cancer prevention.

EVIDENCE IN SUPPORT OF SUPPLEMENTATION TO AND ABOVE THE DRI: No RDA or AI established. Flavonoids may contribute to the health benefits of various plant-based foods, but most of

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the evidence in support of flavonoid supplementation remains preliminary and based mostly on observations studies. RCTs of flavonoid-rich foods have shown reduced blood pressure with chocolate, reduced low-density lipoprotein (LDL) with green tea, and reduced blood pressure and LDL with soy.*a*

Related to diabetes, green tea may reduce fasting blood glucose, although an RCT showed no effect on fasting blood insulin or glycosylated hemoglobin (A1c).*b* An isolated isoflavone supplement resulted in a lower incidence of prostate cancer in an RCT among Japanese men taking, but only for those 65 years of age or older.*c* Soy isoflavone might also be safe and effective for vasomotor symptoms in postmenopsual women*d* and may result in lower LDL in both sexes.*e* Semi synthetic HER, closely related to the natural flavoid, rutin, are of clear benefit in venous insufficiency, consistently producing greater improvements in pain, cramping, swelling, and tired and restless legs than placebo.*f* A recent systematic review and meta-analysis suggests that flavonoid supplementation decreases the incidence of upper respiratory tract infection in the general population.*j*

Recommended Intake Range (US RDA): There is no RDA for flavonoids, nor is there an obvious source for a generalizable recommendation for an intake range for all adults. On the basis of various lines of evidence from diverse sources, an argument could be made that total flavonoid intake in the range 1–2 g/1,000 kcal would likely offer health benefits without any appreciable risk relative to the typical American intake of <500 mg/1,000 kcal.

AVERAGE INTAKE, US ADULTS	<1 g/day
ESTIMATED MEAN PALEOLITHIC INTAKE (ADULT)*g*	Uncertain; likely in the range of 3–6 g/day
COMMON DOSE RANGE FOR USE AS SUPPLEMENT	Varies with particular compound; from 50 mg to 1 g
DO DIETARY PATTERNS MEETING GUIDELINES PERMIT INTAKE IN THE SUPPLEMENT RANGE?	Yes
INCLUDED IN TYPICAL MULTIVITAMIN/MULTIMINERAL TABLET?	No
DEFICIENCY	
Intake Level	None known with certainty
Syndromes	Vascular permeability
TOXICITY	
Intake Level	None known with certainty
Syndromes	Prooxidant effects. Consuming black tea may increase blood pressure.*a*

Flavonoids Dietary Sources*h*: The flavonoid content of specific foods is available via the USDA database for the flavonoid content of selected foods, created in 2003 (http://www.nal.usda.gov/fnic/foodcomp/Data/Flav/flav.html).*i* Flavonoids are concentrated in the brightly colored outer layers, skin, or peel of many fruits and vegetables. Concentrated sources include citrus fruits, berries, grapes, peaches, tomatoes, red cabbage, onion, peppers, beans, sage, soy, dark chocolate, green tea, and red wine.

Effects of Food Preparation and Storage: Flavonoids are relatively heat resistant. Food processing is not thought to substantially alter flavonoid content or activity.

Additional details, evidence, and references for dosing and safety for many nutrients and

substances individuals might choose to ingest can be found at http://www.mayoclinic.com/health/search/search, http://ods.od.nih.gov/, and http://www.nlm.nih.gov/medlineplus/

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[a]Hooper L, Kroon PA, Rimm EB, et al. Flavonoids, flavonoid-rich foods, and cardiovascular risk: a meta-analysis of randomized controlled trials. *Am J Clin Nutr*. 2008;88(1):38–50.

[b]Zheng XX, Xu YL, Li SH, et al. Effects of green tea catechins with or without caffeine on glycemic control in adults: a meta-analysis of randomized controlled trials. *Am J Clin Nutr*. 2013;97(4):750–762. doi:10.3945/ajcn.111.032573.

[c]Miyanaga N, Akaza H, Hinotsu S, et al. Prostate cancer chemoprevention study: an investigative randomized control study using purified isoflavones in men with rising prostate-specific antigen. *Cancer Sci*. 2012;103(1):125–130. doi: 10.1111/j.1349-7006.2011.02120.x.

[d]Nahas EA, Nahas-Neto J, Orsatti FL, et al. Efficacy and safety of a soy isoflavone extract in postmenopausal women: a randomized, double-blind, and placebo-controlled study. *Maturitas*. 2007;58(3):249–258.

[e]Zhuo XG, Melby MK, Watanabe S. Soy isoflavone intake lowers serum LDL cholesterol: a meta-analysis of 8 randomized controlled trials in humans. *J Nutr*. 2004;134(9):2395–400.

[f]Poynard T, Valterio C. Meta-analysis of hydroxyethylrutosides in the treatment of chronic venous insufficiency. *Vasa*. 1994;23(3):244–250.

[g]Eaton SB, Eaton SB. Paleolithic vs. modern diets—selected pathophysiological implications. *Eur J Nutr*. 2000;39:67–70.

[h]The nutrient composition of most foods can be checked by accessing the US Department of Agriculture nutrient database, at http://www.nal.usda.gov/fnic/foodcomp/search. Flavonoid data are available for a limited food list. See: http://www.nal.usda.gov/fnic/foodcomp/Data/Flav/flav.html.

[i]Kuhnau J. The flavonoids: A class of semi-essential food components. *World Rev Nutr Diet*. 1976;24:117–191.

[j]Somerville VS, Braakhuis AJ, Hopkins WG. Effect of flavonoids on upper respiratory tract infections and immune function: a systematic review and meta-analysis. *Adv Nutr*. 2016 May 16;7(3):4884–97.

Sources: Ensminger AH, Ensminger ME, Konlande JE, et al. The concise encyclopedia of foods and nutrition. Boca Raton, FL: CRC Press, Inc., 1995.

Margen S. The wellness nutrition counter. New York, NY: Health Letter Associates, 1997.

Murray MT. Encyclopedia of nutritional supplements. Rocklin, CA: Prima Publishing, 1996.

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National Research Council. Recommended dietary allowances, 10th ed. Washington, DC: National Academy Press, 1989.

Otten JJ, Hellwig JP, Meyers LD, eds. Dietary reference intakes. The essential guide to nutrient requirements. Washington, DC: National Academies Press, 2006.

Pizzorno JE, Murray MT. Textbook of natural medicine, 3rd ed. St. Louis, MO: Church Livingstone Elsevier, 2006.

Shils ME, Shike M, Ross AC, et al., eds. Modern nutrition in health and disease, 10th ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2005.

US Department of Agriculture. USDA nutrient database for standard reference. Release 19. 2006.

US Department of Agriculture. USDA nutrient intake from NHANES 2001–2002 data.

Ziegler EE, Filer LJ Jr, eds. Present knowledge in nutrition, 7th ed. Washington, DC: ILSI Press, 1996.

FOLATE/Vitamin B_9

BIOLOGICAL FUNCTION(S) IN HUMANS/KEY PROPERTIES: Folate, also referred to as folic acid or folacin, is a part of the B vitamin complex, and it functions in the transfer of single carbon units in metabolic processes. Folate is an essential cofactor in amino acid and nucleic acid synthesis and is thus fundamental to all cell replication.

ABSORPTION/SOLUBILITY/STORAGE/PHARMACOKINETICS: Folate is water soluble and absorbed efficiently with saturation kinetics in the jejunum. Approximately 5–10 mg is stored in the average adult, half of which is in the liver. Excretion occurs through both urine and bile.

Rationale for Supplementation: There is now widespread consensus that folate intake should be at least 400 µg/day to prevent neural tube defects in infants (see Chapters 27 and 29) and vascular injury due to elevated homocysteine levels in older adults (see Chapter 7).*a* While compliance with guidelines for fruit and vegetable intake could lead to the recommended level of folate from the diet, there is evidence that between 80% and 90% of adults in the United States consume less than the recommended level of folate. The usual intake of folate in the United States is thought to be approximately 280–300 µg/day in men and less in women. Nominal folate deficiency is considered the most common nutritional deficiency in the United States. Although greater folate intake could be achieved with simple dietary modification (e.g., choosing whole wheat bread over enriched white bread for >50% more folate),*b* absorption of folate in supplement form is more complete than absorption from food. Routine use of 400 µg of supplemental folate by at least women of child-bearing age and older adults may be appropriate. Common mutations in the methylenetetrahydrofolate reductase (MTHFR) gene influence the metabolism of folate and, when present, may justify supplementation with activated methylfolate rather than synthetic folic acid.*p*

A very limited literature suggests that megadoses of folate, in the range of 10 mg/day (25 times the current recommended intake level), may be beneficial in cervical dysplasia and that a dose of 15 mg/day may be beneficial in depression. In neither case is the literature adequate to support routine clinical application.

EVIDENCE IN SUPPORT OF SUPPLEMENTATION TO AND ABOVE THE DRI: The evidence that

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intake of at least 400 µg of folate/day around the time of conception can reduce the risk of neural tube defects is strong and is the basis for fortification of the US food supply.[c] Prenatal vitamins typically contain 1,000 µg of folate. Evidence that folate intake can influence the risk of CVD via effects on serum homocysteine (see Chapter 7) is also strong[d,e] with some suggestive evidence for a modest benefit in stroke prevention but not other vascular outcomes or mortality.[g] Baseline homocysteine level may matter.[h] Other effects on homocysteine, related to diabetes, suggest modest benefit for glycemic control with folate supplementation.[i] Beneficial effects of folate supplementation on vascular reactivity (endothelial function) have been demonstrated.[j]

Recommended Intake Range (US RDA): An intake of 400 µg/day of total folate is recommended for all adults and women of reproductive age. All women and teen girls who could become pregnant should consume 400 µg of folic acid daily from supplements, fortified foods, or both in addition to the folate they get naturally from foods.[k]

FOLATE RECOMMENDED INTAKE RANGE (US RDA):

	Infancy (age 0–6 mo)	Infancy (age 7–12 mo)	Childhood (age 1–3 y)	Childhood (age 4–8 y)	Adolescence (age 9–13 y)
Male	65 µg	80 µg	150 µg	200 µg	300 µg
Female	65 µg	80 µg	150 µg	200 µg	300 µg

	Adolescence (age 14–18 y)	Adult (age 19 y)	Pregnancy (all ages)	Lactation (all ages)
Male	400 µg	400 µg	—	—
Female	400 µg	400 µg	600 µg	500 µg

AVERAGE INTAKE, US ADULTS	194–250 µg/day
ESTIMATED MEAN PALEOLITHIC INTAKE (^{A}DULT)[i]	360 µg/day
COMMON DOSE RANGE FOR USE AS SUPPLEMENT	400–1,000 µg/day
DO DIETARY PATTERNS MEETING GUIDELINES PERMIT ADEQUATE INTAKE?	Yes
Included in typical multivitamin/multimineral tablet?	Yes (dose: 600 µg; prenatal vitamin dose: 1,000 µg)
DEFICIENCY	
Intake Level	100 µg/day to prevent overt deficiency; 400 µg/day to prevent nominal deficiency
Syndromes	Megaloblastic anemia; neural tube defects; hyperhomocysteinemia
TOXICITY	
Intake Level	Intake at the RDA can mask vitamin B_{12} deficiency; doses in excess of 10 mg/day (25 times DRI) may be toxic.

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FOLATE TOLERABLE UPPER INTAKE LEVELS (UL)[k]

	Infancy (age 0–6 mo)	Infancy (age 7–12 mo)	Childhood (age 1–3 y)	Childhood (age 4–8 y)
Male	—	—	300 µg	400 µg
Female	—	—	300 µg	400 µg

	Adolescence (age 9–13 y)	Adolescence (age 14–18 y)	Adult (age ≥19 y)	Pregnancy (age 14–18 y)
Male	600 µg	800 µg	1,000 µg	—
Female	600 µg	800 µg	1,000 µg	800 µg

	Pregnancy (age 19–50 y)	Lactation (age 14–18 y)	Lactation (age 19–50 y)
Male	—	—	—
Female	1,000 µg	800 µg	1,000 µg

Syndromes: Masking vitamin B_{12} deficiency with resultant neurologic sequelae; seizures in susceptible individuals with megadosing. Meta-analyses of RCTs have come to conflicting conclusions about whether folic acid supplementation increases cancer incidence;*n* if there is a true effect, it is likely modest.

Folate Dietary Sources[o]: Green vegetables, beans, legumes, and whole grains; to a lesser extent, fruit and fruit juice.

Food	Serving Size	Energy (kcal)	Folate (µg)	Food	Serving Size	Energy (kcal)	Folate (µg)
Lentils	1 cup (198 g)	230	358	Orange juice	1 cup (248 g)	112	74
Kidney beans	1 cup (177 g)	225	230	Radishes (raw)	1 medium (4.5 g)	1	1
Asparagus	4 spears (60 g)	11	81	Peas	1 cup (160 g)	134	101
Avocado	1 whole (201 g)	322	163	White beans	1 cup (179 g)	249	145
Wheat germ	1 cup (115 g)	414	323	Wild rice	1 cup (164 g)	166	43
Pinto beans	1 cup (171 g)	245	294	Banana	1 medium (118 g)	105	24
Chickpeas	1 cup (164 g)	269	282	Endive	1 head (513 g)	87	728
Lima beans	1 cup (188 g)	216	156	Broccoli, 1 medium stalk	(180 g)	63	194
Spinach	1 cup (180 g)	41	263	Brussels sprouts	1/2 cup (78 g)	28	47
Oatmeal with water	100 g	55	43	Lettuce (butterhead)	1 head (163 g)	21	119

Effects of Food Preparation and Storage: Not reported to be a generally important determinant of

dietary intake levels.
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Additional details, evidence, and references for dosing and safety for many nutrients and substances individuals might choose to ingest can be found at http://www.mayoclinic.com/health/search/search, http://ods.od.nih.gov/, and http://www.nlm.nih.gov/medlineplus/

[a]Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Institute of Medicine. *Dietary Reference Intakes for thiamin, riboflavin, niacin, vitamin B_6, folate, vitamin B_{12}, pantothenic acid, biotin, and choline*. Washington, DC: National Academy Press, 2000.

[b]Whitney EN, Rolfes SR. *Understanding nutrition*, 7th ed. St. Paul, MN: West Pub.; 1996.

[c]Toriello HV; Policy and Practice Guideline Committee of the American College of Medical Genetics. Policy statement on folic acid and neural tube defects. *Genet Med*. 2011;13(6):593–596. doi:10.1097/GIM.0b013e31821d4188; Blencowe H, Cousens S, Modell B, et al. Folic acid to reduce neonatal mortality from neural tube disorders. *Int J Epidemiol*. 2010;39(suppl 1):i110–i121. doi:10.1093/ije/dyq028.

[d]Christensen B, Landaas S, Stensvold I, et al. Whole blood folate, homocysteine in serum, and risk of first acute myocardial infarction. *Atherosclerosis*. 1999;147:317–326.

[e]Bunout D, Garrido A, Suazo M, et al. Effects of supplementation with folic acid and antioxidant vitamins on homocysteine levels and LDL oxidation in coronary patients. *Nutrition*. 2000;16:107–110.

[f]Yang HT, Lee M, Hong KS, et al. Efficacy of folic acid supplementation in cardiovascular disease prevention: an updated meta-analysis of randomized controlled trials. *Eur J Intern Med*. 2012;23(8):745–754. doi:10.1016/j.ejim.2012.07.004; Huo Y, Qin X, Wang J, et al. Efficacy of folic acid supplementation in stroke prevention: new insight from a meta-analysis. *Int J Clin Pract*. 2012;66(6):544–551. doi:10.1111/j.1742-1241.2012.02929.x.

[g]Zhou YH, Tang JY, Wu MJ, et al. Effect of folic acid supplementation on cardiovascular outcomes: a systematic review and meta-analysis. *PLoS One*. 2011;6(9):e25142. doi:10.1371/journal.pone.0025142.

[h]Miller ER 3rd, Juraschek S, Pastor-Barriuso R, et al. Meta-analysis of folic acid supplementation trials on risk of cardiovascular disease and risk interaction with baseline homocysteine levels. *Am J Cardiol*. 2010;106(4):517–527. doi:10.1016/j.amjcard.2010.03.064.

[i]Sudchada P, Saokaew S, Sridetch S, et al. Effect of folic acid supplementation on plasma total homocysteine levels and glycemic control in patients with type 2 diabetes: a systematic review and meta-analysis. *Diabetes Res Clin Pract*. 2012;98(1):151–158. doi:10.1016/j.diabres.2012.05.027.

[j]Woo KS, Chook P, Lolin YI, et al. Folic acid improves arterial endothelial function in adults with

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hyperhomocystinemia. *J Am Coll Cardiol*. 1999;34:2002–2006.

[k]Office of Dietary Supplements. Folate. Available at http://ods.od.nih.gov/factsheets/Folate-QuickFacts/; accessed January 8, 2021.

[l]Eaton SB, Eaton SB. Paleolithic vs. modern diets—selected pathophysiological implications. *Eur J Nutr*. 2000;39:67–70.

[m]Office of Dietary Supplements. Folate (for health professionals). Available at http://ods.od.nih.gov/factsheets/Folate-HealthProfessional/; accessed January 8, 2021.

[n]Vollset SE, Clarke R, Lewington S. Effects of folic acid supplementation on overall and site-specific cancer incidence during the randomised trials: meta-analyses of data on 50,000 individuals. *Lancet*. 2013;381(9871):1029–1036; Baggott JE, Oster RA, Tamura T. Meta-analysis of cancer risk in folic acid supplementation trials. *Cancer Epidemiol*. 2012;36(1):78–81. doi:10.1016/j.canep.2011.05.003.

[o]The nutrient composition of most foods can be checked by accessing the US Department of Agriculture nutrient database, at http://www.nal.usda.gov/fnic/foodcomp/search.

[p]Greenberg JA, Bell SJ, Guan Y, Yu YH. Folic Acid supplementation and pregnancy: more than just neural tube defect prevention. *Rev Obstet Gynecol*. 2011 Summer;4(2):52–59.

Sources: Ensminger AH, Ensminger ME, Konlande JE, et al. The concise encyclopedia of foods and nutrition. Boca Raton, FL: CRC Press, Inc., 1995.

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National Research Council. Recommended dietary allowances, 10th ed. Washington, DC: National Academy Press, 1989.

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Pizzorno JE, Murray MT. Textbook of natural medicine, 3rd ed. St. Louis, MO: Church Livingstone Elsevier, 2006.

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LYCOPENE

BIOLOGICAL FUNCTION(S) IN HUMANS/KEY PROPERTIES: Lycopene is a non-provitamin A carotenoid with 11 carbons arranged linearly in conjugated double bonds and no ionone ring. The antioxidant capacity of carotenoids is related to the number of conjugated double bonds; the antioxidant capacity of lycopene is the greatest of known carotenoids and exceeds that of *β*-carotene by a factor of 2. Lycopene is thought to serve as a potent quencher of oxygen-free radicals within cells and on the inner surfaces of cell membranes; other functions in human physiology remain to be elucidated. Lycopene is not known to be an essential nutrient.

ABSORPTION/SOLUBILITY/STORAGE/PHARMACOKINETICS: In general, carotenoids are protein bound and lipid soluble. Heating foods can cause dissociation of such complexes and enhance carotenoid bioavailability. Carotenoids in general and lycopene in particular are more efficiently absorbed when ingested with a lipid source, such as oil. Lycopene is hydrophobic and transported predominantly near the core of lipoprotein particles, in particular LDL; levels are lower in small, dense LDL particles than in normal LDL particles. Serum concentrations vary over a wide range, from 50 to 900 nM/L. Serum lycopene changes gradually in response to varied intake, with a plasma depletion half-life of between 12 and 33 days; levels in chylomicrons are a better marker of short-term change. Lycopene is prominently stored in the adrenal glands, testes, liver, and prostate. Storage in adipose tissue varies with as yet undetermined factors.

Rationale for Supplementation: None known. The rationale for increasing lycopene intake is enhanced antioxidant activity and possible protection against gastrointestinal and prostate cancers. Protection against myocardial infarction has also been suggested.*a*

EVIDENCE IN SUPPORT OF SUPPLEMENTATION TO AND ABOVE THE DRI: No RDA or AI established. Circulating lycopene levels appear to correlate with reduced prostate cancer risk, but a meta-analysis of prostate-related trials concluded “Given the limited number of RCTs published, and the varying quality of existing studies, it is not possible to support, or refute, the use of lycopene for the prevention or treatment of BPH or prostate cancer.”*b* Nonetheless, supplemental lycopene may improve high-density lipoprotein and reduce systemic inflammation, relevant to cardiovascular disease.*c* Lycopene also seems to improve lichen planus, a dermatologic condition rooted in oxidative stress*d*, and may have some benefit for male infertility.*e*

Recommended Intake Range (US RDA)	None.
AVERAGE INTAKE, US ADULTS	5.2–7.9 mg/day
ESTIMATED MEAN PALEOLITHIC INTAKE (A_{DULT})*f*	Not known. Paleolithic intake may have been low, given that tomatoes are the predominant source of lycopene and tomatoes entered the human diet only recently; the tomato plant was originally discovered as a weed in fields of maize and beans in Central America.*g*
COMMON DOSE RANGE FOR USE AS SUPPLEMENT	Internet sites advertise supplements providing between 5 and 10 mg lycopene.
DO DIETARY PATTERNS MEETING GUIDELINES permit	Yes, provided that tomato and tomato-product intake is high.

intake in the supplement range?	
INCLUDED IN TYPICAL MULTIVITAMIN/MULTIMINERAL TABLET?	Not consistently but included in some products
Deficiency	
Intake Level	None known
Syndromes	None known
Toxicity	
Intake Level	None known
Syndromes	None known. A trial of supplemental lycopene given to first-time pregnant women to prevent preeclampsia resulted in worse outcomes: higher rates of preterm birth and low birth weight than with placebo (and no benefit for preeclampsia).*h*

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Lycopene Dietary Sources*i*

Effects of Food Preparation and Storage: Heating foods, particularly in the presence of oil, enhances the absorption and bioavailability of lycopene. Freezing preserves lycopene content.

Additional details, evidence, and references for dosing and safety for many nutrients and substances individuals might choose to ingest can be found at http://www.mayoclinic.com/health/search/search, http://ods.od.nih.gov/, and http://www.nlm.nih.gov/medlineplus/

[a]Kohlmeier L, Kark JD, Gomez-Garcia E, et al. Lycopene and myocardial infarction risk in the EURAMIC Study. *Am J Epidemiol*. 1997;146:618–626.

[b]Ilic D, Misso M. Lycopene for the prevention and treatment of benign prostatic hyperplasia and prostate cancer: a systematic review. *Maturitas*. 2012;72(4):269–276. doi:10.1016/j.maturitas.2012.04.014.

[c]McEneny J, Wade L, Young IS, et al. Lycopene intervention reduces inflammation and improves HDL functionality in moderately overweight middle-aged individuals. *J Nutr Biochem*. 2013;24(1):163–168. doi:10.1016/j.jnutbio.2012.03.015.

[d]Saawarn N. Lycopene in the management of oral lichen planus: a placebo-controlled study. *Indian J Dent Res*. 2011;22(5):639–643. doi:10.4103/0970-9290.93448.

[e]Gupta NP, Kumar R. Lycopene therapy in idiopathic male infertility—a preliminary report. *Int Urol Nephrol*. 2002;34(3):369–372.

[f]Eaton SB, Eaton SB. Paleolithic vs. modern diets—selected pathophysiological implications. *Eur J Nutr*. 2000;39:67–70.

[g]Tannahill R. *Food in history*. New York, NY: Three Rivers Press, 1988.

[h]Banerjee S, Jeyaseelan S, Guleria RJ. Trial of lycopene to prevent pre-eclampsia in healthy

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primigravidas: results show some adverse effects. *Obstet Gynaecol Res*. 2009;35(3):477–482. doi:10.1111/j.1447-0756.2008.00983.x.

[i]Lycopene content is derived from Gerster H. The potential role of lycopene for human health. *J Am College Nutr*. 1997;16:109–126. The nutrient composition of most foods can be checked by accessing the US Department of Agriculture nutrient database, at http://www.nal.usda.gov/fnic/foodcomp/search. However, at present, the lycopene content of foods is not reported in the nutrient database.

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Stahl W, Sies H. Lycopene: a biologically important carotenoid for humans? Arch Biochem Biophys. 1996;336:1–9.

US Department of Agriculture. USDA nutrient database for standard reference. Release 19. 2006.

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Ziegler EE, Filer LJ Jr, eds. Present knowledge in nutrition, 7th ed. Washington, DC: ILSI Press, 1996.

MAGNESIUM

BIOLOGICAL FUNCTION(S) IN HUMANS/KEY PROPERTIES: Magnesium is known to function in more than 300 enzyme systems in the human body, impacting virtually all aspects of metabolism.

ABSORPTION/SOLUBILITY/STORAGE/PHARMACOKINETICS: Roughly 33% of ingested magnesium is absorbed in the upper small bowel. Poorly understood homeostatic mechanisms generally maintain a plasma magnesium concentration of 1.4–2.4 mg/dL (0.65–1.0 mM/L). Excretion occurs through the urine;

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when serum magnesium begins to fall, the kidney compensates by reabsorbing most filtered magnesium. Approximately 20–28 g of magnesium is stored in the body of an adult, with slightly more than half (60%) in the skeleton and slightly less than half in muscles and soft tissue; 1% of body stores are distributed in extracellular fluid. Thiazide diuretics and alcohol increase urinary losses. Long-term use of proton pump inhibitors (PPIs) may cause hypomagnesemia.*a*

Rationale for Supplementation: Average intake in the United States is estimated to be below the RDA level. Therefore, the risk of nominal magnesium deficiency exists with typical American dietary patterns. Supplementation is a reasonable means of precluding such deficiency.

Doses up to approximately twice the RDA are advocated for the treatment of myocardial ischemia, cardiac dysrhythmia, CHF, hypertension, claudication, osteoporosis, fibromyalgia, osteoporosis, and premenstrual syndrome. Supplementation during pregnancy has been advocated to reduce the risk of preeclampsia.

EVIDENCE IN SUPPORT OF SUPPLEMENTATION TO AND ABOVE THE DRI: Evidence supporting intake of magnesium at approximately the RDA is considerable, and in the aggregate represents the rationale for the particular recommendations made. To the extent that supplementation is required to achieve the RDA, supplementation is therefore of likely benefit. Evidence of benefit from supplementation beyond the RDA is generally suggestive at best. Magnesium depletion may accompany diuretic use in CHF, and there is some evidence of acute*b* and sustained*c* suppression of ventricular dysrhythmias in such patients. Magnesium supplementation may improve cardiac function in those with coronary artery disease, improving exercise tolerance and LVEF.*d* There is inconsistent evidence of increased bone density with magnesium supplementation,*e*,*f* although a randomized trial in healthy girls showed benefit for bone mineral content of the hip (not other sites) with supplementation.*g* Supplemental magnesium may produce small reductions in blood pressure (3–4 mm Hg systolic, 2–3 mm Hg diastolic) with greater effect at greater doses.*h* Evidence does not support magnesium supplementation in pregnancy for maternal or neonatal outcomes.*i*,*j* Magnesium deficiency is associated with insulin resistance; magnesium supplementation past sufficiency may reduce c-peptide concentration and possibly fasting insulin, with improvement with some metabolic parameters*k* but no improvement in glycemic control or lipid profiles.*l*

Recommended Intake Range (US RDA): An intake of 310–420 mg/day of total magnesium is recommended for adults.

MAGNESIUM RECOMMENDED INTAKE RANGE (US RDA)*m*

	Infancy (age 0–6 mo)	**Infancy (age 7–12 mo)**	**Childhood (age 1–3 y)**	**Childhood (age 4–8 y)**	**Adolescence (age 9–13 y)**
Male	30 mg*	75 mg*	80 mg	130 mg	240 mg
Female	30 mg*	75 mg*	80 mg	130 mg	240 mg
	Adolescence (age 14–18 y)	**Adult (age ≥19 y)**	**Pregnancy (age ≤18 y)**	**Pregnancy (age 19–30 y)**	**Pregnancy (age 31–50 y)**
Male	410 mg	400–420 mg**	—	—	—
Female	360 mg	310–320 mg**	400 mg	350 mg	360 mg
	Lactation (age ≤18 y)	**Lactation (age 19–30 y)**	**Lactation (age 31–50 y)**		
Male	—	—	—		

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Female	360 mg	310 mg	320 mg

AVERAGE INTAKE, US ADULTS	242–324 mg/day
ESTIMATED MEAN PALEOLITHIC INTAKE (ADULT)[n]	1,223 mg/day
COMMON DOSE RANGE FOR USE AS SUPPLEMENT	100–1,000 mg/day
DO DIETARY PATTERNS MEETING GUIDELINES permit adequate intake?	Yes
Included in typical multivitamin/multimineral tablet?	Yes (dose: 50 mg)

* AI. All other values in table are for RDA.

** Lower values are for 19–30 years, higher values are for >=31 years.

DEFICIENCY

Intake Level Variable; deficiency is often due to malabsorption, alcoholism, or use of diuretics.

Syndromes Weakness, muscle tremors, tetany, cardiac dysrhythmia, mental status changes, effects on vitamin D metabolism, seizures.

TOXICITY

Intake Level Variable, depending on renal function; toxicity of oral magnesium is limited. Children 1–3 and 4–8 years of age have a tolerable upper limit at 65 mg/day and 110 mg/day, respectively. However, individuals above 9 years of age have an upper limit up to 350 mg/day.

Syndromes Diarrhea, nausea, vomiting, hypotension; if extreme, respiratory depression and asystole.

Magnesium Dietary Sources[o]: Magnesium is abundant in leafy green vegetables, grains, legumes, certain fish, nuts, seeds, and chocolate.

Food	Serving Size	Energy (kcal)	Magnesium (µg)	Food	Serving Size	Energy (kcal)	Magnesium (µg)
Sunflower seeds	1 oz (28 g)	165	52	Soybeans	1 cup (172 g)	298	148
Wild rice	1 cup (164 g)	166	52	White beans	1 cup (179 g)	249	113
Wheat germ	1 cup (115 g)	414	275	Peaches	1 medium (150 g)	58	14
Halibut	1/2 fillet (159 g)	379	53	Bulgur wheat	1 cup (182 g)	151	58
Avocado	1 medium (201 g)	322	58	Navy beans	1 cup (182 g)	255	96
Mackerel	1 fillet (112 g)	230	85	Oatmeal	100 g	55	23
Almonds	1 oz (28 g)	164	78	Lettuce (butterhead)	1 head (163 g)	21	21

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Chocolate (semi-sweet)	1 oz (28 g)	136	33	Banana	1 medium (118 g)	105	32
Spinach	1 cup (180 g)	41	157	Buckwheat	1 cup (168 g)	155	86
Cashews	1 oz (28 g)	157	83	Swiss chard	1 cup (175 g)	35	150

Effects of Food Preparation and Storage: Not reported to be a generally important determinant of dietary intake levels.

Additional details, evidence, and references for dosing and safety for many nutrients and substances individuals might choose to ingest can be found at http://www.mayoclinic.com/health/search/search, http://ods.od.nih.gov/, and http://www.nlm.nih.gov/medlineplus/

[a]FDA. Proton Pump Inhibitor drugs (PPIs): Drug Safety Communication—low magnesium levels can be associated with long-term use. Available at http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/

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[c]Bashir Y, Sneddon JF, Staunton HA, et al. Effects of long-term oral magnesium chloride replacement in congestive heart failure secondary to coronary artery disease. *Am J Cardiol*. 1993;72:1156–1162.

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[e]Martini LA. Magnesium supplementation and bone turnover. *Nutr Rev*. 1999;57:227–229.

[f]Doyle L, Flynn A, Cashman K. The effect of magnesium supplementation on biochemical markers of bone metabolism or blood pressure in healthy young adult females. *Eur J Clin Nutr*. 1999;53:255–261.

[g]Carpenter TO, DeLucia MC, Zhang JH, et al. A randomized controlled study of effects of dietary magnesium oxide supplementation on bone mineral content in healthy girls. *J Clin Endocrinol Metab*. 2006;91(12):4866–4872.

[h]Kass L, Weekes J, Carpenter L. Effect of magnesium supplementation on blood pressure: a meta-analysis. *Eur J Clin Nutr*. 2012;66(4):411–418. doi:10.1038/ejcn.2012.4. Epub 2012 Feb 8.

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[j]Makrides M, Crowther CA. Magnesium supplementation in pregnancy. *Cochrane Database*

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Syst Rev. 2001;(4):CD000937.

[k]Chacko SA, Sul J, Song Y, et al. Magnesium supplementation, metabolic and inflammatory markers, and global genomic and proteomic profiling: a randomized, double-blind, controlled, crossover trial in overweight individuals. *Am J Clin Nutr*. 2011;93(2):463–473. doi:10.3945/ajcn.110.002949.

[l]de Valk HW, Verkaaik R, van Rijn HJ, et al. Oral magnesium supplementation in insulin-requiring type 2 diabetic patients. *Diabet Med*. 1998;15(6):503–507.

[m]Office of Dietary Supplements. Magnesium. Available at http://ods.od.nih.gov/factsheets/Magnesium-HealthProfessional/; accessed 01/08/2021.

[n]Eaton SB, Eaton SB. Paleolithic vs. modern diets—selected pathophysiological implications. *Eur J Nutr*. 2000;39:67–70.

[o]The nutrient composition of most foods can be checked by accessing the US Department of Agriculture nutrient database, at http://www.nal.usda.gov/fnic/foodcomp/search.

Sources: Ensminger AH, Ensminger ME, Konlande JE, et al. The concise encyclopedia of foods and nutrition. Boca Raton, FL: CRC Press, Inc., 1995.

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PHOSPHOROUS

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BIOLOGICAL FUNCTION(S) IN HUMANS/KEY PROPERTIES: Phosphorous is an essential dietary mineral. Most (85%) of the 800–850 g stored in the body of an adult is incorporated in the hydroxyapatite matrix of bone in a ratio of 1:2 with calcium. Phosphorous is essential to the hardening of both bone and tooth mineral. Phosphorous participates in the regulation of blood pH. It is present as a component of lipid particles (phospholipids). Phosphorous is a key component of many chemical messengers, including cyclic AMP (adenosine monophosphate), cyclic GMP (guanine monophosphate), and 2,3-diphosphoglyecerate. Renal calcitriol production is in part mediated by serum phosphate levels. Phosphorous also plays a role in the transport of many nutrients into cells, and is required for the synthesis of DNA and RNA. Phosphate bonds in ATP are the principal source of energy for metabolism.

ABSORPTION/SOLUBILITY/STORAGE/PHARMACOKINETICS: Phosphorous absorption takes place in the small intestine by a mechanism independent of calcium and vitamin D; by a mechanism dependent on both calcium and vitamin D; and by a mechanism dependent on vitamin D but independent of calcium. Nearly 90% of phosphorous in human milk is absorbed by infants. Adults absorb more than 50% of ingested phosphorous, with absorption rising as habitual intake falls. The skeleton is the principal storage depot for phosphorous. Virtually all phosphorous lost from the body is excreted in the urine.

Rationale for Supplementation: Phosphorous deficiency does not normally occur but can be seen with extensive use of phosphate-binding antacids (i.e., aluminum based) by adults or in premature infants. In infants, phosphorous deficiency leads to hypophosphatemic rickets, while in adults it induces bone loss, weakness, and malaise.

There appears to be no rationale for megadosing of phosphorous.

EVIDENCE IN SUPPORT OF SUPPLEMENTATION TO AND ABOVE THE DRI: None.

Recommended Intake Range (US RDA)[a]

PHOSPHORUS RECOMMENDED INTAKE RANGE (US RDA)

	Infancy (age 0–6 mo)	**Infancy (age 7–12 mo)**	**Childhood (age 1–3 y)**	**Childhood (age 4–8 y)**
Male	100 mg*	275 mg*	460 mg	500 mg
Female	100 mg*	275 mg*	460 mg	500 mg
	Adolescence (age 9–13 y)	**Adolescence (age 14–18 y)**	**Adult (age ≥ 19 y)**	**Pregnancy (age ≤18 y)**
Male	1,250 mg	1,250 mg	700 mg	—
Female	1,250 mg	1,250 mg	700 mg	1,250 mg
	Pregnancy (age 19–50 y)	**Lactation (age ≤18 y)**	**Lactation (age 19–50 y)**	
Male	—	—	—	
Female	700 mg	1,250 mg	700 mg	

AVERAGE INTAKE, US ADULTS	Approximately 1,126–1,565 mg/day for adult men, 313–395 mg/day for women.
ESTIMATED MEAN PALEOLITHIC I_{NTAKE} (A_{DULT})[b]	3,200 mg/day
COMMON DOSE RANGE FOR USE AS SUPPLEMENT	N/A

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DO DIETARY PATTERNS MEETING GUIDELINES PERMIT ADEQUATE INTAKE?	Yes (dose: 120 mg)
Included in typical multivitamin/multimineral tablet?	Yes (approximately 125 mg)
DEFICIENCY	
Intake Level	Uncertain; a 1:1 ratio with ingested calcium is the recommended minimum.
Syndromes	Hypophosphatemic rickets in neonates; osteopenia and malaise in adults. Acute hypophosphatmia can cause myopathy, cardiomyopathy, and rhabdomyolysis. When the product of calcium ion and phosphate ion (the double product) is less than 0.7 mmol/L, there is likely to be a bone mineralization defect.
TOXICITY	
Intake Level	More than twice the intake level of calcium

* AI. Other values = RDA.

PHOSPHORUS TOLERABLE UPPER INTAKE LEVELS (UL)[a]

	Infancy (age 0–6 mo)	**Infancy (age 7–12 mo)**	**Childhood (age 1–3 y)**	**Childhood (age 4–8 y)**	**Adolescence (age 9–13 y)**
Male	—	—	3,000 mg	4,000 mg	4,000 mg
Female	—	—	3,000 mg	4,000 mg	4,000 mg
	Adolescence (age 14–18 y)	**Adult (19–70 y)**	**Adult (age ≥70 y)**	**Pregnancy (all ages)**	**Lactation (all ages)**
Male	4,000 mg	4,000 mg	3,000 mg	—	—
Female	4,000 mg	4,000 mg	3,000 mg	3,500 mg	4,000 mg

Syndromes	High intake of phosphorous does not appear to be toxic when calcium and vitamin D intake are adequate. When either calcium or vitamin D intake is marginal, high phosphorous intake may induce hypocalcemia. Neither this nor the hyperparathyroidism induced in laboratory animals is a clinical entity that ordinarily occurs. Acute hyperphosphatemia can cause hypocalcemic tetany. When the calcium phosphate ion double product is greater than 2.2 mmol/L, soft-tissue calcification is likely.

Phosphorous Dietary Sources[c]: Phosphorous is particularly abundant in fish, poultry, meat, and dairy products.

Food	**Serving Size**	**Energy (kcal)**	**Phosphorous (μg)**
Wheat germ	1 cup (115 g)	414	968
Sunflower seeds	1 cup (128 g)	745	1,478
Sardines	1 can (92 g)	191	451
Wild rice	1 cup (164 g)	166	134
Pumpkin seeds	1 cup (64 g)	285	59
Salmon	1/2 fillet (154 g)	280	394

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Tuna, white, canned	1 can (172 g)	220	373
Flounder/sole	1 fillet (127 g)	149	367
Skim milk	1 cup (247 g)	86	249
Yogurt, nonfat	1 cup (245 g)	137	385

Effects of Food Preparation and Storage: Phosphorous is relatively unaffected by food processing.

Additional details, evidence, and references for dosing and safety for many nutrients and substances individuals might choose to ingest can be found at http://www.mayoclinic.com/health/search/search, http://ods.od.nih.gov/, and http://www.nlm.nih.gov/medlineplus/

[a]Dietary reference intakes for calcium, phosphorous, magnesium, vitamin d, and fluoride (1997). Available at https://www.ncbi.nlm.nih.gov/books/NBK109825/; accessed 01/08/2021.

[b]Eaton SB, Eaton SB 3rd, Konner MJ. Paleolithic nutrition revisited: a twelve-year retrospective on its nature and implications. *Eur J Clin Nutr*. 1997;51:207–216.

[c]The nutrient composition of most foods can be checked by accessing the US Department of Agriculture nutrient database, at http://www.nal.usda.gov/fnic/foodcomp/search.

SELENIUM

BIOLOGICAL FUNCTION(S) IN HUMANS/KEY PROPERTIES: Selenium is a mineral that functions as a component of glutathione peroxidase, an essential antioxidant system. It is involved in the metabolism of vitamin E and in thyroid function.

ABSORPTION/SOLUBILITY/STORAGE/PHARMACOKINETICS: Selenium is generally well absorbed in the small bowel and is transported in circulation bound to protein. The mineral is concentrated in liver and kidney, and to a lesser extent myocardium. Excretion is primarily in the urine, secondarily in stool. An adult of average size stores approximately 15 mg of selenium.

Rationale for Supplementation: The typical diet in the United States provides well in excess of the RDA for selenium. Supplementation is indicated to prevent deficiency syndromes in parts of the world where the soil is selenium deficient. Selenium deficiency has been most extensively evaluated in rural areas of China with selenium-poor soil and little access to outside food sources. Under such conditions, selenium supplementation in the range of the RDA is indicated to prevent overt deficiency, manifested as Keshan disease, a cardiomyopathy,*a*,*b* and Kashin–Beck syndrome, a form of arthritis,*c* as well as to reduce cancer risk.*d*,*e*

Selenium supplementation beyond the RDA is advocated for putative benefits in cancer prevention, CVD prevention (especially the prevention of events in those with established coronary artery disease), immune enhancement, rheumatoid arthritis, cataract prevention, and the prevention of sudden infant death syndrome (SIDS). However, the evidence for most of these effects is either limited to conditions of selenium deficiency or is highly speculative. As selenium toxicity is well established at a dose of 1 mg (1,000 µg) per day, there is no rationale for megadosing.

Evidence in Support of Supplementation to and Above the DRI: Some evidence suggests a reduced risk of prostate cancer with selenium supplementation.*f* More general reductions in cancer risk may be most pronounced among those having low selenium levels at baseline,*g* but the totality of evidence for selenium supplementation preventing cancer in general remains overall inconsistent and unconvincing.*h*

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Selenium supplementation may be of benefit to select individuals with Hashimoto's thyroiditis, based on baseline antibody levels,*i* and as an adjunct to medication for patients with chronic asthma.*j* Evidence does not support selenium supplementation for cardiovascular disease,*k* or Alzheimer's disease.*l*

Recommended Intake Range (US RDA): An intake of 45–70 µg/day of total selenium is recommended for adults.

Selenium Recommended Intake Range (US RDA)*m*:

	Infancy (age 0–6 mo)	**Infancy (age 7–12 mo)**	**Childhood (age 1–3 y)**	**Childhood (age 4–8 y)**	**Adolescence (age 9–13 y)**
Male	15 µg*	20 µg*	20 µg	30 µg	40 µg
Female	15 µg*	20 µg*	20 µg	30 µg	40 µg

	Adolescence (age 14–18 y)	**Adult (age ≥19 y)**	**Pregnancy (all ages)**	**Lactation (all ages)**
Male	55 µg	55 µg	—	—
Female	55 µg	55 µg	60 µg	70 µg

AVERAGE INTAKE, US ADULTS	90.9–127.1 µg/day
ESTIMATED MEAN PALEOLITHIC INTAKE (ADULT)*n*	Not available
COMMON DOSE RANGE FOR USE AS SUPPLEMENT	50–200 µg/day
DO DIETARY PATTERNS MEETING GUIDELINES PERMIT ADEQUATE INTAKE?	Yes
INCLUDED IN TYPICAL MULTIVITAMIN/MULTIMINERAL TABLET?	Yes (dose: 25 µg)
DEFICIENCY	
Intake Level	<10–20 µg/day.
Syndromes	Cardiomyopathy (Keshan disease), arthritis (Kashin–Beck syndrome), immunosuppression, increased susceptibility to cancer.
TOXICITY	
Intake Level	<1,000 µg/day.*µ*

* AI. Other values = RDA.

SELENIUM TOLERABLE UPPER INTAKE LEVELS (UL)

	Infancy (age 0–6 mo)	**Infancy (age 7–12 mo)**	**Childhood (age 1–3 y)**	**Childhood (age 4–8 y)**	**Adolescence (age 9–13 y)**
Male	45 µg	60 µg	90 µg	150 µg	280 µg
Female	45 µg	60 µg	90 µg	150 µg	280 µg

	Adolescence (age	**Adult (age ≥19**	**Pregnancy (all**	**Lactation (all**

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	14–18 y)	y)	ages)	ages)
Male	400 µg	400 µg	—	—
Female	400 µg	400 µg	400 µg	400 µg

Syndromes Hair and nail brittleness and loss, nausea and vomiting, neuropathy.

Selenium Dietary Sources[o]: Organ meats, fish, and shellfish are generally selenium rich. The selenium content of grains and other plant-based foods varies with the soil content.

Food	Serving Size	Energy (kcal)	Selenium (µg)	Food	Serving Size	Energy (kcal)	Selenium (µg)
Tuna	1 can (172 g)	220	113	Yogurt (nonfat)	1 cup (245 g)	137	9
Oysters	6 medium (42 g)	58	30	Skim milk	1 cup (247 g)	86	5
Flounder (or sole)	1 fillet (127 g)	149	74	Peanut butter	2 tablespoons (32 g)	188	2
Wheat germ	1 cup (115 g)	414	91	Pecans	1 oz (28 g)	196	1
Turkey	1 lb (112 g)	212	32.6	White bread	1 slice (25 g)	67	6
Chicken	1/2 breast (98 g)	193	24	Egg	1 large (50 g)	78	15
Farina	1 cup (233 g)	112	21	Almonds	1 oz (28 g)	164	1
Shrimp	4 large (22 g)	22	9	Walnuts, English	1 oz (28 g)	185	1
Mushrooms	1/2 cup (78 g)	22	9	Mozzarella (part skim)	1 slice (28 g)	72	4
Barley, pearled	1 cup (157 g)	193	14	Swiss cheese	1 slice (28 g)	106	5

Effects of Food Preparation and Storage: Not known to be a significant factor.

Additional details, evidence, and references for dosing and safety for many nutrients and substances individuals might choose to ingest can be found at http://www.mayoclinic.com/health/search/search, http://ods.od.nih.gov/, and http://www.nlm.nih.gov/medlineplus/

[a]Neve J. Selenium as a risk factor for cardiovascular diseases. *J Cardiovascu Risk*. 1996;3:42–47.

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[c]Moreno-Reyes R, Suetens C, Mathieu F, et al. Kashin-Beck osteoarthropathy in rural Tibet in relation to selenium and iodine status. *N Engl J Med*. 1998;339:1112–1120.

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[e]Taylor PR, Li B, Dawsey SM, et al. Prevention of esophageal cancer: the nutrition intervention trials in Linxian, China. Linxian Nutrition Intervention Trials Study Group. *Cancer Res*. 1994;54:2029s–2031s.

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[l]Loef M, Schrauzer GN, Walach H. Selenium and Alzheimer's disease: a systematic review. *J Alzheimers Dis*. 2011;26(1):81–104. doi:10.3233/JAD-2011-110414.

[m]Office of Dietary Supplements. Selenium. Available at http://ods.od.nih.gov/factsheets/Selenium-HealthProfessional/; accessed 01/08/2021.

[n]Eaton SB, Eaton SB. Paleolithic vs. modern diets—selected pathophysiological implications. *Eur J Nutr*. 2000; 39:67–70.

[o]The nutrient composition of most foods can be checked by accessing the US Department of Agriculture nutrient database, at http://www.nal.usda.gov/fnic/foodcomp/search.

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Pyridoxine/VITAMIN B_6

BIOLOGICAL FUNCTION(S) IN HUMANS/KEY PROPERTIES: Several forms of vitamin B_6, pyridoxine, pyridoxal, and pyridoxamine, function in a variety of metabolic pathways, especially transamination, decarboxylation, and racemization of amino acids. Vitamin B_6 is vital to protein metabolism, the manufacture of neurotransmitter production, gluconeogenesis, and glycogenolysis. Vitamin B_6 requirements vary directly with protein intake.

ABSORPTION/SOLUBILITY/STORAGE/PHARMACOKINETICS: Water soluble. Intestinal absorption is nonsaturable. Storage occurs primarily in plasma in a complex with albumin and in erythrocytes.

Rationale for Supplementation: Intake below the RDA is apparently widespread, especially among the older adults and both pregnant and lactating women. Low vitamin B_6 intake is associated with elevated plasma homocysteine, a risk factor for cardiovascular disease.

Claims for megadoses of vitamin B_6 have been made for therapeutic roles in asthma, immunodepression, carpal tunnel syndrome, pregnancy-induced nausea, and premenstrual syndrome, among other conditions.

EVIDENCE IN SUPPORT OF SUPPLEMENTATION TO AND ABOVE THE DRI: There is consensus that supplementation to meet the RDA is appropriate among groups at risk of deficiency. In addition, low levels are widespread among smokers, women taking oral contraceptives, during pregnancy and lactation, and among individuals taking isoniazid and other drugs that alter vitamin B_6 status; supplementation is recommended for these groups. Supplementation in the form of a multivitamin tablet generally provides up to 150% of the RDA for adults. The use of supplements for certain conditions is supported by randomized trials,*a*,*b* but these are mostly small, and there is lack of consensus. The evidence does not support a benefit for cognitive function,*c* pregnancy/labor outcomes,*d* cardiovascular events,*e* incident cancer,*f* or depression in cardiovascular-disease survivors.*g* Doses of up to 250 mg/day are considered safe.

Recommended Intake Range (US RDA)

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VITAMIN B_6 RECOMMENDED INTAKE RANGE (US RDA)[h]

	Infancy (age 0–6 mo)	Infancy (age 7–12 mo)	Childhood (age 1–3 y)	Childhood (age 4–8 y)
Male	0.1 mg*	0.3 mg*	0.5 mg	0.6 mg
Female	0.1 mg*	0.3 mg*	0.5 mg	0.6 mg
	Adolescence (age 9–13 y)	**Adolescence (age 14–18 y)**	**Adult (age 19–30 y)**	**Adult (age ≥31 y)**
Male	1.0 mg	1.3 mg	1.3 mg	1.7 mg
Female	1.0 mg	1.2 mg	1.3 mg	1.5 mg
	Pregnancy (all ages)	**Lactation (all ages)**		
Male	—	—		
Female	1.9 mg	2.0 mg		

AVERAGE INTAKE, US ADULTS	1.53–2.24 mg
ESTIMATED MEAN PALEOLITHIC INTAKE (ADULT)[i]	Unknown
COMMON DOSE RANGE FOR USE AS SUPPLEMENT	50–100 mg/day
DO DIETARY PATTERNS MEETING GUIDELINES permit adequate intake?	Yes
Included in typical multivitamin/multimineral tablet?	Yes (dose: 5.0 mg)
Deficiency	
Intake Level	Below 0.016 mg vitamin B_6/g dietary protein.
Syndromes	Dermatitis, cheilosis (scaling on the lips and cracks at the corners of the mouth) and glossitis (swollen tongue), anemia, depression, seizures.
TOXICITY	
Intake Level	Above 200 mg/day for extended periods (months).

* AI. All other values in table represent RDA.

VITAMIN B_6 TOLERABLE UPPER INTAKE LEVELS (UL)[h]

	Infancy (age 0–6 mo)	Infancy (age 7–12 mo)	Childhood (age 1–3 y)	Childhood (age 4–8 y)
Male	—	—	30 mg	40 mg
Female	—	—	30 mg	40 mg
	Adolescence (age 9–13 y)	**Adolescence (age 14–18 y)**	**Adult (age ≥19 y)**	**Pregnancy (age 14–18 y)**
Male	60 mg	80 mg	100 mg	—

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Female	60 mg	80 mg	100 mg	80 mg
	Pregnancy (age 19–50 y)	**Lactation (age 14–18 y)**	**Lactation (age 19–50 y)**	
Male	—	—	—	—
Female	100 mg	80 mg	100 mg	

Syndromes Ataxia, myalgia, peripheral neuropathy, irritability, dermatological lesions.

Vitamin B_6 Dietary Sources[b]: B_6 is widespread in the food supply; especially abundant in poultry, bananas, avocados, and organ meats.

Food	Serving Size	Energy (kcal)	Vitamin B_6 (mg)	Food	Serving Size	Energy (kcal)	Vitamin B_6 (mg)
Tuna, yellowfin, cooked	3 oz (85 g)	118	0.88	Carrot juice	1 cup (236 g)	94	0.51
Avocado, Florida	One (304 g)	365	0.24	Snapper	3 oz (85 g)	109	0.39
Potato, with skin	One (173 g)	115	0.36	Beef, sirloin	3 oz (85 g)	211	0.36
Banana	1 medium (118 g)	105	0.43	Sweet potato	One (medium); 114 g	103	0.33
Salmon	3 oz (85 g)	127	0.2	Halibut	3 oz (85 g)	119	0.34
Chicken	1/2 breast (98 g)	193	0.55	Swordfish	3 oz (85 g)	132	0.32
Chickpeas	1 cup (164 g)	269	0.23	Tuna, white, canned	3 oz (85 g)	109	0.18
Turkey	1 lb (112 g)	212	0.54	Pepper (green)	1 medium (119 g)	24	0.27
Prune juice	1 cup (256 g)	182	0.56	Sunflower seeds	1 oz (28 g)	165	0.23
Lentils	1 cup (198 g)	230	0.35	Walnuts, English	1 oz (28 g)	185	0.15

Effects of Food Preparation and Storage: Freezing and processing of meats, grains, fruits, and vegetables can result in losses of up to 70% of native Vitamin B_6.

Additional details, evidence, and references for dosing and safety for many nutrients and substances individuals might choose to ingest can be found at http://www.mayoclinic.com/health/search/search, http://ods.od.nih.gov/, and http://www.nlm.nih.gov/medlineplus/

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ASCORBIC ACID/VITAMIN C

BIOLOGICAL FUNCTION(S) IN HUMANS/KEY PROPERTIES: An essential cofactor for eight known enzymes; functions as an electron donor. Facilitates hydroxylation reactions. Vital for a range of metabolic pathways. Required for the biosynthesis of collagen, L-carnitine, and certain neurotransmitters. Involved in protein metabolism. Cannot be synthesized by humans.

ABSORPTION/SOLUBILITY/STORAGE/PHARMACOKINETICS: Water soluble. Absorbed via sodium-dependent transport mechanism in small intestine. Body stores are largely intracellular and saturate in adults at a level of approximately 3 g. Steady-state levels rise minimally with intakes exceeding 200 mg/day and are maximized at an intake level of 500 mg/day.*a*

Rationale for Supplementation: Vitamin C is a potent water-soluble antioxidant. Megadosing is touted to prevent cancers, heart disease, respiratory infections, and a wide range of other health problems. Doses up to 10 g/day have been advocated to the public.

EVIDENCE IN SUPPORT OF SUPPLEMENTATION TO AND ABOVE THE DRI: Available evidence derives predominantly from observational studies and is based primarily on vitamin C in whole foods rather than supplement form. In short-term trials, vitamins C has been shown to produce modest reductions in systolic and diastolic blood pressure, about 3.8 mm Hg and about 1.5 mm Hg, respectively.*b* Some vitamin C trials conducted in those living in crowded lodgings (e.g., military recruits and marathon runners) have demonstrated reductions in the incidence of respiratory infections,*c* but evidence does not support vitamin C supplementation for respiratory conditions like asthma*d* except possibly in the case of exercise-induced bronchospasm.*e* Evidence also does not support vitamin C supplementation to prevent atrial fibrillation after coronary artery bypass grafting *f*or to prevent preeclampsia or other adverse pregnancy outcomes.*g*

Recommended Intake Range (US RDA)*h*

VITAMIN C (ASCORBIC ACID) RECOMMENDED INTAKE RANGE (US RDA)

	Infancy (age 0–6 mo)	Infancy (age 7–12 mo)	Childhood (age 1–3 y)	Childhood (age 4–8 y)
Male	40 mg*	50 mg*	15 mg	25 mg
Female	40 mg*	50 mg*	15 mg	25 mg

* AI

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	Adolescence (age 9–13 y)	Adolescence (age 14–18 y)	Adult (age ≥19 y)	Pregnancy (age ≤18 y)
Male	45 mg	75 mg	90 mg	—
Female	45 mg	65 mg	75 mg	80 mg

	Pregnancy (age 19–50 y)	Lactation (age ≤18 y)	Lactation (age 19–50 y)
Male	—	—	—
Female	85 mg	115 mg	120 mg

AVERAGE INTAKE, US ADULTS	85.7–103.7 mg
ESTIMATED MEAN PALEOLITHIC INTAKE (ADULT)[i]	604 mg
COMMON DOSE RANGE FOR USE AS SUPPLEMENT	100 mg to several grams
DO DIETARY PATTERNS MEETING GUIDELINES permit adequate intake?	Yes
Included in typical multivitamin/multimineral tablet?	Yes (dose: 90 mg)
DEFICIENCY	
Intake Level	Below 10 mg/day in adults
Syndromes	Scurvy, dyspnea, edema, fatigue, depression
Toxicity	
Intake Level	Above 3,000 mg/day in adults

* AI. All other values in table represent RDA.

VITAMIN C TOLERABLE UPPER INTAKE LEVELS (UL)[h]

	Infancy (age 0–6 mo)	Infancy (age 7–12 mo)	Childhood (age 1–3 y)	Childhood (age 4–8 y)
Male	—	—	400 mg	650 mg
Female	—	—	400 mg	650 mg

	Adolescence (age 9–13 y)	Adolescence (age 14–18 y)	Adult (age ≥19 y)	Pregnancy (age 14–18 y)
Male	1,200 mg	1,800 mg	2,000 mg	—
Female	1,200 mg	1,800 mg	2,000 mg	1,800 mg

	Pregnancy (age 19–50 y)	Lactation (age 14–18 y)	Lactation (age 19–50 y)
Male	—	—	—
Female	2,000 mg	1,800 mg	2,000 mg

Syndromes	Diarrhea, nausea, abdominal cramps, and other gastrointestinal disturbances due to the osmotic effect of unabsorbed vitamin C in the gastrointestinal tract; prooxidant effects

VITAMIN C (ASCORBIC ACID) DIETARY SOURCES[i]: VITAMIN C IS ABUNDANT IN A VARIETY OF FRUITS AND VEGETABLES.

Food	Serving Size	Energy (kcal)	Vitamin C (mg)	Food	Serving Size	Energy (kcal)	Vitamin C (mg)
Acerola (West Indian cherry)	1 cup (98 g)	31	1644	Cantaloupe	1 cup (156 g)	53	57
Sweet red peppers, raw	1 cup (149 g)	39	190	Red cabbage, raw	1 cup (70 g)	22	40
Sweet green peppers, raw	1 cup (149 g)	30	120	Peas, boiled	1/2 cup (80 g)	34	38
Orange juice, fresh	1 cup (248 g)	112	124	Tomatoes, raw	1 medium (123 g)	22	16
Orange juice, frozen concentrate	1 cup (249 g)	112	97	Raspberries	1 cup (123 g)	64	32
Grapefruit juice, pink	1 cup (247 g)	96	94	Sweet potato, baked	1 medium (114 g)	103	22
Strawberries	1 cup (152 g)	49	89	Potato with skin, baked	1 medium (173 g)	161	17
Broccoli	1 cup (91 g)	31	81	Salsa	1/2 cup (130 g)	35	3
Oranges, navel	One (140 g)	69	83	Avocado, Florida	One (304 g)	365	53
Kiwi	One (76 g)	46	71	Onions, raw	1 cup (160 g)	64	12

Effects of Food Preparation and Storage: Not reported to be a generally important determinant of dietary intake levels.

Additional details, evidence, and references for dosing and safety for many nutrients and substances individuals might choose to ingest can be found at http://www.mayoclinic.com/health/search/search, http://ods.od.nih.gov/, and http://www.nlm.nih.gov/medlineplus/

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CHOLECALCIFEROL/VITAMIN D

BIOLOGICAL FUNCTION(S) IN HUMANS/KEY PROPERTIES: Refers to calciferol and related chemical compounds. Essential if inadequate skin exposure to ultraviolet light. Vitamin D functions as a hormone, regulating the metabolism of calcium and phosphorus via promotion of intestinal absorption. Promotes bone formation, inhibits parathyroid hormone secretion, and has immunomodulatory activity.

ABSORPTION/SOLUBILITY/STORAGE/PHARMACOKINETICS: Fat soluble. Once ingested, vitamin D is hydrolyzed in the liver and kidney to its biologically active form, 1,25-dihydroxyvitamin D. Breast milk provides approximately 25 IU vitamin D/L. Vitamin D is stored in adipose tissue, making it less bioavailable to obese individuals with increased body fat.

RATIONALE FOR SUPPLEMENTATION: Bone health, defense against osteoporosis; defense against cancer; enhanced immunity.

EVIDENCE IN SUPPORT OF SUPPLEMENTATION TO AND ABOVE THE DRI: In some populations (e.g., darker skin, little outdoor exposure, living in northern latitudes, malabsorption conditions), vitamin D deficiency is common and the benefits of supplementation may depend to a large extent on baseline vitamin D status. For instance, it is unlikely that vitamin D supplements are beneficial for bone health in children and in adolescents with normal vitamin D levels*a* or for muscle strength in nondeficient adults.*b* For older adults, however, supplementation with vitamin D seems to improve strength, gait, and balance, regardless of vitamin D status.*c* Vitamin D supplementation may also reduce the risk of fractures in older women, but is most effective when combined with calcium supplementation.*d* Vitamin D supplements do not seem to reduce cardiovascular risk, except in perhaps for those who are vitamin D deficient (e.g., those with renal disease).*e* Data on vitamin D related to cardiometabolic outcomes are uncertain; some trials show improved insulin resistance but do not show consistent or significant effects on glycemic control, diabetes incidence, blood pressure, or cardiovascular outcomes.*f* Data on cancer prevention are mixed, for cancer overall and for specific malignancies; some studies suggest vitamin D supplementation increases cancer incidence, some that it decreases it.*g* A recent systematic review and meta-analysis demonstrated no effect on all cause or cardiovascular mortality but a 16% reduction in cancer mortality.*l* Vitamin D supplementation clearly reduces mortality rates in those who are vitamin D deficient: 8 of 9 trials included in a meta-analysis showing a mortality benefit were in populations with baseline vitamin D levels that were deficient (serum level ≤20 ng/mL) and the ninth trial was in a population that was vitamin D insufficient (serum level ≤30 ng/mL).*h* Whether vitamin D supplementation confers a mortality benefit in individuals with baseline blood levels >30 ng/mL (considered by most experts to be the level of sufficiency) is an open question.

Recommended Intake Range (US RDA)*i:*

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Age	Male	Female	Pregnancy	Lactation
0–12 mo*	400 IU (10 µg)	400 IU (10 µg)		
1–13 y	600 IU (15 µg)	600 IU (15 µg)	600 IU (15 µg)	600 IU (15 µg)
14–18 y	600 IU (15 µg)	600 IU (15 µg)	600 IU (15 µg)	600 IU (15 µg)
19–50 y	600 IU (15 µg)	600 IU (15 µg)		
51–70 y	600 IU (15 µg)	600 IU (15 µg)		
≥70 y	800 IU (20 µg)	800 IU (20 µg)		

AVERAGE INTAKE, US ADULTS[i]	144–288 IU/d
ESTIMATED MEAN PALEOLITHIC INTAKE (ADULT)	Unavailable
COMMON DOSE RANGE FOR USE AS SUPPLEMENT	200–400 IU
DO DIETARY PATTERNS MEETING GUIDELINES permit adequate intake?	Yes (provided fortified foods like dairy products are included, although most vitamin D comes from sun exposure rather than from dietary sources)
INCLUDED IN TYPICAL MULTIVITAMIN/MULTIMINERAL TABLET?	Yes
DEFICIENCY	
Intake Level	Serum 25(OH)D values <20–25 mmol/L, or <200 IU/day.
Syndromes	Rickets in children, osteomalacia in adults, possibly decreased muscle strength and coordination, and earlier mortality.
Toxicity	
Intake Level[i]	

* Adequate Intake (AI)

Age	Male	Female	Pregnancy	Lactation
0–6 mo	1,000 IU (25 µg)	1,000 IU (25 µg)		
7–12 mo	1,500 IU (38 µg)	1,500 IU (38 µg)		
1–3 y	2,500 IU (63 µg)	2,500 IU (63 µg)		

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4–8 y	3,000 IU (75 µg)	3,000 IU (75 µg)		
≥9 y	4,000 IU (100 µg)	4,000 IU (100 µg)	4,000 IU (100 µg)	4,000 IU (100 µg)
Syndromes	Soft-tissue calcification, kidney stones, hypercalcemia. Nausea, vomiting, constipation, anorexia, weight loss, polyuria, and heart arrhythmias. Possibly greater risk of cancer at some sites like the pancreas, greater risk of cardiovascular events, and more falls and fractures among the older adults. Possibly greater all-cause mortality.			

VITAMIN D DIETARY SOURCES[k]

Food	Serving Size	Energy (kcal)	Vitamin D (IU)
Cod liver oil	1 tablespoon (15 mL)	123	1,360
Sardines	1 can (92 g)	191	250
Tuna, canned in oil	1 can (3 oz)	158	200
Milk, fortified	1 cup	146	100
Salmon, cooked	3.5 oz	181	360
Egg	1 whole	78	20
Mushrooms	½ cup (3 oz)	22	2,700 (if UV exposed)
Margarine, fortified	1 tablespoon	101	60

Additional details, evidence, and references for dosing and safety for many nutrients and substances individuals might choose to ingest can be found at http://www.mayoclinic.com/health/search/search, http://ods.od.nih.gov/, and http://www.nlm.nih.gov/medlineplus/

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TOCOPHEROL/VITAMIN E

BIOLOGICAL FUNCTION(S) IN HUMANS/KEY PROPERTIES: Vitamin E refers to a group of compounds, collectively known as tocopherols and tocotrienols. The most abundant and biologically active is *α*-tocopherol (*α*-TE). Vitamin E functions as a lipid antioxidant, protecting and preserving the integrity of cellular and subcellular membranes.

ABSORPTION/SOLUBILITY/STORAGE/PHARMACOKINETICS: Absorption of vitamin E is relatively inefficient, ranging from 20% to 80% of the amount ingested. Vitamin E is lipid soluble and transported along with lipoprotein particles. It is stored preferentially in liver and organs with high lipid content, such as the adrenal glands.

Rationale for Supplementation: Many individuals, particularly those with low intakes of vegetable oils, nuts, and seeds (that may both contain vitamin E and support its absorption through accompanying fat), may have intake below the recommended level.

The antioxidant effects of vitamin E are thought to be of benefit in the prevention of a variety of chronic diseases, including CVD and cancer. Antioxidants are thought to have an antiaging effect as well. Increasingly, evidence suggests that antioxidant benefit is greatest when lipid-soluble antioxidants (such as vitamin E) and water-soluble antioxidants (such as vitamin C) are combined. However, recent trial evidence mitigates consistently against such benefits and against the use of supplemental vitamin E for disease prevention.

EVIDENCE IN SUPPORT OF SUPPLEMENTATION TO AND ABOVE THE DRI: Data from the Cambridge Heart Antioxidant Study suggest a benefit of supplemental vitamin E in the prevention of second myocardial infarction, although evidence of a mortality benefit was not found.*a* Beneficial effects of acute vitamin E supplementation on endothelial function have been reported. However, in the GISSI–Prevenzione trial, patients with recent myocardial infarction (*n* = 11,324) randomly assigned to vitamin E supplementation (300 mg) did not do better than those assigned to placebo with regard to myocardial infarction or death.*b* Similarly, the HOPE trial demonstrated no significant benefit of vitamin E supplementation (400 IU) with regard to both myocardial infarction and death in high-risk coronary patients.*c* Recent trial data and meta-analyses mitigate against use of supplemental vitamin E for the prevention of cancer or cardiovascular disease.*d–j* Likewise, meta-analyses demonstrate no benefit for vitamin E + vitamin C in pregnancy to prevent preeclampsia*k* or for vitamin E alone with regard to glycemic control.*l* Most importantly, vitamin E supplementation does not appear to have an overall mortality benefit,*m* and may actually increase mortality at high doses (>400 IU/d).*n*

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Recommended Intake Range (US RDA)[o]

VITAMIN E RECOMMENDED INTAKE RANGE (US RDA)

	Infancy (age 0–6 mo)	Infancy (age 7–12 mo)	Childhood (age 1–3 y)	Childhood (age 4–8 y)	Adolescence (age 9–13 y)
Male	4 mg (6 IU)*	5 mg (7.5 IU)*	6 mg (9 IU)	7 mg (10.4 IU)	11 mg (16.4 IU)
Female	4 mg (6 IU)*	5 mg (7.5 IU)*	6 mg (9 IU)	7 mg (10.4 IU)	11 mg (16.4 IU)

	Adolescence (age 14–18 y)	Adult (age ≥19 y)	Pregnancy (all ages)	Lactation (all ages)
Male	15 mg (22.4 IU)	15 mg (22.4 IU)	—	—
Female	15 mg (22.4 IU)	15 mg (22.4 IU)	15 mg (22.4 IU)	19 mg (28.4 IU)

AVERAGE INTAKE, US ADULTS	6.3–8 mg *a*-TE
ESTIMATED MEAN PALEOLITHIC INTAKE (A_{DULT})[p]	33 mg *a*-TE
COMMON DOSE RANGE FOR USE AS SUPPLEMENT	133–533 mg *a*-TE (200–800 IU)
DO DIETARY PATTERNS MEETING GUIDELINES permit adequate intake?	Yes
Included in typical multivitamin/multimineral tablet?	Yes (dose: 20.3 mg)
DEFICIENCY	
Intake Level	Intake below RDA and/or fat malabsorption for years.
Syndromes	Neurologic dysfunction/neuropathy, ataxia, muscle weakness, hemolysis, impaired vision, myopathy, retinopathy, and impairment of the immune response
TOXICITY	
Intake Level	Uncertain; in excess of 1,200 IU/day (although risk of death begins to increase at a dose almost 10 times lower)[n]

* AI. All other values in table are for RDA.

VITAMIN E TOLERABLE UPPER INTAKE LEVELS (UL)[o]

	Infancy (age 0–6 mo)	Infancy (age 7–12 mo)	Childhood (age 1–3 y)	Childhood (age 4–8 y)
Male	—	—	200 mg (300 IU)	300 mg (450 IU)
Female	—	—	200 mg (300 IU)	300 mg (450 IU)

	Adolescence (age	Adolescence (age 14–	Adult (age ≥19 y)	Pregnancy (age 14–18

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	9–13 y)	18 y)	y)	
Male	600 mg (900 IU)	800 mg (1,200 IU)	1,000 mg (1,500 IU)	—
Female	600 mg (900 IU)	800 mg (1,200 IU)	1,000 mg (1,500 IU)	800 mg (1,200 IU)

	Pregnancy (age 19–50 y)	Lactation (age 14–18 y)	Lactation (age 19–50 y)
Male	—	—	—
Female	1,000 mg (1,500 IU)	800 mg (1,200 IU)	1,000 mg (1,500 IU)

Syndromes Diarrhea, headache, coagulopathy, increased risk of hemorrhagic stroke, and possibly earlier mortality.

Vitamin E Dietary Sources *q*: Vitamin E is relatively abundant in vegetable oils, nuts, seeds, and whole grains.

Food	Serving Size	Energy (kcal)	Vitamin E (mg *α*-TE)	Food	Serving Size	Energy (kcal)	Vitamin E (mg *α*-TE)
Wheat germ oil	1 tablespoon (13.6 g)	120	20.3	Corn oil	1 tablespoon (13.6 g)	120	1.9
Sardines	1 can (92 g)	191	1.9	Avocado	1 medium (201 g)	322	4.2
Almonds	1 oz (28 g)	164	7.3	Flounder	1 fillet (127 g)	149	0.8
Peanut butter	2 tablespoons (32 g)	188	2.9	Swiss chard (boiled)	1 cup (175 g)	35	3.3
Blueberries	1 cup (148 g)	84	0.8	Broccoli	1 spear (37 g)	13	0.5
Tomato puree	1 cup (250 g)	95	4.9	Nectarines	1 medium (142 g)	62	1.1
Canola oil	1 tablespoon (14 g)	124	2.4				

Effects of Food Preparation and Storage: Vitamin E will be lost if fat or oil is removed during cooking or preparation.

Additional details, evidence, and references for dosing and safety for many nutrients and substances individuals might choose to ingest can be found at http://www.mayoclinic.com/health/search/search, http://ods.od.nih.gov/, and http://www.nlm.nih.gov/medlineplus/

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ZINC

BIOLOGICAL FUNCTION(S) IN HUMANS/KEY PROPERTIES: Zinc functions in nearly 100 enzyme systems with prominent roles in CO_2 transport and digestion. Zinc also influences DNA and RNA synthesis, immune function, collagen synthesis, olfaction, and taste. Recent interest in zinc has focused on its role in immune function. Zinc lozenges and sprays have been studied for the treatment of upper respiratory infection, and zinc has been found to confer some benefit in lower respiratory infections.*a*,*b* Evidence of benefit is inconsistent, however, and refuted by the results of some trials.*c*,*d*

ABSORPTION/SOLUBILITY/STORAGE/PHARMACOKINETICS: The efficiency of zinc absorption varies inversely with body stores. The absorption of zinc is impeded by fiber phytates, and influenced by the stores and dietary intake of other minerals. Zinc is stored in bone and muscle, but these stores do not readily exchange with the circulation, and therefore cannot compensate rapidly for dietary deficiency.

Rationale for Supplementation: The typical American diet provides approximately 5 mg of zinc/1,000

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kcal. An intake of 15 mg/day is recommended for men, 12 mg/day for women. Older adults in particular are unlikely to take in sufficient calories to meet the RDA for zinc without supplementation.

Supplementation in the range 15–60 mg/day is advocated to enhance immune function; improve pregnancy outcomes; improve male sexual function and fertility; and provide a therapeutic effect in rheumatoid arthritis, acne, Alzheimer's dementia, and macular degeneration. Zinc supplementation may be beneficial in Wilson's disease, a state of copper overload, because zinc interferes with copper absorption.

EVIDENCE IN SUPPORT OF SUPPLEMENTATION TO AND ABOVE THE DRI: Mechanistic studies suggest that zinc plays a role in cell-mediated immune function. Targeted dosing of zinc to the upper airway has shown benefit in some studies of viral infections but not in others.*d* In zinc-deficient populations, zinc supplementation is of benefit against infectious diseases. For HIV-infected individuals (who are commonly zinc deficient), supplementation may help boost CD4 counts, protect against opportunistic infections, and prevent diarrhea.*e* In developing countries, supplementation helps prevent pediatric pneumonia and infectious diarrhea,*f* but does not seem to prevent malaria or malarial deaths.*g* In nondeficient populations, zinc supplementation appears to be of no benefit in pediatric pneumonia,*h* or as a measure to prevent childhood diarrhea.*i* However, zinc supplementation does show a weak relationship with lower risk of preterm birth, which, if causal, might reflect a reduction in maternal infection (a primary cause of prematurity).*j* Beyond infectious considerations, RCTs demonstrate no benefit of zinc supplementation for attention deficit hyperactivity disorder (ADHD) in children*k* or for Alzheimer's disease or cognitive decline in the older adults.*l* Other trials suggest a modest effect of zinc supplementation in reducing glucose concentration in diabetics, but without statistically significant reductions in A1c.*m* Zinc supplementation does not appear to prevent the incidence of diabetes in those with baseline insulin resistance.*n*

Recommended Intake Range (US RDA): An intake of 8–13 mg/day of total zinc is recommended for adults.

ZINC RECOMMENDED INTAKE RANGE (US RDA)*o*

	Infancy (age 0–6 mo)	**Infancy (age 7–12 mo)**	**Childhood (age 1–3 y)**	**Childhood (age 4–8 y)**
Male	2 mg*	3 mg	3 mg	5 mg
Female	2 mg*	3 mg	3 mg	5 mg
	Adolescence (age 9–13 y)	**Adolescence (age 14–18 y)**	**Adult (age ≥19 y)**	**Pregnancy (age 14–18 y)**
Male	8 mg	11 mg	11 mg	—
Female	8 mg	9 mg	8 mg	12 mg
	Pregnancy (age 19–50 y)	**Lactation (age 14–18 y)**	**Lactation (age 19–50 y)**	
Male	—	—	—	
Female	11 mg	13 mg	12 mg	

AVERAGE INTAKE, US ADULTS	9.9–14.4 mg/day
ESTIMATED MEAN PALEOLITHIC INTAKE (ADULT)*o*	43.4 mg/day
COMMON DOSE RANGE FOR use as Supplement	15–60 mg/day

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Do dietary patterns meeting guidelines permit adequate intake?	Yes
Included in typical multivitamin/multimineral tablet?	Yes (dose: 15.0 mg)

* AI. All other values in table represent RDA.

DEFICIENCY

Intake Level Below RDA.

Syndromes Impaired taste and smell; impaired immune function and wound healing; deficiency may lead to eye and skin lesions, alopecia, growth retardation and delayed sexual maturation, impotence, hypogonadism, and mental lethargy.

TOXICITY

Intake Level ≥50 mg/day.

ZINC TOLERABLE UPPER INTAKE LEVELS (UL)[o]

	Infancy (age 0–6 mo)	Infancy (age 7–12 mo)	Childhood (age 1–3 y)	Childhood (age 4–8 y)
Male	4 mg	5 mg	7 mg	12 mg
Female	4 mg	5 mg	7 mg	12 mg
	Adolescence (age 9–13 y)	**Adolescence (age 14–18 y)**	**Adult (age ≥19 y)**	**Pregnancy (age 14–18 y)**
Male	23 mg	34 mg	40 mg	—
Female	23 mg	34 mg	40 mg	34 mg
	Pregnancy (age 19–50 y)	**Lactation (age 14–18 y)**	**Lactation (age 19–50 y)**	
Male	—	—	—	
Female	40 mg	34 mg	40 mg	

Syndromes Nausea, vomiting, loss of appetite, abdominal cramps, diarrhea, and headaches; impaired copper status; at higher intake levels, reduced high-density lipoprotein and impaired hematopoiesis.

Zinc Dietary Sources[q]: Zinc is found abundantly in shellfish, red meat, legumes, and nuts.

Food	Serving Size	Energy (kcal)	Zinc	Food	Serving Size	Energy (kcal)	Zinc
Oysters	6 medium (42 g)	58	76	White beans	1 cup (179 g)	249	2.5
King crab	1 leg (134 g)	130	10.2	Almonds	1 oz (28.3 g)	164	1
Wheat germ	1 cup (115 g)	414	14.1	Avocado	1 medium (201 g)	322	1.3

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Sardines	1 can (92 g)	191	1.2	Barley, pearled	1 cup (157 g)	193	1.3
Lamb	3 oz (85 g)	219	3.7	Chick peas	1 cup (164 g)	269	2.5
Turkey breast	1 lb (112 g)	212	2.3	Lentils	1 cup (198 g)	230	2.5
Cashews	1 oz (28 g)	157	1.6	Chicken breast	1/2 breast (98 g)	193	1
Swordfish	1 piece (106 g)	164	1.6	Oat bran	1 cup (219 g)	88	1.2
Tofu	1/2 cup (126 g)	85	1.1	Oatmeal	100 g	55	0.5

Effects of Food Preparation and Storage: Not reported to be a generally important determinant of dietary intake levels.

Additional details, evidence, and references for dosing and safety for many nutrients and substances individuals might choose to ingest can be found at http://www.mayoclinic.com/health/search/search, http://ods.od.nih.gov/, and http://www.nlm.nih.gov/medlineplus/

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Resources for Nutrient Composition of Foods

RESOURCE MATERIAL

ONLINE RESOURCES

The nutrient composition of most foods can be checked by accessing the US Department of Agriculture nutrient database, at http://www.nal.usda.gov/fnic/foodcomp/search; accessed on 12/06/2020. Simply enter the name of the food of interest in the search box. A list of food choices within the pertinent category will be displayed. Once a specific food is chosen, portion size options are displayed. Once the portion is selected, a table of nutrient composition is displayed.

Many nutrient content questions can now be “googled”. On the main search page, simply type the following:

“How many/how much [A] in [B] of [C]?” and get an instantaneous answer, which is generally sourced from the USDA database mentioned earlier.

[A] can be any information on a Nutrition Facts label (i.e., calories, total fat, saturated fat, polyunsaturated fat, monounsaturated fat, cholesterol, sodium, potassium, total carbohydrate, dietary fiber, sugar, protein, vitamin A, calcium, vitamin B_6, vitamin B_{12}, vitamin C, iron, or magnesium).

[B] can be any units in terms of numerical quantity (e.g., “3”), volume (e.g., “oz” or “ounces”, “c” or “cups”), or weight (e.g., “g” or “grams”).

[C] can be just about any whole food (fruit, vegetable, nut, meat, dairy), nonproprietary processed food (e.g., potato chips, pretzels, crackers, ice cream), or nonproprietary mixed food (e.g., lasagna, hamburger, chicken fingers, pizza).

Depending on the food selected, Google displays pulldown menus to distinguish different preparations (e.g., baked vs. fried) and varieties (e.g., low-fat vs. regular).

The USDA also publishes a series of downloadable/printable posters for nutrition information for raw fruit, vegetables, and fish at https://www.fda.gov/food/food-labeling-nutrition/nutrition-information-raw-fruits-vegetables-and-fish

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Diet–Drug Interactions

EXAMPLES OF DIET–DRUG INTERACTIONS

Alcohol: Alcohol increases the potential hepatotoxicity of many drugs, acetaminophen being a noteworthy example.*a*

Folate: Phenytoin depletes folate, and folate facilitates the maintenance of steady-state phenytoin levels. Folate (500 mg/day) should be supplemented when phenytoin is prescribed.*b*

Grapefruit Juice: Grapefruit juice inhibits the cytochrome P450 enzyme CYP3A4, thereby potentially affecting the levels of the many drugs metabolized in the P450 system.*c*

Vitamin K: Warfarin (Coumadin) is opposed by dietary vitamin K. Dark green vegetables are rich sources of vitamin K, but distribution in the food supply is wide. If anticoagulation is difficult, a dietary assessment is indicated*d*

REFERENCE MATERIAL

ONLINE SOURCES

Online information about food and drug interactions is available from the FDA at https://www.fda.gov/consumers/consumer-updates/avoiding-drug-interactions

An online food–drug interaction guide from Drugs.com : https://www.drugs.com/drug_interactions.html

The TRC natural medicines database is a well-referenced database of food, herb, supplement, and drug interactions that is available by subscription at https://naturalmedicines.therapeuticresearch.com/

Mayo Clinic https://www.mayoclinic.org/patient-care-and-health-information (search for specific nutrients and find drug–nutrient interactions)

Medline Plus https://medlineplus.gov/ (search for specific nutrients to find drug–nutrient interactions)

National Institutes of Health—Office of Dietary Supplements https://ods.od.nih.gov/factsheets/list-all/ (search for specific nutrients and find drug–nutrient interactions)

Safety information on herbs and supplements from the National Institutes of Health is available at https://medlineplus.gov/druginfo/herb_All.html

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APPENDIX H

Nutrient Remedies for Common Conditions: Patient Resources

RESOURCE MATERIAL

ONLINE RESOURCES

Guidance on use of diet in specific health conditions from the US Government: https://www.nutrition.gov/topics/diet-and-health-conditions

General information and resources about dietary supplements from the US Government: https://www.nutrition.gov/topics/dietary-supplements/vitamin-and-mineral-supplements

English translation of German Commission E Monographs through American Botanical Council: http://cms.herbalgram.org/commissione/index.html

TRC Natural Medicines Database (Requires subscription): https://naturalmedicines.therapeuticresearch.com/

Medscape: Herbals and Supplements: https://reference.medscape.com/drugs/herbals-supplements
Nutritionals: https://reference.medscape.com/drugs/nutritionals

PRINT RESOURCES

Craig SY, Haigh J, Harrar S, eds. *The complete book of alternative nutrition*. Emmaus, PA: Rodale Press, Inc., 1997.

Balch JF, Stengler M. *Prescription for natural cures*, 3rd ed. Turner, 2016.

Gaby, A. *The Natural Pharmacy 3rd Ed Complete A-Z Reference to Natural Treatments for Common Health Conditions*. *Harmony*, 2009.

Greger M. How Not To Die. *Flatiron*, 2015.

Lininger SW, ed. *The natural pharmacy: from the top experts in the field, your essential guide to vitamins, herbs, minerals and homeopathic remedies*. Rocklin, CA: Prima Publishing, 1998.

Murray MT, Pizzorno J. *Encyclopedia of Natural Medicine*. Atria, 2012.

Tyler VE. *The doctor's book of herbal home remedies: cure yourself with nature's most powerful healing agents: advice from 200 experts for more than 150 conditions*. Emmaus, PA: Rodale Press, 2000.

https://nhathuocngocanh.com

Print and Web-Based Resource Materials for Professionals

RESOURCE MATERIAL

Readers are referred to the books included under “Suggested Readings” in the bibliographies provided at the end of each chapter.

NEWSLETTERS

The Nutrition Source: Nutrition updates published by the Harvard T.H. Chan School of Public Health: https://www.hsph.harvard.edu/nutritionsource/

OVID nutrition resources: https://www.ovid.com/search-result.html?q=nutrition

WEB-BASED RESOURCES

http://www.healthfinder.gov

This site, useful to both professional and lay users, is maintained by the US Department of Health and Human Services and serves as a directory to credible sources of health information on the web. A search engine allows for easy identification of nutrition sites of interest.

https://fdc.nal.usda.gov/

This site provides access to the US Department of Agriculture Nutrient Data Laboratory. The nutrient composition of virtually any food can be found in the database. To determine the nutrient composition of a food, click “Search” and enter the name of the food.

https://acl.gov/programs/health-wellness/nutrition-services

The Administration on Aging maintains this website, which details the Elderly Nutrition Program, an assistance program for older adults. The information is of use in efforts to provide nutrition to older patients with limited ability to maintain a balanced diet.

https://www.fns.usda.gov/contacts

The US Department of Agriculture maintains this site, which indexes food assistance program offices for children by state.

https://www.cdc.gov/nchs/nhanes/index.htm

This site, maintained by the National Center for Health Statistics at the Centers for Disease Control and Prevention, provides access to dietary intake data from the National Health and Nutrition Examination Survey.

http://www.eatright.org

This site, maintained by the American Dietetic Association, provides information about the services of dietitians as well as a search engine to find a local dietitian listed with the association.

https://www.niddk.nih.gov/health-information/diet-nutrition

This site is maintained by the National Institute of Diabetes, Digestive and Kidney Disease (NIDDK) at the National Institutes of Health.

https://www.fns.usda.gov/cnpp/dietary-guidelines-americans

This site, maintained by the US Department of Agriculture, provides updated dietary guidelines.

https://nhathuocngocanh.com

https://www.nhlbi.nih.gov/

This site, maintained by the National Heart, Lung, and Blood Institute at the National Institutes of Health, provides professional and layperson links to information on the management of cardiovascular risk factors, including hypertension, obesity, and hyperlipidemia.

http://ods.od.nih.gov/

The National Institutes of Health Office of Dietary Supplements website, which provides overviews of individual vitamins, minerals, and other dietary supplements with links (e.g., to nutrient recommendations and Dietary Reference Intakes), “QuickFacts”, and detailed “Fact Sheets”

https://nhathuocngocanh.com

APPENDIX J

Print and Web-Based Resource Materials for Patients

RESOURCE MATERIAL

NEWSLETTERS/MAGAZINES

Eating Well. Where good taste meats good health. Charlotte, VT. http://www.eatingwell.com

A magazine about both food and health, with excellent recipes.

Harvard Health Letter https://www.health.harvard.edu/newsletters/harvard_health_letter

Print and digital newsletters and special topic reports from Harvard Health Publishing

Oldways e-newsletters. https://oldwayspt.org/

News and information relating to the Mediterranean diet

Nutrition Action: Nutrition newsletter published by the Center for Science in the Public Interest: https://www.nutritionaction.com/

Tufts University Health & Nutrition Letter https://www.nutritionletter.tufts.edu/

Sound nutrition advice for the layperson from a leading school of nutrition.

University of California, Berkeley Wellness Letter
https://www.healthandwellnessalerts.berkeley.edu/bookstore/wellness-letter/

Excellent and credible advice on health promotion, including nutrition, fitness, and lifestyle.

BOOKS

COOKBOOKS

Books listed as follows are considered particularly helpful but are a representative sample only; books to guide nutritious cooking are available by virtually every category of cuisine and health condition. The patient with a specific interest not addressed in the following books should be referred to an actual or online bookstore.

Americas Test Kitchen. The Complete Mediterranean Cookbook: 500 vibrant, kitchen tested recipes for a living and eating well every day. *ATK*, 2016

Bittman M. *How to cook everything vegetarian*, 2nd ed. Houghton Mifflin Harcourt, 2017.

Goldfarb A. *The six o'clock scramble*. New York, NY: St. Martin's Press, 2006.

Guynet S. *The hungry brain: outsmarting the instincts that make us overeat*. Flatiron Press, 2017.

Hagman B. *The gluten-free gourmet cooks fast and healthy: wheat-free with less fuss and fat*. New York, NY: Henry Holt, 1997.

Lair C. *Feeding the whole family*. Sasquatch Books, 2016.

Madison D. *The new vegetarian cooking for everyone*. Ten Speed Press, 2014

Ottolenghi Y. *Ottolenghi simple: a cookbook*. Ten Speed Press, 2018

Oldways. *Make every day Mediterranean: and oldWays 4-week menu plan*. Oldways. 2019.

Pannell M, ed. *Allergy free cookbook (healthy eating)*. New York, NY: Lorenz Books, 1999.

Pascal C. *The whole foods allergy cookbook: two hundred gourmet & homestyle recipes for the food*

allergic family. Ridgefield, CT: Vital Health Publishing, 2005.
https://nhathuocngocanh.com
Ponichtera BJ. *Quick & healthy volume II*. Dalles, OR: Scale Down Publishing, 1995.

Terry B. *Vegetable Kingdom: The abundant world of vegan recipes*. Ten Speed Press, 2020.

DIET AND HEALTH

Bittman M, Katz DL. *How To Eat: all your food and diet questions answered*. Houghton Mifflin Harcourt, 2020

Buettner, D. *The Blue Zones 2nd Ed: 9 lessons for living longer from the people who've lived the longest*. National Geographic, 2012.

Campbell, TC. *The China study: revised and expanded edition*. BenBella Books, 2016.

Castelli WP, Griffin GC. *Good fat, bad fat: how to lower your cholesterol and reduce the odds of a heart attack*. Tucson, AZ: Fisher Books, 1997.

D'Agostino J. *Convertible cooking for a healthy heart*. Easton, PA: Healthy Heart, 1991.

Editors of the Wellness Cooking School, University of California at Berkeley. *The simply healthy lowfat cookbook*. New York, NY: Rebus, Inc., 1995.

Katz, DL. *The truth about food*. True Health Initiative. 2018

Katz DL, Colino S. *Disease proof. Plume*. 2013.

Katzen M, Willett WC. *Eat, drink, & weigh less*. New York, NY: Hyperion, 2006.

Mateljan G. *The world's healthiest foods*. Seattle, WA: George Mateljan Foundation, 2007.

Melina V, Forest J, Picarski R. *Cooking vegetarian: healthy, delicious, and easy vegetarian cuisine*. New York, NY: Wiley, 1998.

Nestle M. *What to eat*. New York, NY: North Point Press, 2007.

Nigro N, Nigro S. *Companion guide to healthy cooking: a practical introduction to natural ingredients*. Charlottesville, VA: Featherstone Inc., 1996.

Nixon DW, Zanca JA, DeVita VT. *The cancer recovery eating plan: the right foods to help fuel your recovery*. New York, NY: Times Books, 1996.

Ornish, D. *Undo it!: how simple lifestyle changes can reverse most chronic diseases*. Ballantine books. 2019.

Pensiero L, Olivieria S, Osborne M. *The Strang cookbook for cancer prevention*. New York, NY: Dutton, 1998.

Pollan M. *In defense of food*. Penguin, 2008.

Rolls B. *The volumetrics eating plan: techniques and recipes for feeling full on fewer calories*. New York, NY: Harper Paperbacks, 2007.

Rosso J. *Great good food*. New York, NY: Crown/Turtle Bay Books, 1993.

Willett WC. *Eat, drink and be healthy*. New York, NY: Simon and Schuster Source, 2001.

Wood R. *The new whole foods encyclopedia: a comprehensive resource for healthy eating*. New York, NY: Penguin Books, 1999.

WEB-BASED RESOURCES

https://health.gov/myhealthfinder

This site, useful to both professional and lay users, is maintained by the US Department of Health and Human Services and serves as a directory to credible sources of health information on the web. A search engine allows for easy identification of nutrition sites of interest.

https://www.myplate.gov/

https://nhathuocngocanh.com

These sites provide images of the US Department of Agriculture's MyPlate meal planning guide.

https://fdc.nal.usda.gov/

This site provides access to the US Department of Agriculture Nutrient Data Laboratory. The nutrient composition of virtually any food can be found in the database. To determine the nutrient composition of a food, click "Search" and enter the name of the food.

https://www.heart.org/en/healthy-living/healthy-eating

This site, maintained by the American Heart Association, provides a wealth of information about heart-healthy eating and cooking, including detailed recipes.

https://www.fda.gov/about-fda/center-food-safety-and-applied-nutrition-cfsan/what-we-do-cfsan

This site provides links to the programs overseen by the US Food and Drug Administration's Center for Food Safety and Applied Nutrition.

https://acl.gov/programs/health-wellness/nutrition-services

Maintained by the Administration on Aging, this site provides advice on diet and physical activity for health promotion that is tailored to older adults.

https://ific.org/

This site, maintained by the International Food Information Council, provides consumer-oriented information on food safety.

https://www.fda.gov/food/new-nutrition-facts-label/how-understand-and-use-nutrition-facts-label

This site, maintained by US Food and Drug Administration Center for Food Safety and Applied Nutrition, provides detailed information on the interpretation of food labels, including their use for specific health goals.

https://www.eatright.org/

This site, maintained by the American Dietetic Association, provides information about the services of dietitians as well as a search engine to find a local dietitian listed with the association.

https://kidshealth.org/

A private foundation, the Nemours Center for Children's Health Media, maintains this website, which offers detailed information on nutrition for the newborn. Information on diet and nutrition for older children, through adolescence, is easily accessible from this site.

https://www.niddk.nih.gov/health-information/diet-nutrition

This site, maintained by the National Center for Diabetes, Digestive and Kidney Diseases (NIDDK) at the National Institutes of Health, provides extensive references on cooking and nutrition in the management of diabetes.

https://www.mayoclinic.org/healthy-lifestyle/recipes

This site provides a virtual cookbook maintained by the Mayo Foundation for Medical Education and Research of the Mayo Clinic. Patients can select from a variety of recipes and see the nutritional composition for standard and modified recipes side by side.

https://www.cancer.gov/about-cancer/treatment/side-effects/appetite-loss/nutrition-pdq

This site, maintained by the National Cancer Institute at the National Institutes of Health, provides detailed information on diet and nutrition in cancer care.

https://www.fda.gov/food/buy-store-serve-safe-food/safe-food-handling

This site, maintained by the Food and Drug Administration Center for Food Safety and Applied Nutrition, provides the consumer information on safe food handling, storage, and preparation.

http://www.tops.org

This is the home page for Take Off Pounds Sensibly, an international club that provides information and

support for sensible weight loss.
https://nhathuocngocanh.com
https://www.nhlbi.nih.gov/health/educational/lose_wt/wtl_prog.htm

This site, maintained by the National Heart, Lung, and Blood Institute at the National Institutes of Health, provides guidance in choosing a safe and reasonable weight loss program.

https://www.niddk.nih.gov/health-information/weight-management/choosing-a-safe-successful-weight-loss-program

This site, maintained by the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK) at the National Institutes of Health, provides guidance in choosing a safe and reasonable weight-loss program.

https://www.healthydiningfinder.com/

This site provides a guide to better-for-you chain restaurant meals.

https://ods.od.nih.gov/factsheets/list-all/

The National Institutes of Health Office of Dietary Supplements website, which provides overviews of individual vitamins, minerals, and other dietary supplements with links (e.g., to nutrient recommendations and Dietary Reference Intakes) and “QuickFacts.”

https://nhathuocngocanh.com

Patient-Specific Meal Planners

For patients with or at risk for high blood pressure, see in the following:

NIH-NHLBI DASH Diet resources: https://www.nhlbi.nih.gov/health-topics/dash-eating-plan

7-Day DASH Diet Meal plan by EatingWell: http://www.eatingwell.com/article/289964/7-day-dash-diet-menu/

Mayo Clinic DASH diet guide: https://www.mayoclinic.org/healthy-lifestyle/nutrition-and-healthy-eating/in-depth/dash-diet/art-20048456

For patients with, or at risk for, heart disease, heart-healthy recipes are available from the National Heart, Lung, and Blood Institute at

https://healthyeating.nhlbi.nih.gov/

A portal to meal plans and recipes for diabetes management and prevention is provided by the American Diabetes Association at

https://www.diabetes.org/nutrition/meal-planning

Meal plans for a weight loss and a variety of health conditions may be developed at

https://www.sparkpeople.com/

https://www.noom.com/

Meal plans, recipes, and cooking courses for plant-based diets can be found at the following:
https://www.forksoverknives.com/
https://www.bluezones.com/
https://oldwayspt.org/

https://nhathuocngocanh.com

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